Quarraisha Abdool Karim
Salim S. Abdool Karim
Cheryl Baxter *Editors*

The CAPRISA Clinical Trials: HIV Treatment and Prevention

Springer

The CAPRISA Clinical Trials: HIV Treatment and Prevention

Quarraisha Abdool Karim
Salim S. Abdool Karim · Cheryl Baxter
Editors

The CAPRISA Clinical Trials: HIV Treatment and Prevention

Springer

Editors
Quarraisha Abdool Karim
CAPRISA
University of KwaZulu-Natal
Durban
South Africa

Cheryl Baxter
CAPRISA
University of KwaZulu-Natal
Durban
South Africa

Salim S. Abdool Karim
CAPRISA
University of KwaZulu-Natal
Durban
South Africa

ISBN 978-3-319-47517-2 ISBN 978-3-319-47518-9 (eBook)
DOI 10.1007/978-3-319-47518-9

Library of Congress Control Number: 2016953917

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Contents

Part I
Introduction/Background

Chapter 1
Studies Linked to the Evolving HIV Epidemic in South Africa: Informing the CAPRISA Scientific Agenda

Quarraisha Abdool Karim, Cheryl Baxter and Salim S. Abdool Karim

1 Introduction

Since the first reported cases of AIDS in the USA in 1981, there is no country in the world that has been untouched by HIV/AIDS. Globally, HIV/AIDS is a major global public health challenge and is one of the top ten causes of death. The evolving HIV epidemic is dynamic and needs to be monitored very carefully to understand:

(i) The magnitude and severity of the epidemic;
(ii) Temporal trends of new HIV infections;
(iii) Identify risk factors associated with HIV infection;
(iv) Target and prioritise interventions to prevent and mitigate the impact of the epidemic;
(v) Monitor the impact and effectiveness of the interventions;
(vi) Identify research gaps that need to be filled to enhance responses to the epidemic.

Two of the founding members of CAPRISA, Salim and Quarraisha Abdool Karim, are epidemiologists who were trained at Columbia University in 1988. On

Q. Abdool Karim (✉) · C. Baxter · S.S. Abdool Karim
Centre for the AIDS Programme of Research in South Africa (CAPRISA), University of KwaZulu-Natal, Durban, South Africa
e-mail: quarraisha.abdoolkarim@caprisa.org

C. Baxter
e-mail: cheryl.baxter@caprisa.org

S.S. Abdool Karim
e-mail: salim.abdoolkarim@caprisa.org

Q. Abdool Karim · S.S. Abdool Karim
Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, USA

Q. Abdool Karim et al. (eds.), *The CAPRISA Clinical Trials: HIV Treatment and Prevention*, DOI 10.1007/978-3-319-47518-9_1

their return to South Africa, they immediately started to apply these basic tenets of disease surveillance to a number of infectious diseases that disproportionately affected the black population and were major causes of substantial morbidity and mortality in South Africa. At about this time, HIV had been discovered and diagnostic tests became available for detection of antibodies to HIV. The HIV epidemic in North America and Europe was being well described as was the epidemic in Central and West Africa. Reports of HIV in southern Africa, however, were rare.

The first studies of HIV infection undertaken by the Abdool Karims utilized stored sera from other community-based research that had been undertaken prior to 1987 and confirmed that HIV infection in the general population was rare in the 1980s. Subsequent population-based surveys piggybacked on the active Malaria Control Programme from 1990 to 1992 and coincided with the first national antenatal surveys, enabling a more granular understanding of the HIV epidemic from the outset.

These early studies, which highlighted the disproportionate burden of HIV infection in young women, led the Abdool Karims to undertake a series of socio-epidemiological studies to understand the reasons for the high infection rates in young women. These studies in urban mothers, teenagers, rural women and sex workers all highlighted the limitations of the available HIV prevention options also referred to as the "ABCs" or safer sex practices that include **A**bstinence, **B**e faithful, and the use of male **C**ondoms that are all dependent on male co-operation. For women unable to negotiate safer sex practices with their male partner, there were no options available that they could initiate to remain HIV uninfecteddemonstrate that the prevalence, thus revealing the importance of finding women initiated prevention technologies, also referred to as microbicides.

2 The Evolving HIV Epidemic in South Africa

South Africa bears a disproportionate 18 % global burden of HIV-1 Clade C infection, despite being home to less than 1 % of the global population. The dominant mode of transmission is through sex and there is an associated epidemic of transmission from infected mothers to infants. The South African epidemic is described as a generalised, hyper-endemic epidemic where, despite a high HIV prevalence and advancing HIV disease, there continues to be high rates of new HIV infections. It is estimated that there are about 6.8 million people living with HIV in South Africa and each day there continues to be about 1000 new infections. The evolving epidemic in South Africa has been monitored since 1990 through annual, anonymous surveys in pregnant women utilising the public sector health services for antenatal care. These surveys demonstrate that the prevalence of HIV has increased from <1 % in 1990 to a peak of about 30 % that has remained stable for the past 8 years

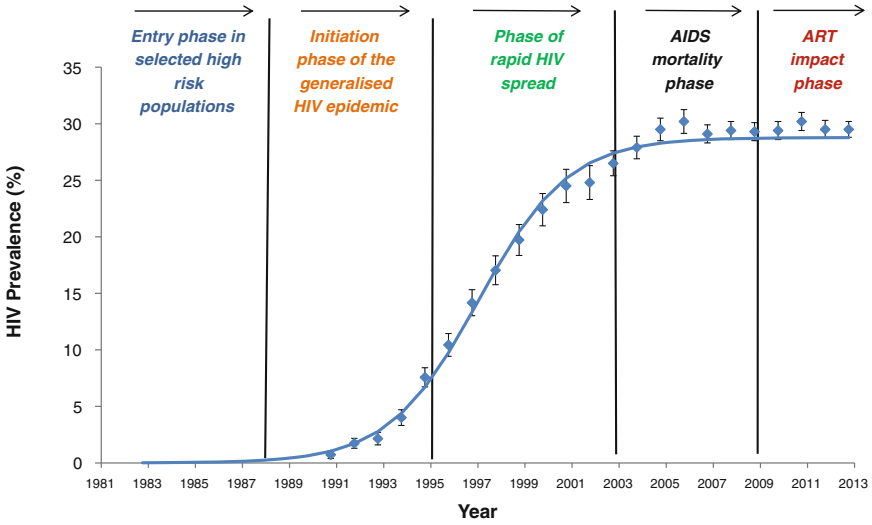

Fig. 1 Temporal trends in HIV infection in South Africa 1990–2014. *Source* Data from South African Department of Health Antenatal Surveys. *Note* The line is based on fitted mathematical models developed by E Gouws

(Fig. 1). These antenatal data, validated by less frequently conducted population-based surveys, reveal that the South African HIV epidemic is made up of a diversity of epidemics within and between the nine provinces. The province of KwaZulu-Natal on the east coast of South Africa and where the CAPRISA headquarters are located, is most severely affected with four of its eleven districts having an HIV prevalence that exceeds 40 % and the remaining 7 districts having an HIV prevalence between 30 and 40 % (Fig. 2). In contrast, the HIV prevalence on the west coast of South Africa is below 5 %.

Population-based studies undertaken since 1990 have highlighted that women have a three to four-fold higher burden of HIV infection compared to males and women acquire HIV infection about 5–7 years earlier than men (Fig. 3). Adolescent girls and young women between the ages of 15–24 years have up to six-fold more HIV infection compared to their male peers.

The convergence of a major pre-HIV era TB epidemic, escalating numbers of TB cases resulting from a maturing HIV epidemic and growing TB drug resistance have resulted in South Africa bearing the brunt of the most serious TB crisis in the world, with increasing numbers of multi-drug resistant (MDR) TB and the emergence of extensively drug resistant (XDR) TB and is a major contributor to mortality in HIV-TB co-infected patients.

The HIV epidemic in South Africa has evolved through five distinct phases (Fig. 1).

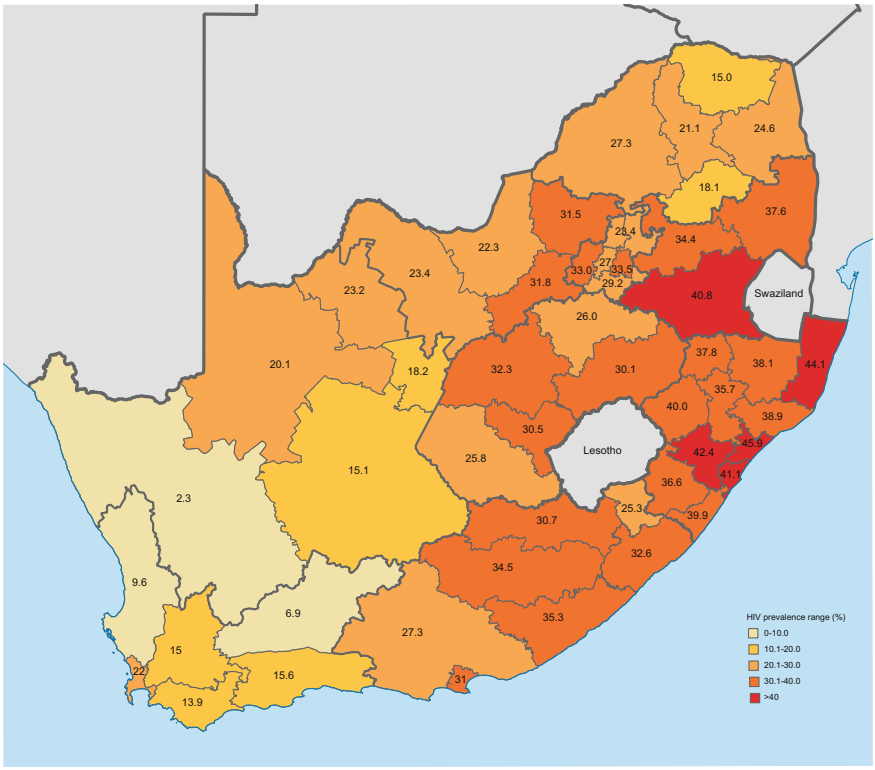

Fig. 2 Diversity of the HIV epidemic within South Africa—HIV in South Africa by district

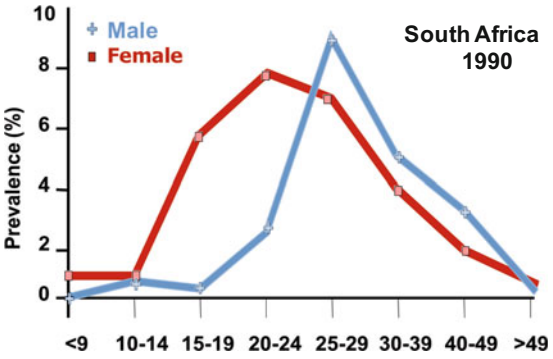

Fig. 3 Age-sex difference in HIV infection

(i) an initial "concentrated epidemic phase" pre-1987,
(ii) the "initiation of the generalised HIV epidemic" phase between 1988 and 1994,
(iii) the "rapid spread of HIV phase" from 1995 to 1999,

(iv) the "AIDS mortality phase" between 2000 and 2006 where deaths due to AIDS became evident and increased rapidly,
(v) the post-antiretroviral (ARV) treatment era from 2006–present.

2.1 Phase 1: Concentrated Epidemic Phase (Pre-1987)

The first cases of AIDS in South Africa were described in 1982 among men who have sex with men (MSM) at about the same time as it was being described in North America, Europe and Australia. The widespread belief that AIDS is a "gay disease" created a sense of complacency about HIV in the general population and the government of South Africa. The gay community, together with a few clinicians, took a more pro-active approach in their response by accessing information about scientific advances on prevention and treatment through networking with advocacy groups in developed countries and laid the foundation for an active evidence-based civil society movement founded on strong human rights principles.

Between 1983 and 1985, prior to the discovery of HIV and the development of diagnostic tests for the detection of HIV, about 100 haemophiliacs acquired HIV through contaminated blood and blood products. The South African government immediately set up a fund to compensate the families of these patients who died prematurely. Although few families accessed the financial compensation available, it created a divide between those infected with HIV, distinguishing "innocent victims" deserving of compensation from those infected from amoral behaviours and therefore not deserving of a state response. The development and subsequent extensive use of HIV antibody diagnostic tests in screening blood and blood products eliminated this mode of HIV transmission. The subtype B human immune deficiency virus was the causative organism in both haemophiliacs and MSM populations.

During this period, HIV infection remained rare in the general population. Sero-prevalence surveys undertaken in rural communities, sex workers, pregnant women and hospital patients did not identify a single infected individual [1]. In 1986, a survey undertaken in about 30,000 mine workers identified three HIV positive men; all were migrant workers from countries north of South Africa. The forced repatriation of these workers and the subsequent government policy barring HIV infected migrant workers set up discriminatory practices in the workplace and generated stigma and fear in communities.

2.2 Phase 2: Initiation of the Generalised Epidemic (1988–1994)

While subtype B HIV continued to spread among MSM, subtype C HIV started to be identified in the general population in about 1987. The first anonymous antenatal

survey among pregnant women utilising public sector health facilities was undertaken in 1990 and since then it has been an important way to monitor the evolving HIV epidemic in the general population (Fig. 1).

Between 1990 and 1994 there was an exponential increase in HIV infection with a doubling time almost every 12 months. HIV prevalence increased from 0.76 % in 1990 to 7.57 % in pregnant women in 1994. Heterosexual transmission has since 1990 been the dominant mode of transmission of HIV infection in South Africa with a concomitant epidemic in infants born to HIV infected mothers. HIV spread has shown a marked and uneven geographical distribution (Fig. 2) across South Africa with the east coast provinces of KwaZulu-Natal and Mpumalanga experiencing the highest rates of HIV infection.

Three population-based surveys undertaken in rural KwaZulu-Natal between 1990 and 1992 by the Abdool Karims highlighted the rapidity of the spread of HIV and identified a unique characteristic of the HIV epidemic in sub-Saharan Africa viz the stark differences in age and sex distribution of HIV infection (Fig. 3). HIV prevalence is highest in teenage girls while it is low in teenage boys; with prevalence rates rising in men about 5–7 years later than in women.

Historically, the political system of apartheid that separated people along racial lines and further forced hundreds of thousands of young males from southern Africa, including rural South Africa, to migrate to cities and the goldmines in Johannesburg created the conditions for the rapid spread of HIV. Young men were separated from their families, creating social instability in rural communities in South Africa and neighbouring countries and were forced to live in over-crowded, poorly ventilated single-sex hostels and returning to their families for short periods of time. This type of "oscillatory migration" where males lived temporarily in the cities and on the mines and periodically visited their wives and families in rural 'homelands', was key to the spread of both TB and sexually transmitted infections, notably syphilis, to rural communities in the nineteenth century. This migrant labour system created the social and behavioural conditions for the introduction of multiple viruses from several neighbouring countries to spread rapidly in South Africa [2–4]; multiple partnerships, especially concurrent multiple partnerships, became the norm (town wife and rural wife) for a large segment of the population. Migrant couples, where at least one partner is a migrant worker, were more likely than non-migrant couples to have one or both partners infected (35 % versus 19 %; $p = 0.026$) [5].

The survey results led the Abdool Karims to initiate several cross-sectional studies in teenagers in schools, in urban mothers of teenagers, in rural men and women, and sex workers to enhance understanding of what was driving HIV risk. These studies highlighted that limited economic opportunities for women made them dependent on males for survival. In many instances, the men were older than the women. As a result, the women experienced difficulty in negotiating safer sex practices. Love and trust within couples made it difficult to use condoms. Another barrier to condom use was access to condoms from family planning providers, who perceived condoms as a fertility control measure rather than a primary mode of infection prevention. Most importantly, even though women perceived their risk of acquiring HIV from their partner as being high, they did not think that they had a

right to insist that their partners use condoms or be faithful to them. This disconnect between vulnerability of young women and limitations of available safer sex practices was what catalysed the Abdool Karims' quest to find women-initiated technologies, including vaccines and microbicides. They undertook their first microbicide trial of nonoxynol-9 film in sex workers in KwaZulu-Natal in 1993.

During this phase the Columbia University-Southern African Fogarty AIDS Training Programme was established to train South Africans in epidemiology and undertake randomised controlled trials. This training programme very quickly expanded to include tuberculosis and basic science training. The seeds of expertise for intervention research started to be laid and a critical mass of scientists to undertake multidisciplinary research started to emerge.

2.3 Phase 3: Rapid Spread of HIV Phase (1995–1999)

During this phase, HIV prevalence increased explosively from 7.6 % in 1994 to 20.5 % in 2000, with wide variations within and between provinces. HIV prevalence in young pregnant women (20–24 years) in a rural KwaZulu-Natal community increased from 21.1 % in 1995, to 39.3 % in 1998 and 50.8 % in 2001 [6].

During this phase, HIV started off as a largely silent asymptomatic epidemic but soon the face of AIDS started to emerge with increasing illness and death rates in young men and women. ARV treatment that was widely available in industrialised countries and had transformed AIDS from an inevitably fatal condition to a chronic and manageable condition, was simply unaffordable in Africa including South Africa.

Technology to sequence the virus started to emerge and phylogenetic mapping of HIV isolated in South Africa shed light on this explosive spread of HIV and the subtypes of HIV in different populations. While Clade B viruses were responsible for the epidemic in MSM and haemophiliacs, Clade C was predominantly spreading in the general population. The diversity of Clade C viruses circulating in South Africa [7] (Fig. 4) captured the numerous mini-epidemics across the country and how with time they started to coalesce to form a generalised, well-established HIV epidemic in the country and laid the foundations for the collaboration with Carolyn Williamson at the University of Cape Town.

The establishment of democracy in South Africa led to academic sanctions against South Africa being lifted and opportunities to be part of the global community started to unfold. A key opportunity during this period was applying for NIH-funded research opportunities. The successful application to join NIH-funded prevention trial networks enabled the Abdool Karims to participate in multi-centre prevention trials, interact with other scientists in the USA and learn about the design and conduct of clinical trials to exacting standards.

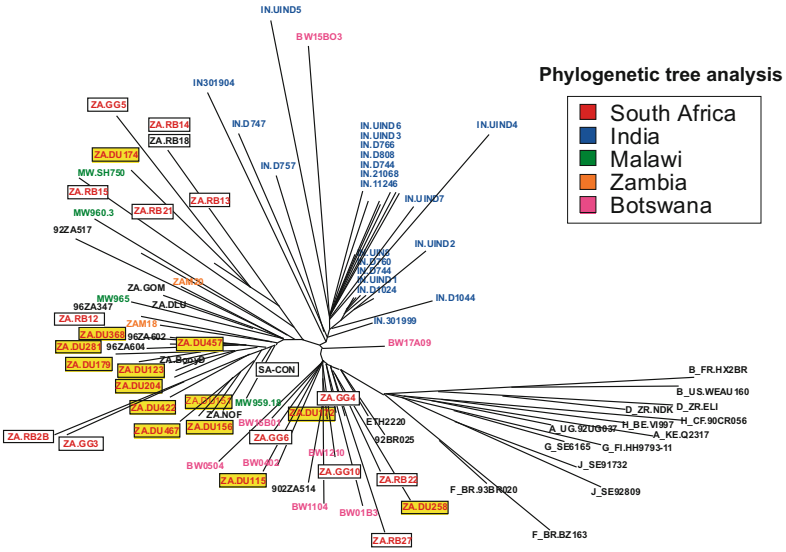

Fig. 4 HIV molecular epidemiology in southern Africa. *Source* Williamson C, Morris L, Maughan MF, Piug L-H, Dryga SA, Thomas R, Reap EA, Cilliers T, Van Harmelen J, Pascual A, Ramjee G, Frelinger J, Johnston R, Abdool Karim SS, Swanstrom R. AIDS Res Hum Retroviruses 2003; 19: 133–144

2.4 Phase 4: AIDS Mortality Phase (2000–2006)

During the period 2000–2005, the national seroprevalence of HIV infection in pregnant women rose from 24.8 % in 2001 to a peak of 30.2 % in 2005 and thereafter decreased slightly to 29.1 % in 2006. However, the incidence rate in 2006 in this group is estimated to be in excess of 5 % per annum [8]. In the midst of continuing high HIV incidence rates, the rising mortality rates resulted in progressively smaller rises in HIV prevalence during this period. Antiretroviral therapy was introduced on a wide scale in 2003, largely through non-governmental organisations funded through the US government's PEPFAR programme. As HIV prevention science researchers, we were faced for the first time with more volunteers testing HIV positive than negative and we simply could not continue to turn AIDS patients away. The newly established CAPRISA had an opportunity to provide ARV treatment through PEPFAR funding.

In 2006, both HIV mortality and incidence were high despite South Africa having one of the largest ARV treatment programmes in the world. Life expectancy declined by several years, and infant and maternal mortality rates [9] were at the highest rates ever. Many adult South Africans in the economically active period of their lives were dying and the average male life expectancy was 48.4 years while the average female life expectancy was 51.6 years [10]. These reversals in trends of key markers for monitoring the millennium development goals (MDGs) provide

some indication of the enormous development challenges that South Africa would be facing in the very near future if the current epidemic trajectories were not reversed.

2.5 *Phase 5: Introduction of ARV Treatment and Reversing Mortality Rates (Post-2006–Present)*

Today, AIDS dominates all aspects of medical practice and health in South Africa. Mitigating the impact of HIV while reducing its spread was the greatest challenge facing the newly elected South African administration in 2009, and they rose to it. While the belated scale-up of ART is widely recognised as a major achievement in South Africa, paradoxically, TB services have lagged behind.

The annual TB mortality rate had increased 2.8-fold from 78/100,000 in 1990 to 218/100,000 in 2006. TB is the most common notified natural cause of death in South Africa [11]. In communities where HIV prevalence exceeds 30 % in pregnant women, annual TB rates as high as 1500/100,000 were reported in 2004 [12]. Much of this TB was HIV-associated, with over 50 % of new TB cases being in HIV co-infected patients. The confluence of increasing TB cases, HIV-TB co-infection, drug-resistant TB cases, and TB mortality constituted a crisis that demanded urgent intervention (Fig. 5).

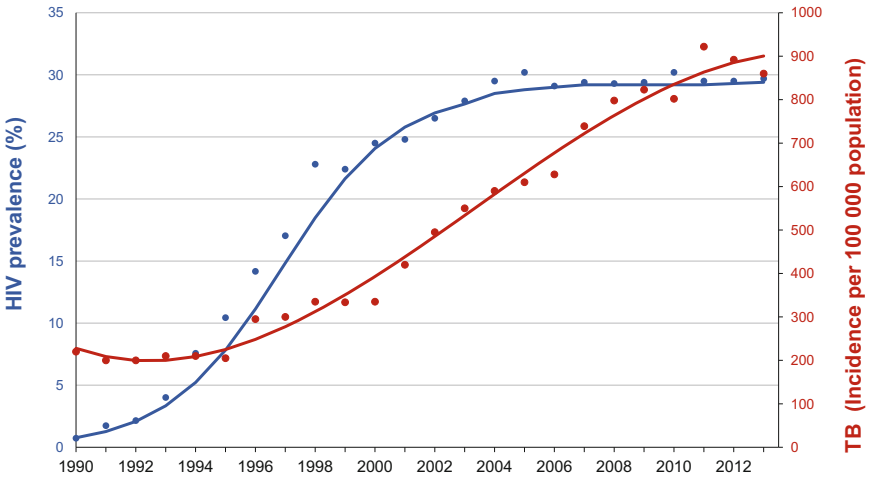

Fig. 5 Intertwining of HIV and TB—HIV prevalence and TB incidence in South Africa: 1990–2013. *Source* Annual point estimates from the South African Department of Health; http://www.tbfacts.org/tb-statistics-south-africa/ and http://data.worldbank.org/indicator/SH.TBS.INCD. *Note* The lines are based on fitted mathematical models developed by E Gouws (HIV) and A Grobler (TB)

3 Conclusion

CAPRISA was established at a time when South Africa was experiencing one of the worst HIV and TB epidemics in the world. The ongoing high HIV incidence rates in young women were an obvious priority for CAPRISA during its inception. Advancing the understanding of subtype C pathogenesis clinically, virologically and immunologically was the second priority area as this subtype accounts for close to 70 % of the circulating viruses globally. The intertwined epidemics of HIV and TB were associated with spiralling mortality. The TB epidemic grew as a result of advancing HIV disease and was a key contributor to increased high mortality rates aggravated by the massive growth of MDR-TB and the emergence of XDR-TB. In the context of increasing access to antiretroviral treatment where HIV status was largely unknown HIV–TB co-infected patients were the obvious group to benefit most. However, when to start antiretroviral treatment in HIV–TB co-infected patients was not known.

These three areas, HIV risk in women, subtype C pathogenesis and treatment of HIV–TB co-infection, were the key challenges that defined the research agenda of CAPRISA at its inception.

References

1. Dusheiko GM, Brink BA, Conradie JD, Marimuthu T, Sher R. Regional prevalence of hepatitis B, delta, and human immunodeficiency virus infection in southern Africa: a large population survey. American Journal of Epidemiology. 1989; 129(1): 138–45.
2. Lurie M, Williams BG, Zuma K, Mkaya-Mwamburi D, Garnett GP, Sturm AW et al. The Impact of Migration on HIV-1 transmission in South Africa: A Study of Migrant and Nonmigrant Men and Their Partners. Sex Transm Dis. 2003; 30: 149–56.
3. Jochelson K, Mothibeli M, Leger JP. Human immunodeficiency virus and migrant labor in South Africa. Int J Health Serv. 1991; 21(1): 157–73
4. Zuma K, Gouws E, Williams B, Lurie M. Risk factors for HIV infection among women in Carletonville, South Africa: migration, demography and sexually transmitted diseases. International Journal of STD & AIDS. 2003; 14(12): 814–7
5. Lurie M, Willaims B, Zuma K, Mkaya-Mwamburi D, Garnett G, Sweat MD et al. Who infects who? HIV-1 concordance and discordance among migrant and non-migrant couples in South Africa. AIDS. 2003; 17: 2245–52.
6. Gouws E, Abdool Karim Q. Chapter 3: HIV Infection in South Africa: the evolving epidemic. In: Abdool Karim SS, Abdool Karim Q, editors. HIV/AIDS in South Africa. Cape Town: Cambridge University Press; 2005. p. pp 48–66.
7. van Harmelen J, Williamson C, Kim B, Morris L, Carr J, Maartens G, et al. Characterisation of full length HIV-1 sequences from South Africa. AIDS Res Hum Retroviruses. 2001; 17: 1527–31.
8. South African Department of Health. National HIV and syphilis prevalence survey in South Africa 2006. Pretoria: Department of Health; 2007.
9. Department of Health. Saving Mothers - Report on Confidential Enquiries into Maternal Deaths in South Africa: 2002-2004. Pretoria: South Africa Department of Health; 2006.

10. Stats SA. Mid-year Population Estimates; Statistical Release P0302, www.statssa.gov.za. Pretoria: Statistics South Africa; 2008.
11. Health Systems Trust. District Health Barometer 2006/2007. Accessible at http: www.hst.org.za/publications/717 [Accessed: January 2009]. 2008.
12. Lawn SD, Bekker LG, Middelkoop K, Myer L, Wood R. Impact of HIV infection on the epidemiology of tuberculosis in a peri-urban community in South Africa: the need for age-specific interventions. Clin Infect Dis. 2006; 42(7): 1040–7

Chapter 2
CAPRISA: Establishing a Research Centre to Undertake HIV Clinical Trials

Salim S. Abdool Karim, Cheryl Baxter and Quarraisha Abdool Karim

1 Background

The HIV/AIDS epidemic in South Africa is amongst the worst in the world. There are several unique features of the sub-Saharan HIV epidemic; it has been characterised as an explosive [1] epidemic, it is predominantly clade C [2], core groups are difficult to identify since the general heterosexual population is severely affected, the peak HIV prevalence rates demonstrate a marked gender difference (15–25 year women and 25–35 year men), and there is a preponderance of women amongst the HIV infected [3]. Denial and stigma were commonplace and discrimination against those infected abounded. Unfortunately, the scale of the response had simply not been able to keep pace with the rapid progression of the epidemic.

The early research response to AIDS in South Africa focused on defining the epidemic, measuring it and trying to predict its future course. Research during the first 10 years of the epidemic, until the mid-1990s, was comprised predominantly of knowledge, attitude and practice studies and HIV seroprevalence surveys. The mid-1990s saw the emergence of three new streams of AIDS research; firstly a re-emergence of molecular research characterising viral subtypes, viral receptor usage and immune responses; secondly the emergence of a clinical research effort, which included pharmaceutical industry sponsored therapeutic trials, and thirdly, the development of a new prevention research effort, comprising mainly phase III

S.S. Abdool Karim (✉) · C. Baxter · Q. Abdool Karim
Centre for the AIDS Programme of Research in South Africa (CAPRISA),
University of KwaZulu-Natal, Durban, South Africa
e-mail: salim.abdoolkarim@caprisa.org

C. Baxter
e-mail: Cheryl.baxter@caprisa.org

S.S. Abdool Karim · Q. Abdool Karim
Department of Epidemiology, Mailman School of Public Health,
Columbia University, New York, NY, USA

Q. Abdool Karim et al. (eds.), *The CAPRISA Clinical Trials: HIV Treatment and Prevention*, DOI 10.1007/978-3-319-47518-9_2

prevention trials, some of which occurred through the US National Institutes for Health (NIH)-funded HIV network known as HIVNET. The clinical research effort in South Africa comprised two components; the first led to several important studies of clinical presentation, diagnosis and management of AIDS and the second led to a multitude of therapeutic trials. In the mid-1990s, the number of prevention and therapeutic trials had increased exponentially. However, a distinct difference in the two types of trials emerged. The prevention trials, like the nonoxynol-9 microbicide trial, Petra Trial, Hlabisa STD trial and the vitamin A/exclusive breastfeeding trial, were being devised by South Africans in response to the pressing local problems of the AIDS epidemic. On the other hand, South Africa served as a convenient site for drug company therapeutic trials in which South African scientists had little contribution or ownership.

In the late 1990s, a new stream of research on HIV vaccines emerged, galvanised by support from the International AIDS vaccine Initiative (IAVI), South African AIDS Vaccine Initiative (SAAVI), the Joint United Program on HIV/AIDS (UNAIDS) and the HIV Vaccine Trial Network (HVTN). The transition from a preponderance of descriptive AIDS research to the dominance of intervention AIDS research occurred through a combination of a growing and maturing AIDS research community, newly established post-apartheid international collaboration and availability of funds from international agencies like UNAIDS, World Health Organisation and NIH.

2 Establishing a Research Centre to Undertake HIV Clinical Trials

As South Africa grappled with the epidemic in the 1990s, local AIDS researchers faced growing pressure to find public health solutions. The NIH's Comprehensive International Program of Research on AIDS (CIPRA) funding opportunity announcement presented a unique opportunity for South African scientists, in collaboration with leading US scientists, to make a new significant contribution to AIDS research.

A network of leading South African AIDS scientists had developed in the 1990s through the Fogarty AIDS training program, the NIH-sponsored HIV Prevention Trials Unit and HIV Vaccine Trials Unit, and the IAVI sponsored Alphavax HIV vaccine project. In 2001, senior AIDS researchers from some of South Africa's major research groups at the University of KwaZulu-Natal (formerly University of Natal), National Institute for Communicable Diseases (formerly National Institute for Virology), University of Cape Town, University of the Western Cape, University of Durban-Westville, Anglo-American's Aurum Health Research Unit and Columbia University in New York decided to combine their efforts to establish a multi-disciplinary collaborative program known as the Centre for the AIDS

Programme of Research in South Africa (CAPRISA). These AIDS researchers had experience with high-risk cohorts of sex workers, migrant workers and adolescents, had a track record of collaboration, well-established sound local leadership and collaborative research and training links with several US institutions. The creation of CAPRISA resulted in a consolidation of this group's previous and existing collaborations and elevated it to the level of a vibrant, well co-ordinated and integrated team.

One of the major strengths of this team was its multi-disciplinary nature; CAPRISA brought together a team of South African researchers who had expertise in the areas of basic and molecular epidemiology, virology, immunology, infectious disease medicine, HIV primary care and service delivery, bioinformatics, social and behavioural science, statistics, ethics and health policy. Several international investigators contributed to the establishment of CAPRISA through their knowledge and experience by providing advice, training and support in HIV therapy, assay development, training and external quality assurance of complex laboratory assays. CAPRISA synergistically combined the complementary contribution of each discipline and each team member to make fundamental contributions to understanding clade C, heterosexually acquired HIV infection, elaborating the mechanisms by which prevention and therapy may impact on HIV natural history, and devising affordable programmatic approaches for making antiretroviral therapy a reality in resource-limited settings (Table 1).

Table 1 Extract of the summary statement and list of participating institutions and key personnel involved in the original CIPRA application

DESCRIPTION. State the application is broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This description is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information
The Collaborative AIDS Program of Research in South Africa (CAPRISA) is a multi-institutional team with well-established local leadership and expertise in the areas of basic and molecular epidemiology, virology, immunology, infectious disease medicine, HIV primary care and service delivery, bioinformatics, social and behavioural science, statistics, ethics and health policy. CAPRISA has three goals; (i) to undertake globally relevant and locally responsive research that contributes to understanding HIV pathogenesis and epidemiology as well as the nexus between tuberculosis and AIDS care, (ii) to build local research infrastructure though cores of expertise and (iii) to provide training through research fellowships tenable both in South Africa and the USA. CAPRISA comprises four research projects. The epidemiological studies on monitoring and deciphering the nuances of the evolving HIV/AIDS epidemic in a rural South African community lay the foundation for assessing the impact of therapeutic and prevention programs at community level. The clinical, immunological and virological studies on acute HIV infection elucidate the host and viral factors influencing the viral set

(continued)

Table 1 (continued)

point and immune escape. Since the set point is currently the best prognostic marker of progression to AIDS, these data could have a substantial impact on future therapeutic and prevention research. Linked to this, is the study on highly exposed persistently seronegative individuals, which will provide clues to the genetic and immunological mechanisms of protection from HIV infection. The innovative clinical study integrating antiretroviral therapy into the tuberculosis directly observed therapy strategy could provide a mechanism for facilitating the implementation of antiretroviral therapy, with high levels of adherence, in developing countries. An Executive Committee comprising the Project and Core Leaders governs CAPRISA. Besides managing the day-to-day CAPRISA operations, this committee also develops plans for future studies for review by the CAPRISA Scientific Advisory Board. Local research infrastructure is built through Cores for administration, epidemiology/biostatistics, viral diversity/bioinformatics and immunology. South African laboratories will be equipped to conduct assays locally and international collaborators will assist with training, advice, support, assay development and quality control. The training program includes several long- and short-term fellowships each year in laboratory science, clinical and epidemiological research and ethics. If successful, CAPRISA could make seminal contributions to understanding the epidemiology of the subtype C, heterosexually acquired HIV infection, elaborating early immune responses in HIV infection, developing an understanding of the phenomenon of resistance to HIV infection, and making a contribution to AIDS care relevant to the developing world.
PERFORMANCE SITE (S) (organisation, city, state)
University of Natal, Durban, South Africa
University of Cape Town, South Africa
National Institute of Virology, Johannesburg, South Africa
University of the Western Cape, Bellville, South Africa
University of Durban-Westville, Durban, South Africa
Aurum Health Research (Pty) Ltd, Welkom, South Africa
Columbia University, New York, USA
Harvard University, Boston, USA
Duke University, Durham, USA
University of Washington, Seattle, USA
Yale University, New Haven, USA
University of North Carolina, Chapel Hill, USA
Henry Jackson Foundation, Rockville, Maryland, USA

Key personnel	
Salim **Abdool Karim**, MBChB, MMED Ph.D.	Principal Investigator
	Core Leader: A
	Project Leader: 4
Clive **Gray**, Ph.D.	Project Leader: 3
Quarraisha **Abdool Karim**, Ph.D.	Project Leader: 1
Brian Gerard **Williamson**, Ph.D.	Core Leader: B
Carolyn **Williamson**, Ph.D.	Core Leader: C

(continued)

Table 1 (continued)

	Project Leader: 2
Lynn **Morris**, DPhil	Core Leader: D
Other key personnel	
South Africa	**U.S.A.**
Farida **Amod**, MBChB, FCPath	Ronald **Bayer**, Ph.D.
Sharon **Cassol**, Ph.D.	Wafaa **El-Sadr**, MD, MPH
Gavin **Churchyard**, Ph.D.	Guido **Ferrari**, MD
Mahomed **Dada**, MBChB, MMed	Gerald **Friedland**, MD
Robert **Dorrington,** Ph.D.	Phillip **Goulder**, MD, MRCP, DPhil
Eleanor **Gouws**, MS, MPH	Scott **Hammer**, MD
Winston **Hide**, Ph.D.	Christine **Hogan**, MD, MPH
Champaklal **Jinabhai**, MBChB, MMed	David **Hoos**, MD, MPH
Honest **Kagoro**, MSc	Bruce **Levin**, Ph.D.
Ayesha **Kharsany**, Ph.D.	Francine **McCutchan**, Ph.D.
Umesh **Lalloo**, MBChB, FCP, MD	Juliana **McElrath**, MD
Gethwana **Makhaye**, B Soc Sci (Hons)	David **Montefiori**, Ph.D.
Maila **Matjila**, MBChB, MMed	James **Mullins**, MD, Ph.D.
Jagidesa **Moodley**, MBChB, MD	Marita **Murrman**, EdD
Landon **Myer**, MA	Paul **Sharp**, Ph.D.
Maria **Papathanasopoulos**, Ph.D.	Zena **Stein**, MD
Adrian **Puren**, Ph.D.	Ezra **Susser**, MD, Dr. PH
Linda **Richter**, Ph.D.	Mervyn **Susser**, MBChB, MRCP
Cathal **Seoighe**, Ph.D.	Ronald **Swanstrom**, Ph.D.
Mpilenhle **Sithole**, Ph.D.	Bruce **Walker**, MD
Willem **Stürm**, Ph.D.	
Jo **van Harmelen**, Ph.D.	

Through CAPRISA, the various existing, and in some cases long-standing, South African-United States collaborations were consolidated and expanded. CAPRISA drew upon the unique strengths of each local and international member of the team to benefit from the synergy of working together.

Through CAPRISA:

- the team moved beyond the conduct of prevention trials by combining this strength with fundamental research that enabled a deeper understanding at the molecular level. This provided an opportunity for South Africa to also contribute to the design of interventions, to an understanding of how interventions work and to better measurement of the impact of interventions,
- the team moved beyond being a site for research to becoming a model of local leadership in excellence in AIDS research embracing innovation, responsiveness to South Africa's needs and training to continue to build local research capacity,

- a strong new foundation and research infrastructure was created for existing and future research, not only for CAPRISA but also for research funded by other sources and being conducted outside the ambit of CAPRISA,
- a longer term vision was created leading to a stable long-term collaboration thereby creating an impetus for neglected areas of AIDS research, such as operational research for the implementation of antiretroviral therapy, and
- South African AIDS research was able to make a significant contribution to global research on AIDS prevention and therapy.

3 The CAPRISA Projects and Cores

The HIV/AIDS epidemic in South Africa had created many new challenges, particularly those related to the distinctive characteristics of the epidemic in this region. Fundamental to understanding these characteristics, was the need for a comprehensive understanding of the epidemiology of HIV in South Africa. The gender differences in HIV prevalence coupled with age-related behavioural and biological factors needed to be elucidated. Factors influencing progression to AIDS and mechanisms of protection from HIV infection were largely unexplored in southern Africa. The issue of whether subtype C viruses were different from others in its natural history, pathogenesis and prognosis was yet another interaction that needed to be further understood.

CAPRISA proposed to establish four inter-related projects that address the need to understand HIV infection at the levels of the community, health service provision, individual host, virus and immune responses. The projects proposed (described below) were supported by four cores dealing with administration, epidemiology/biostatistics, viral diversity/bioinformatics and immunology. The overall goal was to produce a locally appropriate but globally relevant research response to the explosive HIV/AIDS epidemic in South Africa.

The CAPRISA project on the evolving epidemiology of HIV/AIDS (Project 1) aimed to collect the essential epidemiological data to understand trends in HIV prevalence and incidence, AIDS incidence and AIDS mortality. The CAPRISA epidemiological studies on tracking and deciphering the nuances of the evolving South African HIV/AIDS epidemic were the foundation of this program. Not only would these studies provide the essential baseline data for assessing the community level impact of future antiretroviral therapy and HIV prevention interventions, but the process of undertaking these studies would strengthen current efforts to develop and test community-based interventions such as microbicides, vaccines, adolescent behavioural change, voluntary counselling and testing and any other intervention aimed at preventing or treating HIV/AIDS. The studies would also lay the foundation for the assessment of the impact of therapeutic and prevention programs at community level.

The CAPRISA project on acute seroconvertors (Project 2), took the bold step of trying to identify infected individuals even before they acquired HIV. The project proposed to study the viral diversity in the acute seroconvertors in Project 2 and the recently infected individuals from Project 1. The acute seroconvertors in Project 2 were followed-up more intensely to study the host and viral factors that affect the set point. Since the set point was the best prognostic indicator of progression to AIDS, it was one of the most common endpoints used in clinical trials for therapy and, in some instances, prevention. Since little was known about the set point in the southern African setting, this project was an essential prelude to future therapeutic and prevention efficacy trials. The clinical spectrum of acute retroviral disease was also studied to identify any distinguishing symptoms and/or signs that mark a difference from that seen in the developed world. Some of the host factors that may result in differences are HLA distribution, younger age of infection and predominant heterosexual mode of transmission while the viral subtype differences (subtype C in southern Africa versus subtype B in developed countries) were also assessed as they may also impact on the set point.

In the Project 2 acute seroconvertors, the assessment of early CTL responses to Tat, Nef, Gag and other peptides, together with genetic characterization of the earliest viral swarms, provided valuable baseline data to investigate viral escape. The selective pressure of both cellular and later humoral responses were investigated to understand viral escape.

The role of HLA, coreceptor use and humoral responses, was investigated to determine whether they influence the set point. The early evolution of the virus in the presence of initial CTL and neutralising antibody responses provided clues to understanding the mechanisms of viral escape. Project 2 provided important data for future secondary prevention interventions, i.e. interventions aimed at preventing AIDS after HIV has occurred. Such interventions, which aim to reduce the set point, have potential benefits for the patient by reducing the risk of progression to AIDS and, importantly, have potential public health benefits by reducing the risk of transmission of the virus.

Within the cohorts of high risk individuals in Project 2, there are small numbers of individuals who are at high risk but do not become infected with HIV. These highly exposed persistently seronegative individuals were investigated in Project 3 to discover clues to protection from HIV infection. A cohort of HIV negative female sex workers was established. During the follow-up of these Project 3 participants, T cell and macrophage function were examined to determine what role, if any, they play role in protection from HIV infection. In Project 3, the possibility of latent HIV infection in CD4+ T cells was investigated to determine if low-level infection was intermittently stimulating T cell immunity in these individuals. Project 3 also aimed to assess whether stimulation by other sexually transmitted infections induces cytokine/chemokine expression which can render cells of the monocyte/macrophage lineage resistant to HIV infection.

The CAPRISA clinical, immunological and virological studies on acute HIV infection and mechanisms of resistance amongst highly exposed persistently seronegative individuals complemented and strengthened the team's existing research on HIV immunology and natural history.

Highly exposed persistently seronegative individuals are only a small group; the majority of those at high risk of HIV were becoming infected and were progressing to AIDS. The most common AIDS-defining illness in these patients is tuberculosis. As the cost of the antiretroviral drugs was falling and their affordability in middle-income countries was imminent in 2002, the key question in the original CIPRA grant was not *whether* to introduce antiretroviral therapy but *how* to do so.

CAPRISA Project 4 addressed the central issue of therapeutic adherence in the implementation of antiretroviral therapy in resource-constrained settings. A randomised control trial was conducted to assess the effectiveness of integrated tuberculosis and HIV care, including antiretroviral drugs provided through the tuberculosis directly observed therapy program with an enhanced adherence intervention.

Since tuberculosis is the commonest presenting illness in AIDS patients in much of the developing world, the integration of HIV and tuberculosis care was an efficient method of identifying those in greatest need of antiretroviral therapy. Project 4 studied the strategy of linking antiretroviral therapy to the widely available, affordable and sustainable tuberculosis directly observed therapy strategy. It tested whether, by addressing issues of therapeutic potency and adherence, therapeutic outcome for both diseases could be enhanced. This study was innovative and both complemented and strengthened the current efforts by the private sector, in particular, the Anglo-American mining conglomerate to introduce antiretroviral therapy.

3.1 Overall Specific Aims of CAPRISA at Inception

1. To describe the evolving epidemiology of HIV infection, impact of AIDS on the social conditions of a community, impact of AIDS-related clinical illness on healthcare provision, and trends in mortality rates as a prelude to future HIV prevention and therapeutic interventions.
2. To describe the course of acute HIV infection and determine the host and viral factors influencing the level of the set point in anticipation of future intervention studies where it is the primary outcome.
3. To characterise cell-mediated and mucosal immune responses in highly exposed persistently seronegative individuals to decipher clues to the nature of HIV resistance and thereby contribute to devising HIV prevention strategies.
4. To assess the feasibility and effectiveness of the tuberculosis directly observed therapy strategy in maintaining high levels of adherence to antiretroviral therapy in patients co-infected with tuberculosis, the most common presenting AIDS illness in South Africa.

5. To complement and extend the current South African Fogarty AIDS Training Program to build in-country AIDS research capacity.
6. To establish the research infrastructure required for the conduct of current and future basic, clinical, epidemiological and operational research in HIV prevention and care.

4 CAPRISA Is Born!

CAPRISA was established as an independent not-for-profit legal entity to undertake AIDS research in 2002. It was one of five Research Centres established with CIPRA funding throughout the world and has become a well-established, world-renowned AIDS Research Centre conducting innovative research on HIV pathogenesis, TB-HIV treatment and HIV prevention. CAPRISA's research aims to contribute new knowledge on HIV and TB prevention and treatment. The main goals of CAPRISA are to conduct locally responsive and globally relevant research on HIV/AIDS and TB, with a strong focus on HIV prevention, while building research infrastructure and providing research training opportunities for the next generation of scientists. Although CAPRISA was initially funded to only undertake Project 2 and Project 4, the CIPRA grant served as a strong foundation to diversify its funding base and support cutting edge research. CAPRISA has continued to build on the foundation studies funded by CIPRA and has moved on to answering the next set of questions emanating from the completion of the CIPRA-funded research. Research at CAPRISA is currently conducted in four main Scientific Programs namely: HIV Pathogenesis and Vaccines, HIV and TB treatment, Microbicides, and Prevention/Epidemiology with several concurrent studies ongoing in each of the research areas. CAPRISA has a proven track record for conducting high-impact studies which have influenced the microbicide and vaccine fields as well as international TB-HIV treatment guidelines.

Research activities at CAPRISA are currently supported by nine research support cores including Administration, Statistics and Data Management, Information Systems, Laboratory, Quality assurance, Community, Pharmacy, Bioethics, Media and Communications and Training. Many of these cores were not part of the original CIPRA application but once the centre was established, it soon became apparent that other cores would be required. The data management, pharmacy and laboratory cores in particular have proved to be invaluable.

Significant investments were made to establish a state-of-the-art data management system at CAPRISA to cope with the large volume of data being generated by studies. Although both paper-based and electronic data management systems are used, CAPRISA chose to invest in the DataFax system as its primary electronic data management system. CAPRISA has a high-level computing capability including broadband access, made possible by their links, mostly with microwave technology,

with the University of KwaZulu-Natal IT systems. Faxing is seldom, if ever, done through analogue telephone lines.

The Data management systems used in CAPRISA are CFR Part 11 compliant and Data Management standard processes are aligned with the Good Clinical Data Management Processes (GCDMP). The Data Management Department is capable of high-throughput capacity due to experienced staff and a robust information technology infrastructure, with about 150,000 case report forms (CRFs) being successfully processed each year. Some examples of the Core's capacity for high throughput and coordination and management of data for large studies comes from the CAPRISA 004 tenofovir gel trial with 181,000 records successfully faxed and validated in 3 years, and the CAPRISA 007 RHIVA trial with 250,000 records being processed in 2 years.

The CAPRISA Laboratory was established in 2003 with a small, well-defined portfolio that has grown to include the following specialised assays including: Immunophenotyping CD3/CD4/CD8, HIV RNA PCR by Roche TaqMan v 2.0 and Abbott M2000, HIV DNA PCR using the Roche TaqMan v2.0, HIV ELISA manual and using the BEP 2000, HIV Western Blot, rapid Trichomonas and BV testing, wet mount and microscopy, HSV and HPV ELISA, and HPV genotyping. Specimen processing includes: peripheral blood mononuclear cell (PBMC) preparations, cytobrush washing and processing, cervical vaginal lavage processing, and routine serum and plasma processing and storage.

The Laboratory Core (see Chap. 12) supports all research underway at CAPRISA, including providing input during protocol design on the use of suitable assays, development of Laboratory Request Forms (LRF) for documenting laboratory requests and findings, and setting up systems required for ensuring high quality on-site testing, specimen shipment, processing and capturing of all specimens received and following up on outstanding laboratory results. The Laboratory Core also maintains a specimen repository, which has 14 ultrafreezers and five liquid nitrogen freezers, currently holding close to a million barcoded vials such that an individual vial can be retrieved on request within an hour. This bio-bank is an important resource and has generated numerous new research ideas.

The CIPRA funding was also essential for the establishment of the necessary clinical research infrastructure to conduct clinical trials. CAPRISA currently conducts its clinical trials at two CAPRISA Research Clinics in KwaZulu-Natal; one located in Durban (urban site) and the other in Vulindlela (rural site). These sites have well-developed clinical trial infrastructure and trained staff with experience in conducting clinical trials.

The CAPRISA Vulindlela Research Clinic is situated in a rural community with approximately 90,000 residents in the KwaZulu-Natal midlands, about 150 km north-west of Durban. CAPRISA has conducted several clinical trials at this rural research clinic. The Vulindlela Research Clinic is conveniently located adjacent to a provincial department of health run clinic called the Mafakatini Primary Health Care Clinic.

The CAPRISA eThekwini Research Clinic is located adjacent to the Prince Cyril Zulu Communicable Disease Centre, which provides services specifically for the

diagnosis and treatment of STIs and tuberculosis. The clinic is conveniently situated in the Warwick triangle in the transport hub of Durban, making it readily accessible in terms of the transport infrastructure. Annually, approximately 40,000 cases of STIs are treated at this clinic, approximately 36,000 of which are new cases. The majority of the STI patients accessing these facilities are self-referred, either symptomatic with genital ulceration and/or vaginal discharge syndrome or as contacts of patients with a diagnosis of a STI and include both males and females.

5 Progress to a Well-Established AIDS Research Organisation

Since those early days when CAPRISA was created, the organisation is today a well-established and world-renowned research institute. It has undertaken several pivotal studies, breaking new ground on the use of antiretrovirals for HIV prevention and on TB-HIV treatment, amongst others. CAPRISA is recognised as a global Centre of Excellence, producing high-impact research on HIV prevention and treatment. On 13 December 2013, CAPRISA was formally recognised as an independent research organisation eligible for funding from the government's National Research Foundation (NRF). The Department of Science and Technology (DST) declared CAPRISA as one of eight organisations with this official status, as published in Government Gazette (No. 37123) of 2013. This status enables CAPRISA to become part of the research activities, funding streams and fora that constitute the official South African research landscape. CAPRISA is a UNAIDS Collaborating Centre on HIV Research and Policy, a SA MRC Collaborating Centre for HIV and TB Research, a SA MRC-CAPRISA HIV-TB Pathogenesis and Treatment Research Unit and a NRF-DST Centre of Excellence in HIV Prevention.

References

1. Abdool Karim Q, Abdool Karim SS. Epidemiology of HIV infection in South Africa. AIDS. 1999; 13: S4–S7.
2. Williamson C, Engelbrecht S, Lambrick M, van Rensburg EJ, Wood R, Bredell W, et al. HIV-1 subtypes in different risk groups in South Africa. Lancet. 1995; 346(8977): 782.
3. Abdool Karim Q, Abdool Karim SS, Singh B, Short R, Ngxongo S. Seroprevalence of HIV infection in rural South Africa. AIDS. 1992; 6: 1535–9.

Chapter 3
Overview of Clinical Trials

Anneke Grobler

1 What Are Clinical Trials and Why Are Clinical Trials Needed?

A clinical trial is in essence an experiment [1]. It is a prospective study where an intervention is compared to a control or comparator in humans. Clinical trials are usually associated with random assignment of participants to the intervention and control to reduce bias.

Randomised controlled trials (RCTS) are regarded as the highest level of evidence in evaluating new technologies or investigating new products such as drugs or vaccines or novel interventions and providing more reliable evidence than observational studies [2] (Fig. 1). Importantly, as with other study designs, it needs to be appropriate for the research question being asked and not all research questions require an RCT. Often early research undertaken informs and leads to the conduct of a clinical trial as the ultimate confirmatory step in a research process that could have evolved up the evidence pyramid from a case study. The biggest advantage of clinical trials is that they are designed rigorously and robustly answer a specific question by removing many sources of bias that may be present in an observational study.

Clinical trials also have disadvantages. They are not flexible and are generally designed to answer one main question (the primary objective). If the scientific questions of interest change over time a clinical trial might still be in process to answer the slightly out-of-date question. A clinical trial is a bit like a large ship; it is unwieldy and slow to respond to changes. Clinical trials are also often large and therefore expensive. The prospective nature of the studies also increases monitoring costs.

A. Grobler (✉)
Centre for the AIDS Programme of Research in South Africa,
University of KwaZulu-Natal, Durban, South Africa
e-mail: Anneke.grobler@caprisa.org

Q. Abdool Karim et al. (eds.), *The CAPRISA Clinical Trials: HIV Treatment and Prevention*, DOI 10.1007/978-3-319-47518-9_3

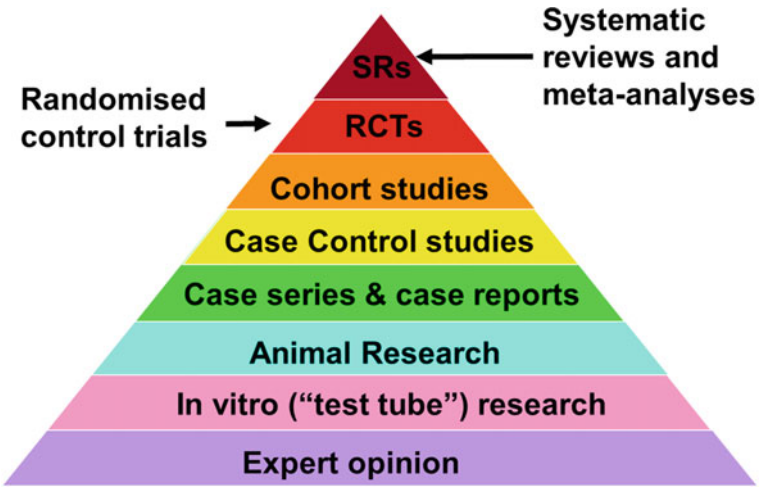

Fig. 1 Research evidence pyramid

Clinical trials always include a comparator, this refers to the "controlled" in the term controlled clinical trials. For example, in the CAPRISA 004 study the comparator was a placebo group that received an identical placebo gel [3]. In the CAPRISA 003 SAPiT study, the control group was participants who received anti-tuberculosis treatment and ART sequentially [4].

How does CAPRISA decide when to use a clinical trial to answer a question? A clinical trial is generally the most appropriate way to answer a question when there is one primary objective that can be answered with one outcome. For example in the CAPRISA 004 study the question answered was: "Does Tenofovir gel prevent HIV infection?" In this instance HIV infection rates in the two treatment arms were measured. When the question is less specific, it might not be appropriate to answer the question using a clinical trial. For example if the question is, "What are the characteristics of women infected with HIV?", an observational study of women infected with HIV is more appropriate than a clinical trial.

A clinical trial is also appropriate when some results from observational studies are already available. If observational studies have already shown that communities with high rates of male circumcision have lower HIV incidence rates, one might want to do a clinical trial to test whether this finding would hold in the experimental setting as well.

Many of the major findings CAPRISA has had over the years came from clinical trials. For example the CAPRISA 003 SAPiT study, which showed that integrating ART and anti-tuberculosis treatment led to lower mortality rates than sequential treatment [4], and the CAPRISA 004 study, which showed that tenofovir gel reduces HIV infections in young women [3], were both clinical trials. This is because clinical trials are regarded as a higher level of evidence and the findings would not have been as compelling if these were made in observational studies. Clinical trials were therefore important to CAPRISA's success.

2 Basic Issues in Clinical Trial Design

2.1 Blinding

Blinding in a clinical trial refers to whether the participants and investigators in the trial know what study product they are assigned to. A rule of thumb is to implement as much blinding as is practically possible given the trial and the study product. The goal of blinding is to reduce the bias introduced when participants know what treatments they are assigned to.

There are four different levels of blinding, each leading to more blinding than the previous. The first is an **open trial or an unblinded trial** with no blinding. In such a trial both the participants and the investigators know the treatment assignment. This is the weakest form of blinding and is open to bias. In this instance participants on placebo treatments might for example not adhere to all study procedures because they know they are receiving only the placebo.

In the CAPRISA 003 SAPiT study it was not possible to blind and the study was done as an open label study. The treatment assignment in the CAPRISA 003 SAPiT study was to assign participants to different times of initiation of ART during anti-tuberculosis treatment. It would have been difficult, if not unethical, to blind participants to the fact that they were receiving ART. The side effect profiles of ART would also have made it difficult to ensure blinding even if dummy tablets were to be used. For this reason the study was an open label study. In the case of open label studies it is important to try and reduce the impact of possible bias. In the case of the CAPRISA 003 SAPiT study the primary outcome was mortality, which is an objective endpoint that was determined independently of treatment assignment. It might be more problematic to reduce bias in an open label study with more subjective endpoints like pain scales or improvement in symptoms.

The second level of blinding is when either the participant or the investigators, but not both, know what treatment the participant was assigned to. This is called **single blind**. In most instances this means that the investigator will know the treatment assignment and the participant will not. Examples of this are where different surgical techniques are studied or where an injection is given. The investigator needs to know which injection to give, but the participant merely knows that an injection was received.

The third level of blinding refers to when neither the investigator nor the participant knows the treatment assignment. This is known as **double blinding**. The CAPRISA 004 study was a double blind study where participants and investigators did not know the treatment assignment.

In order to maintain double blind some additional steps need to be taken by the study investigators. In the CAPRISA 004 study, identical placebo applicators had to be manufactured. These applicators looked exactly the same as the study applicators but did not contain the active ingredient, tenofovir. This adds to the study's complexity, as well as time required for planning and cost.

Blinding was implemented in the CAPRISA 004 study as follows: Enrolled participants were assigned at random to one of the two study treatment arms in equal proportions. However, to facilitate blinding without greatly complicating product distribution logistics, each participant was randomly assigned to one of six different groups (designated by A, B, C, D, E and F) in a 1:1:1:1:1:1 allocation ratio. Three groups corresponded to the placebo gel and three to the tenofovir gel. The pharmacists knew to which of the 6 letters a participant was assigned and dispensed drug from the correct batch to the participant, but did not know whether the participant was assigned tenofovir or placebo. Clinic staff did not even know the letter assignment of any individual participant.

The randomisation statistician provided the study pharmacy at each site with sealed, opaque randomisation envelopes, sequentially labelled by participant identification number. These envelopes were assigned in sequential order to eligible study participants. Upon opening the envelope the pharmacist added his or her name and signature as well as the time and date the envelope was opened. This way we could ensure that participant treatment was unknown to the study staff until the decision was made to enrol the participant.

The fourth level of blinding is **triple blind** where in addition to the double blinding, the committee monitoring response variables are also blinded. In practice, it is almost always possible to blind laboratory technicians or committee members to treatment group assignment and this level of blinding should be done routinely. Even in open label studies it is fairly easy to ensure the endpoint committees are kept blinded to treatment assignment. CAPRISA always ensures that key site and study staff who do not have contact with the participants are blinded, even in open label studies.

2.2 Randomisation

Randomisation is one of the most important ways through which clinical trials reduce the bias present in many observational designs. Randomisation means that individuals do not get to choose to which arm of the study they belong. It is almost as if the flip of a coin determines the treatment assignment and not anything inherent in the participants. With randomisation the investigator also does not get to choose treatment assignment. It is possible in observational studies that certain treatments are more likely to be given to more sick patients, maybe as a last resort, or maybe because the treatments have fewer side effects. This may therefore bias the results observed with the treatments in normal clinical treatment. Randomisation removes this bias.

The method used to assign participants to treatment arms in a clinical trial should meet certain criteria and be able to pass monitoring. Randomisation is done using computer programs and a list of participant numbers and random assignments are generated. This list cannot be used as is at the site level to assign participants to treatments, however, because a list is open and investigators can see the assignment

of all participants at once. Treatment assignment should be unknown when the decision is made to include or exclude a participant.

For open label studies, CAPRISA created tear off envelopes that look like pay slips with the participant's number printed on the outside and the treatment assignment printed on the inside. The treatment assignment is only revealed once the envelope is torn open, therefore ensuring that the treatment assignment remains secret until the participant has been enrolled in the study. The person who opens the envelope signs with the date and time which enables verification that the envelope was only opened after enrolment and that the treatment assignment was unknown at the time the participant was screened and eligibility determined. In double blind studies the site does not need to open an envelope to know treatment assignment. In double blind studies CAPRISA used the same type of envelope that can be used in case of emergency, allowing unblinding in the case of a treatment emergency.

Envelopes are not the only way to do treatment assignment. Popular options are to have a telephone line or web based system doing randomisation. One could either outsource the call centre and pay for each participant randomised, or one could have an in-house call centre. Outsourced call centres are expensive and not always easily available, especially in resource constrained settings. With the volume of studies conducted at CAPRISA, an in-house call centre is not financially viable. However, larger organisations might find this a worthwhile option. Any electronic system, telephone, email or web based, also needs some back-up plan in case the internet or telephone lines are down. This is a real concern when rural sites are involved, as in the case of one of the CAPRISA sites. Electronic systems become less attractive when a parallel backup system also needs to be in place for instances of power failures.

2.3 Parallel Trials, Cross-Over Studies or Factorial Designs

A parallel trial is the most commonly used design for a clinical trial. In a parallel design two or more treatment arms are followed over time. Most CAPRISA studies are designed as parallel treatment arm studies; for example, the CAPRISA 004 study, the CAPRISA 003 SAPiT study and the CAPRISA 001 START study.

A cross-over study is designed so that participants first receive one treatment and, after a washout period, the participants then receive the other treatment. The order of treatments received is determined through randomisation. Cross-over studies have several advantages. Because the same participant receives both the active treatment and the control treatment, participants can be compared to themselves, which reduces variability. These studies require smaller numbers of participants because of this reduced variability and also because the same participant is used in both treatment arms. These studies are also popular for pharmacokinetic (PK) studies. Cross-over studies are suited to conditions that are reversible.

CAPRISA has not yet used a cross-over study design because the type of conditions we have studied to date do not lend themselves to being studied in this manner. It is a requirement of a cross-over study that participants return to the same state they were in at the beginning of the first period. This is not possible in HIV

Table 1 Factorial design study arm assignments

	Treatment 2: Active	Treatment 2: Placebo	Treatment 1
Treatment 1: Active	Arm A	Arm B	A + B Active
Treatment 1: Placebo	Arm C	Arm D	C + D Placebo
Treatment 2	A + C Active	B + D Placebo	

The *pink shaded line* shows active treatment for Treatment 1, the *blue shaded lines* show active treatment for Treatment 2 and the *purple shaded cell* is where participants receive active treatment for both treatments

prevention studies, since a participant who becomes HIV infected cannot be HIV negative at the start of the second period.

Factorial designs are clever designs that enable one to conduct two studies for the price of one, because two different treatments can be compared using the same participants in one trial. In these trials, participants are randomised to one of four treatment arms. In each of the treatment arms a combination of two treatment arms are given (Table 1).

In a factorial design, participants in Arm A receive the active treatment for both Treatments 1 and 2, participants in Arm B receive the active treatment for Treatment 1 but the placebo treatment for Treatment 1. Participants in Arm C receive the active treatment for Treatment 2 but the placebo treatment for Treatment 1. Participants in Arm D receives the placebo treatment for both Treatments 1 and 2. This means that if one wanted to compare Treatment 1 against placebo one would evaluate Arms A and B combined compared to Arms C and D combined. If one wanted to compare Treatment 2 against placebo one would evaluate Arms A and C combined compared to Arms B and D. These comparisons are valid if there is no interaction between the two treatments. The study is the same size as it would have been if only treatment 1 or treatment 2 was tested.

An example where CAPRISA has used a factorial design was in the evaluation of an adherence support intervention within the CAPRISA 003 SAPiT study. Participants enrolled in CAPRISA 003 SAPiT were also randomised to receiving an enhanced adherence support program or standard adherence support as a factorial design. This enabled CAPRISA to investigate both the main question of the CAPRISA 003 SAPiT study as well as whether an enhanced adherence support program could lead to higher levels of ART adherence and better outcomes in co-infected patients.

2.4 Multicentre Studies

CAPRISA has a rural and urban research site where the majority of its clinical trials and other research are undertaken. Most large clinical trials are done at more than one centre. This has several advantages, some practical and some scientific. The practical

advantage is that multiple sites have the ability to enrol more participants faster than a single site. The pool of eligible participants available in the feeder area of one site may be limited. The scientific advantage of multiple sites is that it increases the generalisability of the results of the clinical trial if slightly different study populations are enrolled at different sites and the trial outcomes are similar across all sites.

CAPRISA has the advantage that the populations at the two sites are quite different and the sites enrol participants with different socio-economic and behavioural characteristics.

Multiple sites create some oversight and management complexities for the study. The first is that one needs strict oversight and standardised training to ensure that the trial is conducted in the same way in all participating sites. Staff should use the same definitions, standard operating procedures and protocols at both sites.

One example of where this was challenging was with the definitions and terminology for documentation and reporting of adverse events in the CAPRISA 004 study. When a participant experienced any adverse event during the study, the study clinician was required to document and report these as adverse events. At the rural site the study clinicians recorded diarrhoea rather than gastrointestinal disorders, while at the urban site the doctors recorded gastrointestinal disorders rather than diarrhoea. It is difficult to know whether this is really a case of different adverse event patterns at the two sites, or whether it was just a case of different clinicians calling the same set of symptoms two different things. This triggered a series of training sessions where the doctors of both sites reviewed adverse events and standardised the way to report the symptoms.

Monitoring plays a large role in multi-centre trials to ensure that the protocol is implemented consistently at the two sites. In addition to internal monitoring for safety and fidelity of delivery of the intervention, external monitoring of quality of study conduct is undertaken by a group independent of the study team.

Patient safety in clinical trials is monitored by an independent committee of experts also referred to as the Data Safety and Monitoring Board (DSMB), usually established prior to study initiation. The study specific DSMB is different from the oversight provided by the South African Medicines Control Council and the Institutional Ethics Committees. The DSMB verifies whether the conduct of the study and data quality is acceptable and enrolment targets are met. A DSMB can stop a study early for safety concerns or if there is overwhelming evidence that one of the treatment arms is efficacious. One of the CAPRISA studies, the CAPRISA 003 SAPiT study, was stopped early by a DSMB, because a significant difference in mortality rates was observed in patients who delayed the initiation of ART until after the completion of tuberculosis treatment.

2.5 Loss to Follow-up

The goal of randomising clinical trial participants to treatment groups is to balance the distributions of known and unknown characteristics among these groups prior to

study treatments. Baseline comparability of treatment groups only holds through the trial when data are not missing. It is therefore important to reduce missing data and loss to follow-up.

The results of a clinical trial are more reliable if loss to follow-up is minimised. Guidelines for clinical trials and guidelines for the handling of missing data in clinical trials both concur that it is more useful to try and prevent missing data being generated in the first place than trying to deal with the problems created by having missing data [5].

One way of minimising missing data is to ensure accurate and detailed contact information collection from each participant. For example, in the rural community where there are no street names or addresses, asking the participant to draw a map to get to her home, collecting GPS co-ordinates and marking important landmarks guide tracking of participants who have missed visits. Having a few alternate phone numbers where the participant can be contacted is also helpful since people change phone numbers frequently.

Several points during implementation of the study could be utilised to minimise missing data. These include:

- The use of a run-in period to identify participants who will be able to adhere to the study.
- Selection of populations that would be likely to adhere to the study treatments.
- Use of add-on designs where the drug being studied is added to known effective interventions.
- Shortening the duration of the study.
- Allowing rescue medication when the study treatment is not reducing symptoms.
- Defining outcomes that can be ascertained in most patients; even if visits are missed or the participant is ill.

CAPRISA has implemented some of these guidelines to reduce missing data. The most important is that outcomes such as mortality can be determined in participants even when they are lost to follow-up. In the CAPRISA 003 SAPiT study, if participants did not attend visits, tracking sometimes revealed that the participants had died and mortality as an endpoint could be determined even if participants did not attend the clinic. In the CAPRISA 004 study, it was harder to determine the endpoints when participants were lost to follow-up because a blood sample was required to determine their HIV status. A retention rate of 80–90 % is considered an acceptable and desired retention rate for most RCTs.

Shortening study follow-up and selecting populations that are likely to be adherent to the study procedures also plays a role in higher retention. For example, the screening visit for most studies is split into two visits a week apart. This means that participants who want to be enrolled in the study need to attend at least two visits prior to being eligible for the study. Many participants who are not able to make repeat visits are then not enrolled. If the screening visit was a single visit these participants would have been enrolled after one visit and might not have arrived for the first follow-up visit on study.

CAPRISA has had very good retention rates in its studies. For example the retention rate in the CAPRISA 004 study was 94.8 %. This was due to efforts by the study staff to track participants when they miss visits. Prior to a scheduled study visit participants were reminded by text message that a study visit was due. On a daily basis all participants who did not arrive for their visits were contacted telephonically and asked to come the next day for a visit. Participants who could not be reached by phone were visited at home to remind them of study visits. This greatly reduced the number of missed visits and participants who were lost to follow-up.

Shorter visits with fewer procedures done at each visit also makes it easier for participants to be retained in the study. One should carefully consider inclusion of each procedure in a trial and the degree of invasiveness and acceptability to participants. Procedures that cause physical or emotional discomfort to participants could result in poor retention rates or early voluntary withdrawal from a study. Study visits should also be as short and efficient as possible, with waiting time in queues minimised.

One should not underestimate the importance of the quality of customer care provided during study visits. If participants find a clean, comfortable waiting room with friendly staff, snacks and a supportive environment where they can socialise while waiting for their turn, they are more likely to come back for future visits. Transport difficulties should be addressed. The hours of the clinic also play a role. Participants who work or attend school might prefer clinics to stay open later at night and having clinics on a Saturday could also play a large role in who enrols in studies and reducing missed visit rates.

Data collection should continue for participants who choose to voluntarily withdraw from exposure to intervention to enable valid data analysis even in the presence of non-exposure to the intervention. At CAPRISA, participants who do not want to continue using the study assigned treatment are withdrawn from the medication/intervention, but given the option to remain in the study and continue attending study visits and are still assessed for clinical outcomes. This means that participants who voluntarily withdraw from exposure to study treatment can still be included in the analysis.

2.6 Sample Size Issues

The size of a clinical trial is an important design element. Clinical trials that are too large are unnecessarily expensive, take longer than needed, thus delaying the acquisition of important information, and use important resources that can be better utilized elsewhere. Clinical trials that are too small are underpowered and might lead to inconclusive findings, thus not answering the questions it set out to answer. Both scenarios are not optimal. For this reason it is important to carefully calculate the sample size needed for a clinical trial.

In many instances the information required to do a good sample size calculation are not available, leading to Stephen Senn saying that sample size calculation is a

"guess masquerading as mathematics". Sample size calculation for clinical trials become more meaningful exercises if the guesswork is reduced. This can be done by having good estimates for the numbers that go into the sample size calculation formulas. For example, prior to doing the CAPRISA 004 study we undertook a sero-incidence study in the same population to determine HIV incidence and retention rates, thus enabling a more accurate estimate of HIV incidence and loss to follow-up that was built into the sample size calculation. An additional consideration is the study outcome and defining the number of endpoints upfront ensures that the study duration is not too long or too short.

3 Clinical Trials in HIV Prevention

Clinical trials for HIV prevention are different from clinical trials for HIV treatment in some aspects. In HIV prevention studies HIV negative people at risk of HIV infection are enrolled and followed over time and the number of HIV infections acquired in the two treatment arms are compared. These apply to vaccine studies and prevention studies of oral, topical or any other HIV prevention modality.

These HIV prevention trials are usually done in populations at high risk of HIV infection. This leads to smaller and more feasible clinical trials. The power of the trial is determined by the number of HIV infections acquired during the study, rather than by the number of participants enrolled. Of course, if the risk of HIV infection is the same, more participants enrolled will lead to more events. This means that in statistical power terms CAPRISA 004 was not a small study because it had almost 100 HIV infections. In statistical terms other microbicide studies with more participants had less power because it had less HIV infections.

As is the case with other clinical trials, adherence is important in HIV prevention trials. If participants were not adherent to prevention interventions and became HIV infected, according to the intent to treat (ITT) analysis, these participants will be analysed as if they received the intervention.

The power of CAPRISA's prevention studies was that sub-studies were embedded within the studies to identify correlates of infection or protection, like inflammation. The recommendation is to include more laboratory markers and sub-studies to identify why protection was conferred or not conferred.

4 Cluster Randomised Trials

A cluster randomised trial is a clinical trial where clusters instead of individual participants are randomised to treatment arms. A cluster is defined as either a clinic, school, household or other natural grouping of participants. The advantage of cluster randomised trials is that they allow one to study interventions that are more easily delivered at the cluster level than at the individual level. For example, some

educational interventions can be delivered at school level or class level, but cannot be individualised for each individual learner in the school. This design protects against contamination between the treatment arms when participants are exposed to both treatments.

Although cluster randomised trials are sometimes the only valid design, it does have its shortcomings and should only be used when the specific setting requires it and an individual randomised trial would not be appropriate. A cluster randomised trial will have lower power than the same sized trial where individuals were randomised. The statistical analysis needs to be adjusted for clustering.

The CAPRISA 007 RHIVA study was done as a cluster randomised trial where schools were randomised to one of two treatment arms. Only 14 schools were enrolled and measurements were done at the individual level. In one treatment arm all individuals in the school in certain grades received the intervention, consisting of conditional cash transfers, and in the other treatment arm only standard HIV prevention messages were delivered. A larger study, with more clusters, would have enabled different analysis measures.

The CAPRISA 013 study that will assess factors influencing integration of tuberculosis and HIV services is also a cluster randomised trial. In this instance clinics will be randomised to either receiving quality improvement methods to improve integration of HIV and tuberculosis treatment or to the control group who will be requested to integrate HIV and tuberculosis treatment with no additional support or technical assistance.

5 Answers We Cannot Get from Clinical Trials

Observational studies can sometimes provide answers that cannot be gleaned from clinical trials. Sometimes it is not possible ethically or scientifically to randomise participants to interventions. In these instances observational studies are the only option.

Some of the observational studies done by CAPRISA include the monitoring of antenatal HIV prevalence over time in some of the clinics in the area CAPRISA is working.

The CAPRISA 002 study, also known as the acute infection study, is an example of a prospective study being undertaken where a cohort of recently infected individuals are being followed to understand natural history of Clade C HIV infection clinically, virologically and immunologically.

Some population based surveys are also done where the prevalence of sexually transmitted infections (STIs) and HIV is measured at household levels and the populations are described.

The CAPRISA AIDS treatment project treated thousands of patients with ART at a time when ART was not widely available in South Africa. Patient records with clinical data were available for these patients and were used to answer specific scientific questions about the clinical outcomes of patients receiving certain ART regimens.

The CAPRISA 005 TRUTH study is also an observational study describing tuberculosis reinfection in patients who have previously had tuberculosis and HIV. The tuberculosis biomarkers in these patients are tested to determine what biomarkers are associated with tuberculosis reinfection.

6 Data Collection and Quality Control

Through the vision of CAPRISA's founders, several support cores were established to ensure that the necessary resources are available to undertake research from idea, through protocol development, implementation, analysis and publication. This included the establishment of a data management department and a statistics department to ensure the collection of good quality data meeting the requirements set by good clinical practice (GCP), the specific funders' and regulatory bodies. This means that from the onset data collection meets applicable quality standards.

In clinical trials data quality is important. CAPRISA has built a data management unit who ensure that accurate high quality data are collected. There are many rules governing the data collection and data quality of clinical trials. The design of standardised data collection forms are important in this respect. The data management team at CAPRISA have the capabilities for establishing electronic databases, undertaking quality checks of the data being collected in real-time; and generating the monthly study reports that are used for monitoring study progress in terms of enrolment and accrual targets, retention rates, data quality and other key aspects of the study, e.g. adverse events and or product holds.

In addition to study monitoring, in-house quality assurance ensures ongoing high-quality data collection.

The following chapters will provide more detailed information for each of the pivotal studies undertaken by CAPRISA to date.

References

1. Friedman LM, Furberg CD, DeMets DL. Fundamentals of clincial trials, fouth edition. New York: Springer; 2010.
2. Concato J. Observational Versus Experimental Studies: What's the Evidence for a Hierarchy? NeuroRx 2004; **1**(3): 341–7.
3. Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, et al. Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women. Science (New York, NY) 2010; **329**(5996): 1168–74.
4. Abdool Karim SS, Naidoo K, Grobler A, Padayatchi N, Baxter C, Gray A, et al. Timing of Initiation of Antiretroviral Drugs during Tuberculosis Therapy. The New England Journal of Medicine 2010; **362**(8): 697–706.
5. National Research Council. The prevention and treatment of missing data in clinical trials. Washington DC: The National Academic Press; 2010.

Part II
CAPRISA Clinical Trials for HIV and HSV-2 Prevention

Chapter 4
Antiretrovirals for HIV Prevention: The CAPRISA 004 Tenofovir Gel Trial

Cheryl Baxter, Leila E. Mansoor, Tanuja N. Gengiah, Salim S. Abdool Karim and Quarraisha Abdool Karim

1 Background

1.1 High HIV Burden Among Women

Preventing HIV infection in young women is one of the most crucial challenges in HIV prevention in sub-Saharan Africa. In this region, women represent 59 % of all people living with HIV. Adolescent girls and young women aged 15–24 years are disproportionately affected and have HIV rates up to 8-fold higher [1] and acquire HIV infection at least 5 years earlier than their male peers [2, 3]. This age-sex disparity is a distinct characteristic of the HIV epidemic in sub-Saharan Africa and was first documented in South Africa in the early 1990s [2].

A multitude of biological, social, political and economic factors contribute to the excess vulnerability of young women to HIV infection compared to young men.

C. Baxter (✉) · L.E. Mansoor · T.N. Gengiah · S.S. Abdool Karim · Q. Abdool Karim
Centre for the AIDS Programme of Research in South Africa,
University of KwaZulu-Natal, Durban, South Africa
e-mail: Cheryl.baxter@caprisa.org

L.E. Mansoor
e-mail: Leila.mansoor@caprisa.org

T.N. Gengiah
e-mail: Tanuja.gengiah@caprisa.org

S.S. Abdool Karim
e-mail: salim.abdoolkarim@caprisa.org

Q. Abdool Karim
e-mail: Quarraisha.abdoolkarim@caprisa.org

S.S. Abdool Karim · Q. Abdool Karim
Department of Epidemiology, Mailman School of Public Health,
Columbia University, New York City, NY, USA

Q. Abdool Karim et al. (eds.), *The CAPRISA Clinical Trials: HIV Treatment and Prevention*, DOI 10.1007/978-3-319-47518-9_4

In addition to being more susceptible than men to acquiring HIV [4], factors like intergenerational sexual coupling patterns [5, 6], early sexual debut [5, 7], infection with other sexually transmitted infections and viruses, and interpersonal violence [8] have also been shown to impact on the vulnerability of young women in acquiring HIV infection. In addition to their increased vulnerability, young women are often unable to successfully negotiate safe sex practices such as mutual monogamy and condom use. As a consequence, young women have limited HIV prevention options available that they can directly control. Technologies that empower women to protect themselves from HIV are therefore an essential tool in the fight against the HIV epidemic in sub-Saharan Africa.

1.2 Development of Women-Controlled HIV Prevention Options

Topical microbicides, which are products that can be applied inside the vagina or rectum to protect against sexually transmitted infections (STIs), including HIV and other disease pathogens, have been in development as a female-controlled HIV prevention option since the early 1990s.

Among the first topical microbicide candidates to be evaluated in large efficacy trials were commercially available spermicides, which operated by disrupting cell membranes including several microbes and spermatozoa. The most notable of these products was nonoxynol-9 (N-9), which was tested in various doses and formulations, but was eventually shown to be ineffective in preventing HIV and possibly harmful [9–11]. Another candidate, C31G (SAVVY), which worked in a similar way but had a better safety profile than N-9, was also assessed as a microbicide but failed to demonstrate effectiveness [12, 13]. The next generation of topical microbicides that were assessed included the vaginal defence enhancers like BufferGel™ and the polyanionic sulphated or sulphonated polymers such as Carraguard®, PRO 2000, and Cellulose sulfate (UsherCell™). The Carraguard® and Cellulose sulfate trials also produced disappointing results [14–16]. The NIH-funded HIV Prevention Trials Network (HPTN) 035 trial that assessed BufferGel™ and PRO 2000, however, produced the first hint that a microbicide gel may potentially reduce a woman's risk of becoming infected with HIV. In this study, although BufferGel™ had no impact on HIV infection, 0.5 % PRO 2000 gel was shown to reduce HIV acquisition in women by 33 % but this did not reach statistical significance [17]. Unfortunately, a much larger trial found no impact of 0.5 % PRO 2000 on reducing a woman's risk of becoming infected with HIV [18], thus ending the development of PRO 2000 as a potential candidate.

Most of these microbicide trials had been initiated before the creation of CAPRISA in 2002 (Fig. 1). However, researchers from CAPRISA, particularly Professors Salim Abdool Karim and Quarraisha Abdool Karim, had been involved in the conduct of several of these trials. In 2004, a decision was made for CAPRISA to conduct its own microbicide trial to assess one of the newer antiretroviral-based microbicide candidates. The most advanced candidate in this class at the time was

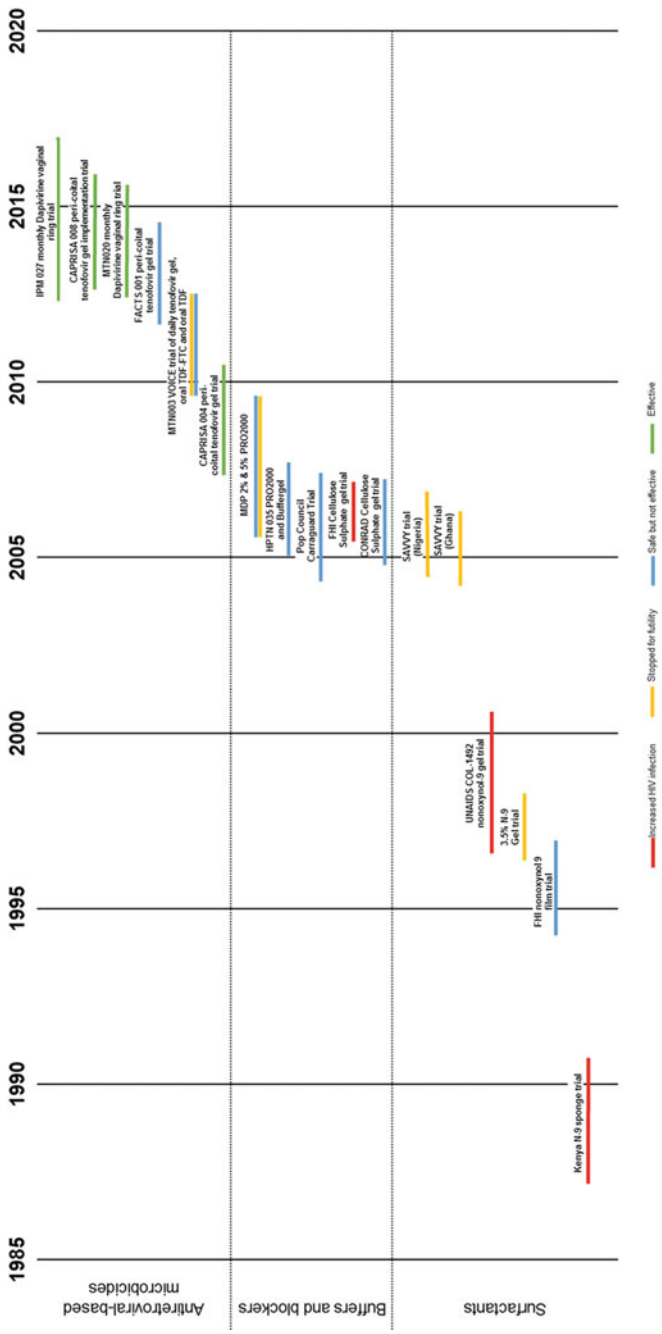

Fig. 1 Microbicide trial effectiveness trials

tenofovir gel. A phase I safety and tolerability study (HPTN050) among 84 low risk women had shown that tenofovir gel was well tolerated in both HIV negative and HIV positive women and another study (HPTN 059) among 200 women from the USA and India reported that both daily and coitally dependent use of tenofovir gel was acceptable and safe. In 2004, Professor Salim Abdool Karim approached Gilead Sciences in California to negotiate the possibility of acquiring tenofovir to manufacture the gel formulation for a large phase IIb trial. In addition to securing the tenofovir gel for the trial, Professor Salim Abdool Karim initiated negotiations for a royalty-free voluntary licence from Gilead Sciences for the South African government to manufacture and distribute the gel locally once licenced.

In partnership with CONRAD and FHI360, the CAPRISA 004 team then spent the next two and a half years developing the protocol and preparing for study implementation. The original plan was to conduct a three arm trial that assessed both 0.5 % PRO 2000 and tenofovir gel against a placebo but with two other PRO 2000 trials [HPTN 035 and Microbicide Development Program (MDP) 301] already underway, a decision was made to focus on tenofovir gel only. There were also some discussions during the planning phase about the possibility of including SAVVY in the trial but given that the dosing strategies for the two products were vastly different, a final decision was made to proceed with a phase IIb, two-arm, double-blind, randomised, controlled trial (NCT00441298) to evaluate the effectiveness and safety of tenofovir gel in preventing sexually transmitted HIV infection (Panel 1).

Panel 1 Panel CAPRISA 004 study schema

Purpose	To assess the safety and effectiveness of tenofovir gel, a candidate vaginal microbicide, in sexually active women at risk for human immunodeficiency virus (HIV) infection in South Africa
Design	Phase IIb, two-arm, double-blind, randomised, controlled trial comparing 1 % tenofovir gel with a placebo gel
Study population	Sexually active, HIV-uninfected women aged 18–40 years in South Africa
Study size	Up to 1250 women
Treatment regimen	Participants will be provided with a supply of single-use, pre-filled applicators according to their randomisation. While in the study, participants will be asked to apply a first dose of the assigned study product, 1 % tenofovir gel or placebo gel, within 12 h prior to coitus and insert a second dose as soon as possible within 12 h after coitus. They will be advised to use only two doses of gel in a 24-h period
Study duration	Approximately 30 months in total. Accrual will require approximately 18 months and follow-up will continue until 92 incident HIV infections are observed in the study, which is expected to occur approximately 12 months after the end of the accrual period

(continued)

Panel 1 (continued)

Primary objective	To evaluate the effectiveness and safety of a candidate vaginal microbicide, tenofovir gel, when applied intravaginally by women, in preventing sexually transmitted HIV infection
Secondary objectives	• To assess the impact, if any, of tenofovir gel on the incidence rate of deep epithelial disruption • To assess the impact, if any, of tenofovir gel on viral load in women who become infected with HIV during the trial • To assess tenofovir resistance in HIV seroconvertors in the trial • To ascertain the impact, if any, of tenofovir gel on pregnancy rates and outcomes • To assess the impact, if any, of product hold at study exit on HIV infection and tenofovir resistance
Ancillary objective	• To assess the impact, if any, of tenofovir gel in preventing sexually transmitted infections, including herpes simplex virus type 2 (HSV-2) and human papillomavirus (HPV) infections
Study sites	• CAPRISA Vulindlela Clinical Research Site, KwaZulu-Natal, South Africa • CAPRISA eThekwini Clinical Research Site, Durban, South Africa
Clinicaltrials.gov registration number	NCT00441298

In this chapter we share our experiences in developing the protocol with specific reference to how the lessons from past microbicide trials helped shape the development of the trial. We also share the scientific rationale behind the dosing strategy selected for the study. Some of the challenges encountered during the study that have wider implications for other research trials are also described. The chapter concludes with a brief summary of the trial results and their implications for the HIV prevention field.

2 Developing the CAPRISA 004 Protocol: Incorporating Lessons from Past Microbicide Trials

2.1 HIV Incidence in Target Population

Although the microbicide trials conducted up until 2004 had all produced disappointing results, there were several valuable lessons learnt from these trials that were used to guide the development of the CAPRISA 004 protocol. The first lesson

was to ensure that we had an accurate estimate of the HIV incidence in the target enrolment population to ensure that a sufficient number of participants were enrolled in the study to adequately evaluate the investigational new product. Two large microbicide trials, which together enrolled over 4000 women from Ghana and Nigeria, were unable to accurately evaluate the effectiveness of their product in preventing HIV because the HIV incidence among enrolled participants was substantially lower than expected [12, 13].

To avoid a similar scenario, CAPRISA established two pre-trial prospective cohorts (CAPRISA 050/051) at the two intended study sites to obtain accurate HIV incidence estimates for the local population. Volunteers were recruited from a rural primary health care clinic and an urban STI clinic and 592 HIV-uninfected women aged 14–30 years were enrolled and followed-up between March 2004 and May 2007. In addition, data from another longitudinal study (CAPRISA 002), which enrolled a cohort of self-identified sex workers, was also factored into the HIV incidence estimate for the study. The HIV incidence rates from these longitudinal studies were 7.9 per 100 person years in the CAPRISA 002 study, 6.4 per 100 person years in the CAPRISA 050 study and 6.5 per 100 person years in the CAPRISA 051 study [19]. These data were then used to estimate the number of endpoints needed to evaluate a 50 % efficacious product and to calculate the sample size and ensure adequate power for the study.

2.2 Minimising Time off Product Due to Pregnancy

High pregnancy rates among women was one of the big challenges in conducting microbicide trials. Given that the microbicides are experimental and the teratogenic effects on the foetus are not fully understood, participants who become pregnant during a trial are taken off the product for safety reasons. High pregnancy rates with discontinued product use has implications for the design, conduct and generalisability of the trial results, including the loss of power and diminished effect size of the study outcome in an intention-to-treat analysis. Pregnancy rates in past microbicide trials had ranged from 8.4 per 100 women years to 63.9 per 100 women years [20] resulting in long periods of time off product.

To minimise the time off product due to pregnancy in the CAPRISA 004 trial, several interventions were incorporated into the study protocol and study procedures. Firstly, women who were either pregnant at screening or those who intended falling pregnant at any time during the trial were excluded from study participation. Secondly, the use of a non-barrier reliable contraceptive was an inclusion criteria and contraceptive counseling was provided at enrolment and throughout the trial. Thirdly, hormonal contraceptives including progesterone-containing injectables (depot-medroxyprogesterone acetate and norethisterone enanthate) and combined oral contraceptives were provided on-site at no cost as part of monthly study visits, and lastly, monthly on-site pregnancy testing was conducted. In addition, to exclude early preclinical pregnancy loss, 3 successive monthly pregnancy tests were

Fig. 2 Materials and props used to support adherence in the CAPRISA 004 trial

conducted after a confirmed pregnancy. Women were able to resume product after giving birth or once the chemical tests (urine, blood, or both) reverted to negative. In total, 17,184 pregnancy tests were conducted during the CAPRISA 004 trial. The overall pregnancy rate was 4.0 (95 % CI: 3.0–5.2) per 100 women years and the total time off product due to pregnancy was 20.9 per 100 women years. These rates were substantially lower than previous microbicide trials.

2.3 Capturing and Assessing Adherence in Relation to Coital Activity

The effectiveness of a microbicide in a clinical trial is dependent on the efficacy of the product as well as the participant's willingness and ability to use the product as instructed. Ensuring high adherence as well as objectively measuring adherence in microbicide trials has, however, proved challenging. Many of the early microbicide trials relied exclusively on self-reported use, which has several limitations. Later studies incorporated dye staining of applicators as an objective method to test vaginal insertion in clinical microbicide trials, but different plastics, dyes, and product formulations may impact the accuracy of this method.

In developing the CAPRISA 004 protocol, we drew upon the experiences from previous microbicide trials, particularly in relation to the importance of adherence support and having accurate measures of adherence. During the CAPRISA 004 trial preparation phase, several structured meetings and discussions were held with the target population and selected study staff (including clinicians, nurses, counsellors,

and research assistants) to develop and modify the design of the adherence activities. Adherence activities were adapted to accommodate participant's literacy levels, cultural beliefs, attitudes and expectations. A comprehensive adherence support programme was developed that included structured motivational counselling as well as several adherence support tools (Fig. 2) [21]. In addition to providing adherence support at all contacts with the participant (screening, enrolment, and monthly follow-up visits), a dedicated Adherence Coordinator was appointed to oversee the adherence aspects in the CAPRISA 004 trial. The Adherence Coordinator conducted regular qualitative, structured debriefing and interactive sessions with the staff responsible for administering the adherence support programme to obtain feedback on the adherence programme. Adherence support materials were revised and adapted as needed during the trial.

Three different measures of gel adherence were used in the CAPRISA 004 trial; (1) self-reported gel use, (2) returned applicators and (3) drug levels. Self-reported data on adherence to the product use for the preceding 30 days, last 7 days and day of last sex act was collected monthly via brief interviewer-administered questionnaires. These questionnaires ascertained the participant's frequency of sexual intercourse, condom use, product use and timing thereof in relation to coitus.

A unique feature of the CAPRISA 004 adherence measurement approach was monthly reconciliation of applicators to establish the number of returned used applicators as a real-time measure of adherence. Women in the trial were asked to return all applicators, used and unused at each study visit. All of the applicators were also visually inspected to confirm use. A total of 181,340 applicators were dispensed to women during follow-up in the CAPRISA 004 trial and 95.2 % of these applicators were returned, either as used or unused. An applicator-based adherence score was then calculated for each participant by dividing the number of reported sex acts per month by half the number of returned used applicators for that month. This was regarded as the primary adherence measure in the study. The adherence rate based on applicator count in relation to all reported sex acts was 72.2 % compared to the 82.0 % self-reported adherence during the last sex act.

In addition to these adherence measures, the genital tract tenofovir concentrations were measured making it possible to objectively assess whether the product had been used or not. The limitation of this method, however, is that we were unable to measure adherence to the placebo. Vaginal fluid specimens collected during the trial at study months 3, 12, 24 (for those who have the opportunity to reach 24 months) and study exit were used to determine the tenofovir drug levels.

An innovative strategy for enhancing measurement of microbicide gel use was also piloted in the CAPRISA 004 trial. The CAPRISA 004 pharmacy team developed the "WiseBag". The CAPRISA Wisebag was a microbicide gel applicator container fitted with cell phone technology to transmit opening events and short message service (SMS) reminders were developed to monitor gel use and adherence. Ten participants were enrolled in a pilot study conducted at both the eThekwini and Vulindlela pharmacies and followed for 2–4 months [22]. The technology was later adopted by the Microbicide Trials Network (MTN) to conduct a feasibility study for monitoring daily gel applicator use.

3 Determining the Dosing Regimen for the CAPRISA 004 Trial—Why a Coitally Dependent Dosing?

Despite significant advances in the microbicide field, the issue of timing of application for microbicides had not been resolved when the CAPRISA 004 protocol was developed. The timing of product insertion related to efficacy is affected by each product's mechanism of action. Hence, the definitive answers on timing of product insertion could only become available when a trial showed an efficacious product.

Two broad approaches had been proposed for the timing of insertion of tenofovir gel; daily dosing or coitally dependent (usually 1 h before sex) dosing. There are groups of women who may benefit from each of these strategies. Daily dosing would require substantially more doses than coitally dependent use (with the concomitant increased costs), but it may be associated with higher adherence in some women. With daily dosing, there may be no specific benefit to be gained from using a vaginal gel formulation as opposed to the standard oral formulation which would be more convenient and less expensive.

In the South African context, there was a specific need for a coitally-dependent microbicide. Our consultations with the communities prior to the study revealed that many women had a low sexual frequency, especially women with migrant partners and certain young women, making a daily dose unfeasible.

Based on the available data, a pre- and post-coital dosing strategy, also referred to as BAT 24, was selected for the CAPRISA 004 trial. Study participants were counseled and supported throughout the study to apply the first dose of the assigned study gel within 12 h **b**efore anticipated sex; a second dose as soon as possible but within 12 h **a**fter sex and, irrespective of the number of coital acts in a day, to apply no more than **t**wo gel doses in **24** h (BAT 24). This dosing strategy was modelled on the HIVNET 012 nevirapine regimen to prevent mother-to-child transmission (Fig. 3).

The scientific rationale for this dosing strategy was based on findings from several macaque challenge studies using both local and systemic administration of tenofovir by either intravenous or subcutaneous routes as well as human safety and

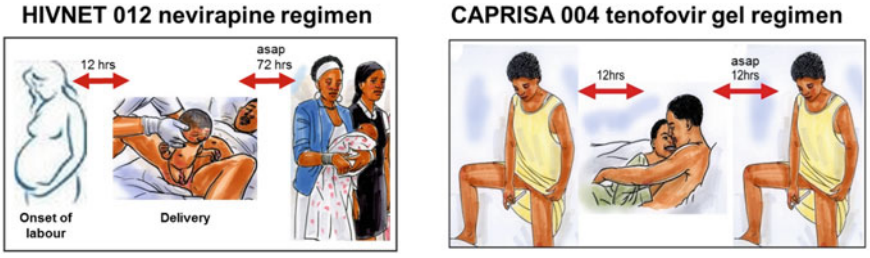

Fig. 3 The CAPRISA 004 dosing regimen was modelled on the HIVNET 012 strategy to prevent mother-to-child transmission of HIV

pharmacokinetic (PK) studies. The broad trend identified from these data was that a single pre-exposure dose is able to prevent infection in macaques when administered subcutaneously, vaginally or rectally.

We hypothesized that a key mechanism of action of tenofovir gel was through its action of inhibiting viral replication in the CD4+ target cells in the lumen and in the layers of cells that make up the genital tract. Hence the achievement of adequate cellular (and tissue) concentrations of drug locally in the genital tract (at the site of infection) was considered important.

The determination of the timing of the pre-exposure dose in the CAPRISA 004 study was based on available human safety data on two doses per day [23], duration of tenofovir in cervicovaginal lavages in women [24], and on a macaque vaginal tissue PK study of radio-labelled tenofovir gel which showed that tissue levels were detected as early as 15 min following administration of 1 % tenofovir gel with peak concentrations being reached between 8 and 12 h.

In animal models, virus replication has been detected as early as 1 h post-challenge and was detectable in draining lymph nodes within 18 h following intravaginal SIV exposure [25]. Cervical explant data, however, suggest that infection may only be first detectable by p24 assays in the tissues about 30 h after exposure to challenge virus, even when mimicking disrupted genital tract epithelium. Hence, sustained tenofovir levels may be required for at least 48 h post-inoculation to prevent viral replication.

These data suggested that although tenofovir may have a long duration of activity, both pre- and post-exposure doses may be important in providing protection. Therefore, to decrease the likelihood of breakthrough infection due to waning levels of tenofovir within this window of opportunity to prevent replication, a second dose of gel to be administered within 12 h of exposure was added to the dosing regimen. While a single dose may have provided adequate levels for this 48 h period, the second dose was considered a valuable component of the dosing strategy to provide sustained levels of tenofovir over the critical first few days post-exposure.

The dosing strategy was limited to not more than two doses in one day because the available human safety data on tenofovir gel are limited to two doses per day.

4 Challenges and Lessons Learned

4.1 Opposition from Some Researchers in the Microbicide Field

The CAPRISA 004 trial, and the dosing strategy in particular, was considered controversial by some scientists. Soon after the trial was initiated, an anonymous complaint was lodged with the Office of the Global AIDS Coordinator (OGAC) of the US government that there was insufficient evidence to warrant proceeding with

a coital tenofovir gel trial and that the CAPRISA 004 trial should be suspended until further tenofovir tissue PK data became available. The anonymous complainant further requested that the United States Agency for International Development (USAID) funding for the study should be withdrawn. It was subsequently learnt that the complainant was from the Bill and Melinda Gates Foundation (BMGF).

The OGAC, which is responsible for overseeing all U.S. funding for AIDS activities outside the U.S., responded to the complaint by convening a high level consultation in June 2007 to discuss the scientific rationale of the study and to make a decision about whether the trial should continue to receive funding from the US government.

The consultation, which was chaired by Tim Farley from the World Health Organisation (WHO), was attended by representatives from CAPRISA, the International Partnership on Microbicides (IPM), BMGF, the Microbicide Alliance, the Centers for Diseases Control and Prevention (CDC), National Institutes of Health (NIH), the International Working Group on Microbicides (IWGM), WHO, Global Campaign for Microbicides (GCM), FHI360, CONRAD, Gilead Sciences and a few others. At the beginning of the consultation, the Chair invited critics of the CAPRISA 004 study to outline their concerns and objections. Five individuals commented at this stage, Zeda Rosenberg and Joe Romano of IPM, Renee Ridzon of BMGF, Lori Heise of GCM and Polly Harrison of the Microbicide Alliance. In response, the available data on tenofovir, the monkey vaginal and rectal challenge studies, and the phase I tenofovir gel study (HPTN 050) were presented by Jim Rooney of Gilead Sciences, Koen van Rompay, who had undertaken the animal studies, and co-Principal Investigator of the CAPRISA 004 trial, Salim Abdool Karim.

After both sets of presentations and detailed discussion, there was broad consensus that it was unlikely that the ongoing CONRAD PK study or any other tissue PK study would be able to provide data that would impact the design of the CAPRISA 004 trial. Instead, it became increasingly clear in the course of the discussion that the only way to address the uncertainties and the critic's concerns was to actually conduct the CAPRISA trial, as it was needed to generate the essential evidence, especially on a drug level that correlates with protection by tenofovir gel. At the end of the consultation, OGAC commented that the scientific rationale for the dosing strategy and trial design were now more clearly justified and they confirmed their continued financial support for the CAPRISA 004 trial, wishing the CAPRISA 004 study team well in conducting this important study.

Subsequently, a small group of scientists, led by John Moore of Weill Cornell Medical College in New York and Robin Shattock of St George's, University of London, submitted an opinion-editorial to Nature explaining their objections to the CAPRISA 004 trial. Nature decided against publishing the opinion piece and instead published a news article [26] written by Erika Check on the controversy under the title "HIV trial doomed by design, say critics". The article included concerns raised by Moore, Shattock, Ridzon, Rosenberg and Heise. Salim and Quarraisha Abdool Karim addressed their points in a letter of reply published in

Nature [27]. More importantly, this article led to the senior scientists of both sides of the controversy, Robin Shattock and Salim Abdool Karim committing themselves to discussing the differences of opinion and resolving them. This constructive engagement through conference calls and face-to-face meetings concluded with a jointly released summary [28] of their discussions: "Throughout, the discussions were very constructive and proved to be both interesting and informative with substantial common ground. We would like to thank everyone for your support. Like you, we are deeply committed to the important goal of a safe and effective microbicide and believe that our common purpose in achieving this goal has enabled us to find common ground and a clear way forward." Fortunately the differing viewpoints were resolved amicably and this ended on a constructive note with the study proceeding to conclusion, to provide in July 2010 the first evidence that antiretrovirals can prevent sexual transmission of HIV in women.

4.2 Co-enrolled Participants

Women who were enrolled in any other study of an investigational product or behaviour modification related to HIV prevention or who had in the past 12 months participated in any research related to any vaginally applied product/s were not eligible for enrolment in the CAPRISA 004 trial. Women were asked to confirm their involvement with other trials at screening. About 9 months into the study, one of the participants returned gel applicators to the CAPRISA pharmacy from another microbicide study (HPTN 035 trial). This trial was being conducted at a nearby site in Durban by the Medical Research Council (MRC). The participant was interviewed and she disclosed that she had not been honest during the screening and that she was simultaneously enrolled in the HPTN 035 trial that was being conducted by the MRC. After checking with the MRC, it was concluded that this was an isolated incident but procedures were put in place to check the identity numbers (ID) numbers of all new women being screened for CAPRISA 004 to avoid any further enrolments of women involved in the MRC microbicide trials. A few months later another participant returned HPTN 035 gel applicators together with her CAPRISA 004 gel applicators and she too admitted that she was simultaneously enrolled in the HPTN 035 study. The CAPRISA and HPTN 035 teams then compared the ID numbers of all participants enrolled in the CAPRISA and MRC studies and found that 185 women had been ineligibly enrolled in the CAPRISA 004 trial; 135 were co enrolled in the HPTN035 trial and 50 had participated in the HPTN 035 trial within the past 12 months. Since these women do not fulfil the trial's inclusion/exclusion criteria and simultaneous participation in multiple studies including trials of investigational products may endanger participant safety, confound safety monitoring of individual participants and compromise the scientific integrity of all studies that the participant is enrolled in, the women were withdrawn from the CAPRISA 004 trial.

To prevent this situation from occurring in the future, a number of procedures were implemented. A custom-designed education program on co-enrolment was implemented and a shared, secure password protected and restricted user access electronic database between research units was established. This shared database is now used for all CAPRISA studies to verify each volunteer's trial participation before they are enrolled in a trial. A biometric fingerprint scanning system was also linked to the shared database and any person volunteering for a study needs to have their fingerprints scanned to verify that they are not already enrolled in another trial. The informed consent forms for studies now include a section on the dangers of co-enrolling in multiple studies and explains that their fingerprints will be used to verify that they are not already participating in other studies.

4.3 Myths and Rumours

When trials of investigational products are conducted there are often myths circulated in the community regarding the products or research. Some of the myths that emerged about the gel and research procedures during the CAPRISA 004 trial included: that the provision of tenofovir gel was CAPRISA's way of sustaining their AIDS Treatment Programme because women who use the gel get infected with HIV (the gel contained HIV), the blood drawn from participants is sold by CAPRISA to make a lot of money, and trial participants are asked to have sex with HIV infected men to prove if tenofovir gel is effective or not in preventing HIV infection.

In addition to addressing myths and rumours directly with participants at site, researchers need to also be prepared to address and contextualise results of other studies that became available during the trial. During the CAPRISA 004 trial, results from three microbicide studies, Cellulose Sulphate, HPTN 035, MDP 301 were released. The early stoppage of the cellulose sulphate trial received a lot of negative media coverage that could have had a profound impact on the recruitment of study volunteers for CAPRISA 004.

Addressing these myths and rumours required a robust community programme and a comprehensive communication plan. CAPRISA has an established Community Programme (described in Chap. 12) that provides an effective interface between the research staff and community representatives. The Community Programme ensured that there was regular, open and consistent dialogue at all levels of government structures, civil society and, in particular, with the community and participants. The communication plan developed for the CAPRISA 004 trial defined the best ways to communicate with the community; including appropriate messages and materials, such as local language translations of simplified "Question and Answer" materials, specific to the local context; assign responsibility for community communications; develop a plan for maintaining contact with community groups, sharing information, and presenting the findings to the community and participants when the study was complete.

5 Study Outcomes and Implications for the HIV Prevention Field

The CAPRISA 004 tenofovir gel trial, involving 889 women in South Africa, showed that tenofovir gel, applied before and after sex reduced HIV incidence by 39 % (95 % CI: 6; 60) overall, and by 54 % in those who used the gel consistently [29].

The results of the CAPRISA 004 tenofovir gel trial were announced at the 18th International AIDS Conference in Vienna in 2010 and were simultaneously published in the journal *Science*. These results created much excitement in the HIV prevention field; the presentation of the results at the International AIDS Conference in Vienna was greeted with several standing ovations and the findings were covered by top-tier news outlets, with hundreds of articles, television and radio coverage and coverage in other print and online publications. The reason for the excitement was the results provided proof-of-concept that antiretroviral microbicides can prevent sexually-acquired HIV infection in women. It was also the first time that women potentially had a method to protect themselves that was completely under their own control.

The trial also found that tenofovir gel reduced the incidence of new genital herpes infections (HSV-2) by 51 % (95 % CI: 22; 70). Genital herpes is the most important global cause of genital ulcer disease. Women who have herpes are also significantly more likely to acquire HIV than those who do not. Besides general safe sex practices, there is no known prevention or cure for genital herpes infection; hence this finding is a major breakthrough potentially becoming a critically important intervention contributing to the global goal of sexually transmitted disease control.

While exciting, these results alone would not be sufficient to licence tenofovir gel for HIV prevention. There was high hope that the VOICE (Vaginal and Oral Interventions to Control the Epidemic) [30] trial, that included daily use of tenofovir gel, would confirm the results from the CAPRISA 004 trial. Disappointingly, none of the three products—tenofovir gel, oral tenofovir disoproxil fumarate (TDF) or oral co-formulated emtricitabine and tenofovir (Truvada)—tested in the VOICE trial were shown to be effective in preventing HIV [31]. An analysis of detectable drug levels in blood has shown that few of the VOICE participants adhered to the daily dosing regimen; adherence was estimated to be 23, 28 and 29 % in the tenofovir gel, oral tenofovir and oral truvada arms respectively [31]. The Follow-on African Consortium for Tenofovir Studies 001 (FACTS 001), which was designed as a confirmatory study for the CAPRISA 004 trial, also produced disappointing results showing that tenofovir gel had no impact on HIV [32]. In the FACTS 001 trial about half of the women trial had detectable drug levels [32]. Both of these studies highlight the importance of achieving high adherence in microbicide trials.

The microbicide field has now shifted towards multi-purpose prevention technologies that are able to simultaneously protect against at least two sexual and reproductive health (SRH) prevention indications, e.g., prevent unintended

pregnancy as well as STIs including HIV, and/or reproductive tract infections as well as long-acting antiretroviral products that potentially decrease adherence challenges.

References

1. UNAIDS. UNAIDS Report on the global AIDS Epidemic 2010. Available from: http://www.unaids.org/globalreport/ [Accessed 11 February 2014]. Geneva: Joint United Nations Programme on HIV/AIDS; 2010.
2. Abdool Karim Q, Abdool Karim SS, Singh B, Short R, Ngxongo S. Seroprevalence of HIV infection in rural South Africa. AIDS. 1992; 6: 1535–9.
3. Shisana O, Rehle T, Simbayi LC, Zuma K, Jooste S, Pillay-van-Wyk V, et al. South African National HIV Prevalence, Incidence, Behaviour and Communication Survey 2008: A turning tide among teenagers? Cape Town: HSRC Press; 2009.
4. Centers for Diseases Control and Prevention. HIV Transmission Risk. Available from: http://www.cdc.gov/hiv/policies/law/risk.html. [Accessed: 29 January 2016]; 2013.
5. Gregson S, Nyamukapa CA, Garnett GP, Mason PR, Zhuwau T, Carael M, et al. Sexual mixing patterns and sex-differentials in teenage exposure to HIV infection in rural Zimbabwe. Lancet. 2002; 359(9321): 1896–903.
6. Kelly RJ, Gray RH, Sewankambo NK, Serwadda D, Wabwire-Mangen F, Lutalo T, et al. Age differences in sexual partners and risk of HIV-1 infection in rural Uganda. J Acquir Immune Defic Syndr. 2003; 32(4): 446–51.
7. Duncan ME, Peutherer JF, Simmonds P, Young H, Tibaux G, Pelzer A, et al. First coitus before menarche and risk of sexually transmitted disease. Lancet. 1990; 335(8685): 338–40.
8. Jewkes RK, Dunkle K, Nduna M, Shai N. Intimate partner violence, relationship power inequity, and incidence of HIV infection in young women in South Africa: a cohort study. Lancet. 2010; 376(9734): 41–8.
9. Roddy RE, Zekeng L, Ryan KA, Tamoufe U, Weir SS, Wong EL. A controlled trial of nonoxynol 9 film to reduce male-to-female transmission of sexually transmitted diseases. New England Journal of Medicine. 1998; 339(8): 504–10.
10. Richardson BA, Lavreys L, Martin HLJ, Stevens CE, Ngugi E, Mandaliya K, et al. Evaluation of a low-dose nonoxynol-9 gel for the prevention of sexually transmitted diseases: a randomized clinical trial. Sexually Transmitted Diseases. 2001; 28(7): 394–400.
11. Van Damme L, Ramjee G, Alary M, Vuylsteke B, Chandeying V, Rees H, et al. Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomized controlled trial. Lancet. 2002; 360:971–977.
12. Peterson L, Nanda K, Opoku BK, Ampofo WK, Owusu-Amoako M, Boakye AY, et al. SAVVY® (C31G) gel for prevention of HIV infection in women: A phase 3, double-blind, randomized, placebo-controlled trial in Ghana. PLoS ONE. 2007; 2(12): e1312.
13. Feldblum PJ, Adeiga A, Bakare R, Wevill S, Lendvay A, Obadaki F, et al. SAVVY vaginal gel (C31G) for prevention of HIV infection: a randomized controlled trial in Nigeria. PLoS ONE. 2008; 3(1): e1474.
14. Skoler-Karpoff S, Ramjee G, Ahmed K, Altini L, Plagianos MG, Friedland B, et al. Efficacy of Carraguard for prevention of HIV infection in women in South Africa: a randomised, double-blind, placebo-controlled trial. Lancet. 2008; 372(9654): 1977–87.
15. Halpern V, Ogunsola F, Obunge O, Wang CH, Onyejepu N, Oduyebo O, et al. Effectiveness of cellulose sulfate vaginal gel for the prevention of HIV infection: results of a Phase III trial in Nigeria. PLoS ONE. 2008; 3(11): e3784.
16. Van Damme L, Govinden R, Mirembe FM, Guedou F, Solomon S, Becker ML, et al. Lack of Effectiveness of Cellulose Sulfate Gel for the Prevention of Vaginal HIV Transmission. N Eng J Med. 2008; 359(5): 463–72.

17. Abdool Karim SS, Coletti A, Richardson B, Ramjee G, Hoffman I, Chirenje M, et al. Safety and Effectiveness of Vaginal Microbicides BufferGel and 0.5 % PRO 2000/5 Gel for the Prevention of HIV Infection in Women: Results of the HPTN 035 Trial [abstract 48LB]. 16th Conference on Retroviruses and Opportunistic infections. Montreal, Canada; 2009.
18. McCormack S, Ramjee G, Kamali A, Rees H, Crook AM, Gafos M, et al. PRO2000 vaginal gel for prevention of HIV-1 infection (Microbicides Development Programme 301): a phase 3, randomised, double-blind, parallel-group trial. 2010. Lancet 2010; 376(9749): 1329–37.
19. Abdool Karim Q, Kharsany AB, Frohlich JA, Werner L, Mashego M, Mlotshwa M, et al. Stabilizing HIV prevalence masks high HIV incidence rates amongst rural and urban women in KwaZulu-Natal, South Africa. Int J Epidemiol. 2011; 40(4): 922–30.
20. Sibeko S, Baxter C, Yende N, Karim QA, Karim SS. Contraceptive choices, pregnancy rates, and outcomes in a microbicide trial. Obstet Gynecol. 2011; 118(4): 895–904.
21. Mansoor LE, Abdool Karim Q, Yende-Zuma N, MacQueen KM, Baxter C, Madlala B, et al. Adherence in the CAPRISA 004 tenofovir gel microbicide trial. AIDS Behav. 2014; 18(5): 811–9.
22. Gengiah T, Mansoor LE, Naidoo A, Upfold M, Abdool Karim Q, Abdool Karim SS, et al. The 'Wisebag': an innovative strategy for enhancing measurement of microbicide gel use in clinical trials. Microbicide 2010. Pittsburg, USA; 2010.
23. Mayer KH, Maslankowski LA, Gai F, El-Sadr WM, Justman J, Kwiecien A, et al. Safety and tolerability of tenofovir vaginal gel in abstinent and sexually active HIV-infected and uninfected women. AIDS. 2006; 20(4): 543–51.
24. Vourvahis M, Tappouni H, Patterson K, Chen Y-C, Rezk N, Fiscus S, et al. A Pharmacologic Basis for the Use of Tenofovir In Pre- and Post-Exposure Prophylaxis: Intra (IC) and Extracellular (EC) Genital Tract (GT) Pharmacokinetics (PK) and Pharmacodynamics from First Dose to Steady State in HIV-1 Infected Men (M) and Women (W). CROI Denver, Colorado; 2006.
25. Hu J, Gardner MB, Miller CJ. Simian Immunodeficiency virus rapidly penetrates the cervicovaginal mucosa after intravaginal inoculation and infects intraepithelial dendritic cells. Journal of Virology. 2000; 74(13): 6087–95.
26. Check E. Doomed by design, say critics. Nature. 2007; 448: 110–1.
27. Abdool Karim SS, Abdool Karim Q. Diverse approaches useful for microbicide trials. Nature. 2007; 449(7158): 24.
28. Abdool Karim S, Shattock R. Joint summary: Salim Abdool Karim & Robin Shattock discuss tenofovir gel dosing. CAPRISA Newsletter. 2007; 6(10): 1–2.
29. Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, et al. Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women. Science. 2010; 329: 1168–74.
30. National Institute of Allergy and Infectious Diseases (NIAID). Safety and Effectiveness of Tenofovir 1 % Gel, Tenofovir Disproxil Fumarate, and Emtricitabine/Tenofovir Disoproxil Fumarate Tablets in Preventing HIV in Women; http://clinicaltrials.gov/ct2/show/NCT00705679 (last accessed: 30 January 2012). 2011.
31. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodi N, Nair G, Palanee T, Nakabiito C, van der Straten A, Noguchi L, Hendrix CW, Dai JY, Ganesh S, Mkhize B, Taljaard M, Parikh UM, Piper J, Mâsse B, Grossman C, Rooney J, Schwartz JL, Watts H, Marzinke MA, Hillier SL, McGowan IM, Chirenje ZM. 2015. Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women. N Eng J Med 372, 509–518.
32. Rees H., Delany-Moretlwe S.A., Lombard C, Baron D, Panchia R, Myer L, et al. FACTS 001 Phase III Trial of Pericoital Tenofovir 1 % Gel for HIV Prevention in Women. [Abstract 26LB]. Conference on Retroviruses and Opportunistic Infections (CROI). Seattle, Washington; 23-26 February 2015.

Chapter 5
Rolling Out of Tenofovir Gel in Family Planning Clinics: The CAPRISA 008 Implementation Trial

Leila E. Mansoor, Kathryn T. Mngadi and Quarraisha Abdool Karim

1 Background

The CAPRISA 004 trial, a Phase IIb, double-blind, randomised, placebo-controlled trial demonstrated a 39 and 51 % protective effect of 1 % tenofovir gel in preventing HIV and herpes simplex type 2 (HSV-2) infections among women in KwaZulu-Natal, South Africa [1]. These results reinvigorated the world of HIV prevention because it was the first time that an antiretroviral drug had been shown to prevent the sexual transmission of HIV infections in women in the 30-year history of the HIV/AIDS epidemic.

However, the CAPRISA 004 study findings were just a first step in offering women an HIV preventive technology that they could initiate and use to protect themselves from acquiring HIV. Shortly after the release of the CAPRISA 004 trial results (20 July 2010), the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) hosted a consultation (25–26 August 2010) to devise a consensus plan for next steps to speedily achieve implementation of tenofovir gel.

L.E. Mansoor (✉) · K.T. Mngadi · Q. Abdool Karim
Centre for the AIDS Programme of Research in South Africa,
University of KwaZulu-Natal, Durban, South Africa
e-mail: Leila.mansoor@caprisa.org

Q. Abdool Karim
Department of Epidemiology, Mailman School of Public Health, Columbia University,
New York, NY, USA
e-mail: Quarraisha.abdoolkarim@caprisa.org

Q. Abdool Karim et al. (eds.), *The CAPRISA Clinical Trials: HIV Treatment and Prevention*, DOI 10.1007/978-3-319-47518-9_5

Three priority steps were defined during this meeting

I. **Priority 1**: Phase IIb/III studies to confirm tenofovir effectiveness in preventing HIV infection
II. **Priority 2**: Phase IIIB/IV implementation science studies—assessing models for health service implementation
III. **Priority 3**: Phase I and II safety studies in adolescents, pregnancy, HBV, etc.

The additional trials were urgently needed to confirm and/or extend the findings of CAPRISA 004 in other epidemic settings and populations, as well as in other formulations and dosing strategies, in order to advance product licensure as a critical next step in terms of women getting access to a safe and effective product. To address the first priority (additional confirmatory studies), the Microbicide Trials Network's (MTN) VOICE study [2] was identified as a crucial trial that could contribute to the evidence of the effectiveness of tenofovir gel. This multi-country, five-arm randomised controlled trial was assessing daily dosing of oral and topical formulations of tenofovir and oral formulation of a tenofovir/emtricitabine (TDF/FTC) combination (also known as Truvada®) for preventing HIV acquisition in sexually active African women. In addition to the VOICE study, the Follow-on African Consortium for Tenofovir Studies (FACTS) 001 study [3] was initiated to address the first priority. This trial was a double-blinded, randomised, placebo-controlled trial that tested whether tenofovir 1 % gel inserted vaginally before and after sex could prevent or reduce HIV and HSV-2 infections. The study was conducted in nine sites in South Africa and included over 2000 sexually active women. FACTS 001 was designed to confirm the CAPRISA 004 study findings in other urban, rural and peri-urban communities in South Africa.

The CAPRISA 008 [4] trial was designed to address the second priority (assessing models for health service implementation) and aimed to: (1) provide post-trial access to tenofovir gel for HIV-uninfected CAPRISA 004 study participants, (2) develop and assess an implementation model for tenofovir gel provision through family planning (FP) services and (3) collect additional safety data on tenofovir gel.

Both the MTN and FACTS consortiums were planning phase I and II safety studies in adolescents and pregnancy to address the third priority.

2 Rationale for the CAPRISA 008 Trial

The CAPRISA 004 trial established proof-of-concept that tenofovir gel was safe and effective in preventing HIV infection in a rigorous clinical trial. However, translating these findings into health service programmes posed many challenges that could be exacerbated in the context of weak healthcare delivery systems. The CAPRISA 008 trial (NCT01691768) provided an opportunity to answer critically important implementation questions about how best to incorporate new HIV prevention technologies, like tenofovir gel, into routine FP health services and how

to make these technologies accessible to women who would benefit most from this product (Panel 1). Undertaking CAPRISA 008 in parallel with the confirmatory study (FACTS 001), as opposed to after the completion of the FACTS 001 trial, enabled us to be better prepared for widespread roll-out access if tenofovir gel were to be licensed and simultaneously meet our post-trial ethical obligations to trial participants.

One approach to programmatic scale-up of tenofovir gel within the public sector health service in South Africa was to integrate its provision into FP services. The integration of HIV prevention and FP services has several advantages, including:

(i) Large numbers of sexually active women, who would benefit from tenofovir gel provision, already utilise FP services and attend these services at regular intervals over long periods;
(ii) FP staff are knowledgeable about reproductive health and have experience providing counselling and adherence support;
(iii) Primary Health Care (PHC) policy requires that the FP service is integrated into all PHC services as part of a minimum package of services provided at no cost through the public sector healthcare delivery system. As a result, FP services are widely available in South Africa;
(iv) FP services are provided as a sexual and reproductive health package for women, which includes contraceptive provision with counselling, HIV risk reduction counselling, HIV testing, screening for STIs, condom distribution and PAP smears; and
(v) HIV prevention services could enhance provision of comprehensive contraceptive counselling and services.

Empiric evidence was urgently needed to assess whether integrating tenofovir gel provision into FP services could achieve similar levels of safety and gel use (if not better than that) observed in the CAPRISA 004 trial. The time when the VOICE and FACTS trials were underway provided a critical window of opportunity to prepare and devise effective strategies for informing future policy and programmatic scale-up of tenofovir gel provision. A priority population for access to tenofovir gel was the participants from the CAPRISA 004 trial who remained HIV-uninfected and were willing to use tenofovir gel. In addition to the personal benefit for individual study participants, important ongoing data on the long-term safety of tenofovir gel could be collected. Tenofovir gel was made available to HIV-uninfected women who previously participated in the CAPRISA 004 study and were willing to use tenofovir gel through this open-label study at the CAPRISA Vulindlela and eThekwini Clinics and their neighbouring FP services.

Given that existing FP services vary in the quality of services provided to clients, a good understanding of the current health system delivery strengths and their challenges was needed. Simply requesting or instructing FP services to add tenofovir gel provision to their existing workload would have led to highly variable outcomes. Hence, a structured and evidence-based approach was needed to facilitate the process of integrating tenofovir gel into existing FP services.

Panel 1 CAPRISA 008 study schema

Purpose:	To assess the effectiveness of an implementation model which integrates tenofovir gel provision into existing family planning services
Study design:	Two-arm, open-label, randomised controlled trial
Study population:	Consenting sexually active, HIV-uninfected women aged 18 years and older who previously participated in the CAPRISA 004 Tenofovir Gel Trial
Study duration:	Maximum duration of follow-up of 30 months
Study intervention:	Participants were randomised to receive 1 % tenofovir gel through either: • Public sector family planning services with 2–3 monthly provision and monitoring of 1 % tenofovir gel and the use of QI methodology to promote reliable service delivery (intervention arm), or • The CAPRISA research clinics with monthly provision and monitoring of 1 % tenofovir gel (control arm) All women in the trial were provided with the standard package of HIV prevention and reproductive health services
Sample size:	382 women were enrolled. This provided 90 % power to demonstrate whether gel use in women attending family planning services is similar to, but no more than 20 % lower than, gel use among women attending the CAPRISA research clinics, stratified by study population and adjusted for 10 % loss to follow-up
Treatment regimen:	Participants in both study arms were provided with a supply of single-use, pre-filled applicators of 1 % tenofovir gel. While in the study, participants were advised and supported to follow the CAPRISA 004 pre- and post-dosing strategy, namely BAT24, where the first dose of tenofovir gel is applied within 12 h before anticipated sex and a second dose as soon as possible but within 12 h after sex, with a maximum of two doses of gel in a 24-h period
Primary objective:	To assess the effectiveness of an implementation model for tenofovir gel provision through family planning services
Primary endpoint:	Mean number of returned used applicators per participant per month
Secondary objectives:	To compare women receiving tenofovir gel through family planning services with women receiving tenofovir gel through clinical trial clinics for the following: 1. Safety of tenofovir gel measured by clinical and laboratory adverse event rates, including pregnancy rates and outcomes 2. HIV incidence rates 3. The estimated proportion of reported sex acts covered by two gel doses, self-reported adherence to the tenofovir gel dosing strategy and factors influencing gel use in relation to sexual activity, condom use, and intravaginal practices 4. Self-reported service acceptability and completion rates of quarterly (or 2 monthly in Nur-isterate users) HIV and pregnancy testing 5. HIV viral load among HIV seroconverters 6. Tenofovir resistance of HIV strains from HIV seroconverters 7. Vaginal cytokines to assess the role of genital inflammation in HIV acquisition

(continued)

Panel 1 (continued)

	8. HSV-2 and human papillomavirus (HPV) incidence rates 9. Tenofovir levels 10. Self-reported product acceptability
Study sites:	CAPRISA eThekwini and CAPRISA Vulindlela Clinics and their neighbouring public sector family planning services in KwaZulu-Natal, South Africa

3 The Quality Improvement (QI) Approach

A quality improvement (QI) approach was utilised to assist public sector FP services to expand their current service delivery to include tenofovir gel provision. The QI approach strengthens health systems using small scale, rapid cycles of improvement that are designed and implemented by local providers to develop reliable processes for service delivery through mentored coaching and support. A key strength of the QI approach is its nurturing of critical thinking and problem-solving skills among clinic staff at the front lines of service delivery. Promoting ownership for the quality of service delivery is empowering for healthcare providers in the face of overwhelming service delivery challenges and allows them to rapidly witness data-supported benefits to clinical practice.

The QI approach is based on the methodology that is grounded in operations research and management science, two well-established fields that have, for more than 90 years, combined the disciplines of statistics, psychology, systems engineering and iterative learning, to have major impact on systems performance across countries and industries. This approach seeks to design systems for maximum effectiveness, efficiency and adaptability and to actively disseminate the best models for health service delivery at the most rapid rate possible. Specialised, evidenced-based tools aimed at rapid-cycle iterative testing of changes, networked collaborative learning, development of institutional capability for continuous improvement and frameworks to guide large-scale change have been developed to facilitate this process (Fig. 1) [5]. The QI approach supports a shift in provider attitudes and practice from a prescriptive mode to one that supports critical thinking and problem-solving skills with continuous review and improvement of service provision.

Healthcare quality improvement principles and the Model for Improvement (Fig. 1) provide an effective approach to help close the gap between evidence-based knowledge and the ability of health systems to implement large-scale programs [6]. This approach places a premium on data-driven front line decision-making, peer-to-peer knowledge exchange, local adaptation of clinical protocols and highly participative management. Originally developed in the United States and widely adopted in the United Kingdom and other high-income nations, these efforts have increasingly found their way, with appropriate modifications, into global health applications in low- and middle-income countries.

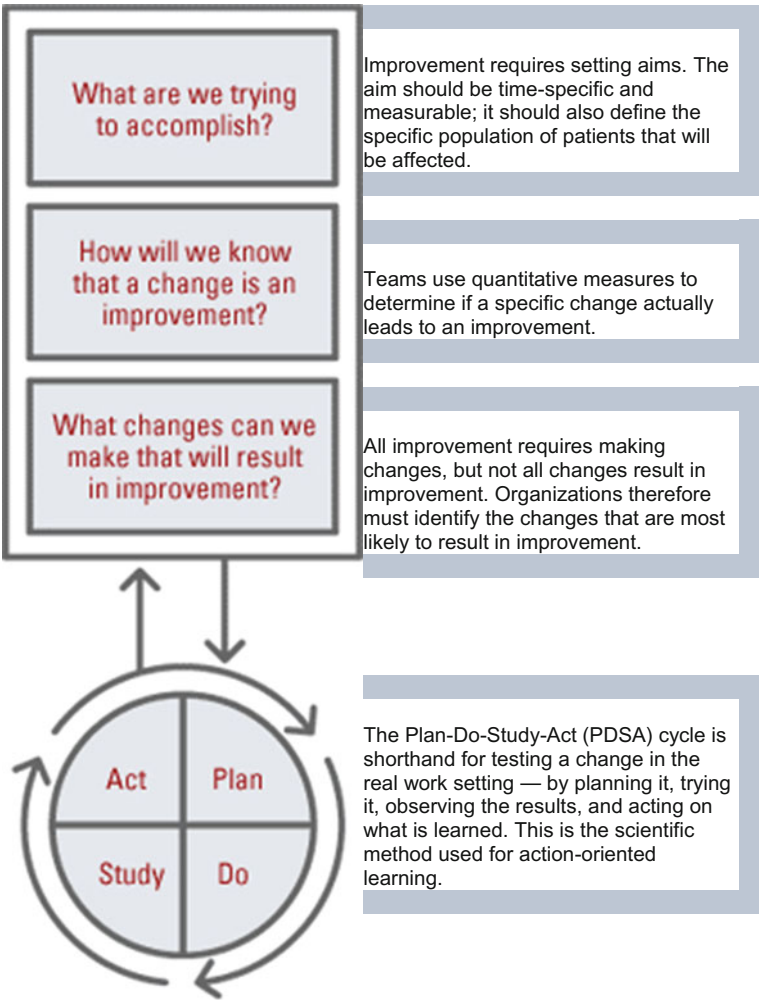

Fig. 1 Model for quality improvement: Setting Aims, Establishing Measures, Selecting Changes and Testing Changes (http://www.ihi.org/resources/Pages/HowtoImprove/default.aspx)

Application of the QI approach to health systems of low- and middle-income countries shows considerable promise. Projects in South Africa demonstrated rapid scale-up of access to HIV care and treatment services and falling rates of mother-to-child transmission of HIV at a district level have been demonstrated [7].

Traditionally this approach is used following policy formulation and where some program implementation experience has already been established. This often means that healthcare providers have to unlearn what they have been doing for years and replace this with new enabling and empowering approaches that involve critical

thinking and problem-solving skills, which have the added advantage of application to other health challenges facing the facility or service.

The CAPRISA 008 trial tested this model in a rigorous manner, i.e. using a randomised clinical trial approach, that included strengthening existing FP services to provide sexual and reproductive health services as a foundation to introduce a new health technology even prior to licensure and importantly pave the way for more rapid, efficient, safe and effective access to a much needed product to women who would benefit most. A strengthened FP service and more engaged providers was of benefit to existing FP services, overall healthcare delivery in these facilities and most importantly, support and benefit the clients of these services.

4 CAPRISA 008 Study Overview

This was a two-arm, open-label, randomised, controlled trial. A total of 382 sexually active, HIV-uninfected women aged 18 years and older who previously participated in the CAPRISA 004 study were enrolled from an urban and rural site in KwaZulu-Natal. The primary endpoint of gel use was assessed as the mean number of returned used applicators per participant per month. The sample size estimated to provide 90 % power to demonstrate whether gel use in women attending FP services is similar, but no more than 20 % lower than gel use among women attending the CAPRISA research clinics, stratified by study population and adjusted for 10 % loss to follow-up. Safety was assessed by the frequency of adverse events using laboratory and clinical markers. While this study was not specifically designed to use HIV incidence rates to assess non-inferiority of the FP clinic arm, HIV incidence rates were observed in the trial as a secondary endpoint and assisted in the interpretation of the primary outcome of the trial. The acceptability of FP services for tenofovir gel provision was assessed using self-report and clinic attendance rates.

The total study duration was approximately 30 months, with active accrual requiring approximately 12 months (following which an open cohort was maintained) and follow-up continuing for approximately 18 months. Potential study participants were screened for eligibility and eligible participants were enrolled in the study within 30 days of screening. At each of the two sites, consenting eligible participants were randomly assigned to receive 1 % tenofovir gel through either FP services (intervention arm) or the CAPRISA clinics (control arm) at both study sites.

Provision of tenofovir gel and study monitoring for women enrolled in the intervention arm was done through local FP services where QI methodology was used to promote reliable delivery of tenofovir gel and FP services. Participants in the intervention arm had monthly visits for the first three months post-enrollment;

thereafter, gel provision and monitoring was scheduled to coincide with each participant's routine FP visit (typically every 2–3 months). Study visits in the intervention arm were scheduled no longer than 3 months apart.

Women assigned to the control arm had monthly scheduled visits at the CAPRISA urban or rural clinic where they were provided with 1 % tenofovir gel.

HIV and pregnancy testing was performed at each study visit in both study arms. HIV/sexually transmitted infection (STI) risk reduction messages and condoms were provided to all participants using consistent prevention messages. Similarly, FP services, tenofovir gel and counselling on product adherence were provided to all participants. Participants in both study arms were requested to return all used and unused applicators at each study visit.

Clinical safety was assessed pre-, during- and post-enrollment. Laboratory safety assessments were done at enrollment, months 6, 12, 18, 24, study exit and additionally if indicated. At these visits, blood samples were collected for urea, electrolytes, creatinine, liver function tests, full blood count, calcium and phosphate levels. Pelvic examinations, including naked eye examination of the external genitalia and speculum examination of the vagina and cervix were conducted at enrollment, months 6, 12, 18, 24, study exit and additionally if indicated. These visits also included collection of blood for storage of serum and plasma and genital specimens for storage to assess for markers of safety, risk exposure, product adherence, potential post-trial assessments of activity against STIs, and tenofovir resistance. For symptoms experienced between scheduled visits, the participant was counselled to report to their assigned study site as soon as possible.

Participants identified with an STI or other treatable reproductive tract infection at a scheduled or participant-initiated visit were provided counselling and clinical care at the study sites in accordance with the South African Department of Health guidelines. Participants with STIs were encouraged to refer their partners for treatment.

While contraceptive services were provided to all CAPRISA 008 participants, those who became pregnant during the study discontinued product use while they were pregnant. Pregnant women were advised to continue with their follow-up visits. When these participants no longer had a positive pregnancy test, the pregnancy outcome was documented and they were re-initiated on tenofovir gel if they chose to continue with study participation.

Participants infected with hepatitis B virus (HBV) at enrollment were closely monitored clinically and using laboratory diagnostics, especially during episodes of product hold. Any participant needing further treatment for HBV was referred to a healthcare provider for further follow-up.

Participants who became HIV-infected during study follow-up were referred to the CAPRISA Acute Infection Study (CAPRISA 002) for ongoing care, antiretroviral treatment and follow-up. Participants who did not wish to enrol in CAPRISA studies were provided with information on other sources of care and support available in the community or appropriate health facilities serving the catchment populations.

5 Study Intervention

5.1 The Intervention Arm

Participants randomised to the intervention arm received tenofovir gel through the FP clinic in Vulindlela and the eThekwini FP clinic in Durban. Following completion of the randomization procedures at the CAPRISA clinics, participants assigned to the intervention arm were escorted to their designated FP services, where they were followed-up monthly for the first three months and 2–3 monthly thereafter.

As part of the study intervention for CAPRISA 008, a QI approach was used to assist the FP services to expand their current services to include tenofovir gel provision. An experienced QI advisor worked with the FP staff to conduct a gap analysis of existing FP service provision prior to the enrollment of study participants at these sites. External and internal ideas were carefully vetted to improve the quality of FP service delivery in the areas of FP counselling and contraception provision, STI/HIV counselling and treatment and general clinic processes (e.g. clinic flow, documentation, follow-up). The QI advisor undertook ongoing monitoring of the quality of each of the two FP services. Once the initial QI process had been completed at the participating FP services, a site initiation assessment was undertaken to ensure procedures were in place for the study, including procedures for dispensing tenofovir gel. Once each FP service met the requirements for site initiation, study participants were enrolled and the same QI approach was used to integrate reliable tenofovir gel provision and monitoring into the FP programs.

FP services include:

- Acknowledgement that FP services need to be strengthened and improved
- Clear commitment by facility-based staff to specific time-limited aims to ensure improvements to the quality of FP services to be provided
- Completion of a facility audit to identify nature of challenges and bottlenecks in system that impede service delivery
- Establishment of a clinic-based multi-disciplinary ‘improvement team’
- Goals and timelines for rapid improvement of outcomes set
- Mapping of relevant clinic-based processes for FP service provision with identification of critical milestones and timelines
- Development of systems tools to support the QI process
- Development and testing of specific changes to the system using the Model for Improvement and the Plan, Do, Study, Act (PDSA) cycle.
- Establishment of logs and data collection forms to monitor progress
- Rapid feedback of clinic data to enable the clinic QI team to identify ongoing challenges and develop solutions.

The introduction of tenofovir gel into FP services built on QI-strengthened FP service delivery.

- FP staff were provided with detailed information on what is known about tenofovir gel and strategies for providing individualised user support
- With support from the experienced QI advisor, the clinic QI team
  - Set clear goals for service delivery improvement
  - Mapped out the critical steps required for provision of tenofovir gel to FP clients
  - Developed system tools to support tenofovir gel provision, including data collection tools to monitor progress
  - Oversaw implementation of the tenofovir gel delivery plan
  - Reviewed data and feedback to FP staff to develop solutions to challenges.

This two-step approach of initially strengthening the FP services and introducing the tenofovir gel using a QI framework created a cadre of service providers who have sufficient training and skills to provide the necessary services and who can remain vigilant about the quality of services provided and cope with unexpected or unanticipated situations in service provision, in contrast to a more traditional prescriptive, top-down approach of service delivery introduced with minimal training and limited ongoing support to providers.

5.2 The Control Arm

Participants randomised to the control arm received tenofovir gel with monthly follow-up visits through the CAPRISA clinics. Their study visits and procedures were similar to those followed in the CAPRISA 004 protocol. There was no additional QI effort in the control clinics beyond what is routinely done by the research clinics.

5.3 Similarities and Differences Between the Intervention and Control Arms

Women in both the intervention and control arms received:

- A comprehensive prevention package comprising education, counselling, condom promotion, STI treatment, annual cervical cancer screening and HIV testing
- FP and reproductive health services
- Tenofovir gel
- Intensive 6 monthly monitoring visits
- Safety monitoring at every study visit.

The differences between the intervention and control arms are summarised below

Intervention arm	Control arm
• Attended the QI-strengthened FP services throughout the study	• Attended CAPRISA clinics throughout the study
• Received all services, including tenofovir gel provision, from FP clinic staff, under the guidance of a quality mentor	• Received all services, including tenofovir gel provision from CAPRISA clinic staff
• Clinic visits were three-monthly, except for women on Nur-isterate injectable contraception where visits were two-monthly	• Monthly Clinic visits
• Tenofovir gel provision was integrated into FP service provision	• Tenofovir gel was provided separately not integrated into FP service provision

6 Challenges and Lessons Learned

6.1 Better Preparation for Post-trial Access

Given the long history of failure of microbicide trials, the study team was not prepared for provision of post-trial access to tenofovir gel. This was the first time that a microbicide had been shown to prevent the sexual transmission of HIV infection in women, with no precedent for post-trial access.

Discussions were initiated with sponsors and regulatory bodies after the CAPRISA 004 results became available and demonstrated efficacy. Another challenge was product availability. Tenofovir gel was prepared in sufficient quantities for the trial and there are time delays in manufacture and quality assurance checks.

Guidance point 19 (Availability of Outcomes) on post-trial access as described in the UNAIDS/WHO guidance document on Ethical Considerations in Biomedical HIV Prevention Trials which states that "*trial sponsors and countries should agree on responsibilities and plans to make available as soon as possible any biomedical HIV preventive intervention demonstrated to be safe and effective… to all participants in the trials in which it was tested, as well as to other populations at higher risk of HIV exposure in the country…*", formed the basis of the CAPRISA 008 study protocol and included two study populations; (1) Consenting HIV-uninfected CAPRISA 004 participants, and (2) Research naïve, sexually active, HIV-uninfected women aged 18 years and older, who are utilising family planning services (within primary healthcare clinics) neighbouring the CAPRISA eThekwini and CAPRISA Vulindlela Clinics.

The South African Medicines Control Council (MCC) made it a requirement that since the product was unlicensed and confirmatory trials were still underway that tenofovir gel be provided under study conditions and under MCC oversight. The first

participants were enrolled at the Vulindlela Research Site on the 7 November 2012 and at the eThekwini Research Site on the 26 November 2012, enabling post-trial access to CAPRISA 004 participants almost 28 months following the release of the CAPRISA 004 trial results. During the more than two-year delay in obtaining regulatory approval for post-trial access to tenofovir gel, 54 of 519 women (10.4 %) who were HIV uninfected at the end of CAPRISA 004 were identified as HIV infected either at the pre-screening or screening visit for CAPRISA 008. This underscores the importance and urgency of women initiated prevention technologies, and more importantly early planning for post-trial access of the successful product.

6.2 Delays with Regulatory Approval

The study protocol was developed and submitted for regulatory and ethics committee approval in November 2010. There was a considerable time lapse between the initial protocol submission (November 2010) and the final approval (May 2012) (Table 1). The University of KwaZulu-Natal's (UKZN) Biomedical Research Ethics Committee (BREC) provisionally approved the study protocol on 29 June 2011. The delay was mainly on the part of the South African MCC.

Table 1 CAPRISA 008 regulatory timeline

Dates	MCC Correspondence	BREC Correspondence
08 November 2010		CAPRISA 008 protocol version 1.0 finalised and submitted to BREC
18 November 2010	CAPRISA 008 protocol version 1.0 submitted to MCC	
22 November 2010		BREC acknowledged receipt of CAPRISA 008 application
12 January 2011		First set of queries received from BREC
20 January 2011	First set of queries received from MCC	
28 January 2011	Response to MCC queries + version 1.1 of protocol submitted	Response to BREC queries + version 1.1 of protocol submitted
10 March 2011		Second set of queries received from BREC
30 March 2011		Response to BREC queries + submission of v1.2 of Screening IC, Enrolment Informed Consent form and PIL

(continued)

Table 1 (continued)

Dates	MCC Correspondence	BREC Correspondence
21 June 2011	Request from MCC (5 months later) for a face-to-face meeting with the investigators on 01 July 2011	
23 June 2011	Response to MCC indicating that the PIs were committed to conference presentations in the USA on this date and requested the meeting to be re-scheduled anytime after mid July 2011	
29 June 2011		BREC provisional approval of CAPRISA 008 protocol v1.1 and of the ICs v1.2 received
14 July 2011	Submission of CAPRISA 008 Ethics Committee approval to MCC	
12 August 2011	Request from MCC for face-to face meeting with the investigators on 26 August 2011	
26 August 2011	Prof. SS Abdool Karim, Prof. Q Abdool Karim, Prof. J Singh, Dr. LE Mansoor and Mr. A Gray attend the face-to-face meeting at the MCC. All queries raised by the MCC were systematically addressed by the team	
21 September 2011	MCC requested a copy of the 1 % tenofovir gel investigator's brochure (Telephonic request). The 4th edition of IB (dated 12 Nov 2010) was submitted via e-mail	
04 October 2011	MCC requested written responses to queries raised and addressed during face-to-face meeting (26 August 2011)	
12 October 2011	Responses to queries submitted the MCC	
16 November 2011	Additional recommendations received from the MCC	
23 November 2011	Response to the MCC's additional recommendations + revised protocol (version 2.0, dated 23 November 2011) submitted	

(continued)

Table 1 (continued)

Dates	MCC Correspondence	BREC Correspondence
14 December 2011	MCC requested the CAPRISA 004 Clinical Study Report (CSR) (Telephonic request)—CAPRISA 004 draft CSR submitted to the MCC	
28 February 2012	MCC requested the final CAPRISA 004 CSR—MCC was informed that the final CAPRISA 004 CSR will be submitted to all regulators on or before the 30 March 2012	
12 March 2012	Letter received from the MCC noting that the review of CAPRISA 008 will commence once the CAPRISA 004 final CSR has been submitted and analysed	
22 March 2012	CAPRISA 004 final CSR submitted to the MCC	
23 April 2012	CAPRISA's attorneys, Weber Wentzel, submitted a letter of demand to the MCC providing them with a detailed account of all correspondence sent to and received from the MCC and instructing them to furnish CAPRISA with a decision and reasons by 30 May 2012, failing which CAPRISA will have no option but to institute legal proceeding against the MCC	
21 May 2012	MCC approval of protocol version 2.0 dated 23 November 2011—with the restriction that only subjects who participated in the CAPRISA 004 trial are eligible for recruitment	
08 June 2012		CAPRISA 008, protocol v2.0, dated 23 November 2011 submitted to BREC for review and approval

(continued)

Table 1 (continued)

Dates	MCC Correspondence	BREC Correspondence
13 September 2012		BREC sub-com approval for protocol v2.0 and ICs (v3) received
03 October 2012		BREC full approval for protocol v2.0 and ICs (v3) received

WHO = World Health Organization; BREC = Biomedical Research Ethics Committee; MCC = Medicines Control Council; CSR = Clinical Study Report

Given that this study was developed based on an MCC requirement to provide product under study conditions, we were surprised by the unanticipated delays by the MCC and the duration thereof.

Following numerous correspondence with the South African MCC, including a letter of demand (dated 23 April 2012) from CAPRISA's lawyers to the MCC instructing them to furnish CAPRISA with a decision and reasons by 30 May 2012, failing which CAPRISA would have no option but to institute legal proceeding against the MCC, approval for the protocol was obtained on 21 May 2012. The MCC restricted post-trial access to CAPRISA 004 study participants only. Thus, we were only able to meet half our obligations in relation to the UNAIDS/WHO guidance point 19.

6.3 Managing Post-trial Participant and Community Expectations

The study participants and community were kept informed of progress on the plans and progress on post-trial access. Patience began to wear thin with the ongoing delays from the MCC and on 26 April 2012 about 500 participants, advocacy groups and community members took to the streets in Pietermaritzburg, South Africa demanding access to tenofovir gel. Advocacy efforts were organised under the umbrella of the '*Siyayifuna i-gel*' campaign. The protestors handed over a memorandum to CAPRISA researchers and the MCC that demanded access to the HIV prevention gel.

6.4 Challenges with Reimbursement

Reimbursement of trial participants remains controversial with significant differences between and sometimes within research sites. Regulatory guidance for post-trial access is minimal. Combining different trial designs within one trial adds

additional complexity to this issue—CAPRISA 008 combined post-trial access and implementation science designs, yet used the existing standard for reimbursement with some modification to approximate what would happen in a real PHC clinic setting.

CAPRISA 008 tried to balance the real-life scenario of no reimbursement for attendance at PHC clinics for those visits where no trial procedures were conducted (standard of care visits) with that of a clinical trial including for those visits that focused mainly on research procedures. A nominal reimbursement to cover transport only to the adjacent FP clinic was offered for 'standard of care' visits, with no reimbursement for time or inconvenience. However, participant perception was that they were involved in a clinical trial, irrespective of which arm they were randomised to, and the lack of reimbursement for time and inconvenience resulted in slower accrual, below standard retention and low participant morale. The protracted delay in regulatory approval did not take into account the increased costs of living, including travel costs during the 2 year delay. This had unanticipated increased cost implications for study conduct.

The Head of Bioethics for CAPRISA was tasked with reviewing the institutional reimbursement policy and to this end a review of relevant guidelines was undertaken, most notably the South African National Health Research Ethics Committee guidelines on reimbursement of 2012, which recommended taking into account participant time, travel and inconvenience in the total reimbursement amount. This resulted in a new institutional guideline which consequently impacted the reimbursement amount for 'standard of care' visits, to acknowledge the increased cost of travel, and reimbursement for these visits was increased accordingly.

The proposal notes that all participants should receive R50-00 for transport. Thereafter participants should be reimbursed for time and inconvenience according to two categories; i.e. less than 4 h and greater than 4 h spent in clinic—calculated at R12-50 per hour, which is based on the minimal approved wage. So if a study visit is anticipated to be less than 4 h long, a participant will receive R50-00 and if greater than 4 h long, a participant will receive R100-00. Based on this proposal the reimbursement figures for the CAPRISA 008 study were adjusted as indicated below.

Study visit	Original reimbursement	Amended reimbursement
Enrolment	R50	R150
Follow-up	R20	R100
Six monthly	R150	R150
Study exit	R150	R150

6.5 Adherence Support

Adherence is a key to ensuring effectiveness of microbicides. The CAPRISA 004 tenofovir gel trial demonstrated 54 % efficacy when adherence to the BAT24 dosing strategy was greater than 80 % for all sex acts. Adherence patterns may differ in a placebo-controlled trial where efficacy is uncertain compared to an open-label trial of a product of known efficacy and also with increasing duration of follow-up compared to an open-label post-trial access study.

In addition to the one-on-one motivational interviewing adherence support sessions, the CAPRISA 008 trial incorporated group adherence support sessions. Participants appreciated attending these group sessions, learning from the experiences of others, and appreciated suggestions made by peers to enhance their product adherence. Participants were more open in sharing their adherence experiences in a group as opposed to individual adherence sessions. The group dynamics and peer support from successful gel users in these sessions supported gel use, in addition to brainstorming innovative strategies to overcome barriers to adherence. In addition, having champions/advocates of the gel proved to be useful in encouraging others to adhere to gel use.

The individual motivational interviewing sessions were used consistently and information provided during the informed consent session was reinforced at all study visits with participants to address any incorrect and incomplete information about the product. This coupled with the group adherence support sessions created a platform for researchers to address any misconceptions, clarify the correct product regime and uncover barriers to product adherence. With the support from their peers, the participants raised issues in the group adherence sessions that they felt inhibited to raise in the individual sessions.

6.6 Confirmatory Studies VOICE and FACTS 001 Were Unsuccessful

The FACTS 001 study results were released on 24 February 2015 at the CROI conference in Seattle, Washington. Unfortunately the gel was shown to be ineffective in this study and did not confirm the results of CAPRISA 004. The incidence rate was 4.0 per 100 women years in both the tenofovir and placebo arms. However, the gel was shown to be effective in women who used it consistently; a sub-group analysis consisting of 214 participants in the tenofovir-treated group, showed that detection of tenofovir in genital fluids was associated with a 52 % reduction in HIV acquisition. In this same sub-group, women who did not use the gel at all (no drug detected in genital samples) were five times more likely to become infected.

These results were very similar to those of the VOICE study, which, in a similar population of women, demonstrated estimates of effectiveness less than zero for

both oral Truvada and oral tenofovir, whereas tenofovir gel was estimated to reduce the risk of HIV by 14.5 % compared to the placebo gel. Adherence to product use was low across all groups; a sub-group analysis indicated that drug was detected in blood samples of 29 % of women in the Truvada group, 30 % of women in the oral tenofovir group and 25 % among those in the tenofovir gel group. Further analysis found that women in the tenofovir gel arm who had drug detected in the sample taken at their first quarterly visit were 66 % less likely to acquire HIV than those who did not have drug detected, a result that was statistically significant.

Since both the VOICE and FACTS 001 study was unable to confirm the CAPRISA 004 study results, it is unlikely that tenofovir gel will be licensed as an HIV prevention technology.

7 Study Outcomes and Implications for the HIV Prevention Field

The CAPRISA 008 trial, which assessed adherence and effectiveness of PrEP provision integrated into FP services, was a 36-month, two-arm, open-label, randomised controlled, non-inferiority trial. Eligible women (n = 372) were randomly assigned to receive tenofovir gel at clinical trial clinics (n = 183) or at FP clinics (n = 189). Adherence, retention, HIV incidence and service preference were assessed.

At baseline, women assigned to trial and FP clinics were similar and study retention rates were 92.3 and 92.1 %, respectively. Adherence (% reported sex acts covered by two gel doses) was 73.9 % (95 % confidence interval (CI): 70.7–77.1) in trial clinics and 79.9 % (CI: 76.7–83.2) in FP clinics. Higher adherence (mean difference = 6.0 % [CI: 1.5–10.6]) in FP clinics met the pre-defined non-inferiority criteria. Mean-monthly sex acts and returned empty applicators were 4.5 (CI: 4.0–5.0) and 6.0 (CI: 5.5–6.5) in trial clinics compared to 3.6 (CI: 3.2–4.1) and 5.2 (CI: 4.7–5.7) in FP clinics, respectively. Genital tenofovir was detected at 1 year in 68/156 women (43.6 %; CI: 36.1–51.4) at trial clinics and 62/157 women (39.5 %; CI: 32.2–47.3) at FP clinics (p = 0.492). Adjusting for peri-coital gel use, genital tenofovir was detected in 58.3 % of 139 women reporting sex within 7 days but only in 28.2 % of 174 women reporting no recent sex. HIV incidence was 3.6 per 100 women years (wy) (CI: 1.9–6.3) in trial clinics and 3.5 per 100 wy (CI: 1.8–6.0) in FP clinics (p = 0.928). Overall HIV incidence rate was 44 % lower than in an age-comparable historical CAPRISA 004 placebo control group (3.5 vs. 6.2 per 100 wy). At study exit 75.1 and 80.3 % of women from trial and FP clinics expressed preference for receiving PrEP from FP clinics.

An important limitation of our study was the absence of a contemporaneous placebo control group. As a placebo control group would be unethical in a post-trial access study, the placebo control group of the CAPRISA 004 trial served as the external comparison group. This control group is from a similar study conducted

about 3 years earlier at the same clinics serving the same catchment population. A second important limitation is the applicability of these results on tenofovir gel to tenofovir-containing pills.

The results from the CAPRISA 008 are, however, of particular relevance to the wider HIV prevention field. Specifically, evidence guiding scale-up of PrEP in African women is required for implementation of new WHO guidelines that recommend the roll-out of PrEP to populations at substantial risk for HIV, which would include young women in Africa. The CAPRISA 008 trial demonstrates that the integration of an HIV prevention technology like tenofovir gel into FP services is feasible and acceptable for African women and achieves adherence equivalent to a clinical trial setting.

While some of the behaviours related to PrEP may be formulation dependent, this study provides broadly applicable information on the motivation of women to initiate PrEP, maintain follow-up and adhere to tenofovir-containing HIV prevention in FP clinic services. This clinical trial evidence may be helpful to policy makers and healthcare providers planning the implementation of oral PrEP as part of their comprehensive HIV prevention package.

References

1. Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, et al. Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women. Science. 2010; 329: 1168–74.
2. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodi N, Nair G, et al. Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women. N Eng J Med. 2015; 372 (6): 509–18.
3. Rees H D-MS, Baron D, Lombard C, Gray G, Myer L, Panchia R, Schwartz J, Doncel G. FACTS 001 Phase III Trial of Pericoital Tenofovir 1 % Gel for HIV Prevention in Women [Abstract 26LB]. Conference on Retroviruses and Opportunistic Infections (CROI); 2015 23–26 February 2015; Seattle, Washington; 2015.
4. Mansoor LE, Abdool Karim Q, Mngadi KT, Dlamini S, Montague C, Nkomonde N, et al. Assessing the implementation effectiveness and safety of 1 % tenofovir gel provision through family planning services in KwaZulu-Natal, South Africa: study protocol for an open-label randomized controlled trial. Trials. 2014; 15: 496.
5. Langley GJ. The improvement guide: a practical approach to enhancing organizational performance. 2nd ed. San Francisco: Jossey-Bass; 2009.
6. Berwick DM. Disseminating innovations in health care. JAMA. 2003; 289(15): 1969–75.
7. Barker PM, McCannon CJ, Mehta N, Green C, Youngleson MS, Yarrow J, et al. Strategies for the scale-up of antiretroviral therapy in South Africa through health system optimization. J Infect Dis. 2007; 196 (Suppl 3): S457–63.

Chapter 6
The Impact of Conditional Cash Transfers in Reducing HIV in Adolescent Girls and Boys (RHIVA): The CAPRISA 007 Matched Pair, Cluster Randomised Controlled Trial

Hilton Humphries, Ayesha B.M. Kharsany, Kerry Leask, Fanelesibonge Ntombela and Quarraisha Abdool Karim

1 Background and Rationale

Adolescent girls and young women acquire HIV infection 5–7 years earlier compared to their male peers [1–3]. This age–sex difference in HIV acquisition is a key to altering epidemic trajectories in sub-Saharan Africa. Whilst there have been encouraging trends globally with a 42 % reduction in new infections in young people (15–24 year old) since 2001, and a 17 % decline since 2010 in sub-Saharan Africa, young women are still twice as likely to become infected than their male counterparts [4]. In South Africa, more than 20 % of pregnant women aged 15–24 years attending antenatal clinics are infected with HIV [5]. CAPRISA studies to monitor the evolving HIV epidemic in Vulindlela, rural KwaZulu-Natal, demonstrated in a prospective cohort study undertaken between March 2004 and February 2005 in young women between the ages of 14 and 30 years, a HIV prevalence of 27.6 % in young women <18 years of age and a HIV incidence rate of 4.7 (95 % CI 1.5–10.9)/100 women years (WY) of follow-up. The pregnancy rate in this group was 23.7 (95 % CI 14.9–35.9)/100 WY [6] highlighting the importance of integrating HIV prevention services with other sexual reproductive health services.

H. Humphries (✉) · A.B.M. Kharsany · K. Leask · F. Ntombela · Q. Abdool Karim
Centre for the AIDS Programme of Research in South Africa,
University of KwaZulu-Natal, Durban, South Africa
e-mail: Hilton.humphries@caprisa.org

Q. Abdool Karim
Department of Epidemiology, Mailman School of Public Health,
Columbia University, New York, USA
e-mail: Quarraisha.abdoolkarim@caprisa.org

Q. Abdool Karim et al. (eds.), *The CAPRISA Clinical Trials: HIV Treatment and Prevention*, DOI 10.1007/978-3-319-47518-9_6

Table 1 HIV in pregnant women by age in rural South Africa (2001–2013)

Age group (years)	HIV prevalence (N = 4818) (%)
≤16	11.5
17–18	21.3
19–20	30.4
21–22	39.4
23–24	49.5
>25	51.9

Source Adapted from Kharsany et al. [7]

The annual antenatal surveys undertaken in the seven primary healthcare clinics in Vulindlela from 2001 to 2013 (Table 1) demonstrates that about 30 % of young women are already infected with HIV by age 20, and that HIV risk increased each year, post-sexual debut.

These data highlight the importance of HIV prevention in adolescent girls and young women and why it is a key priority area of research at CAPRISA. The CAPRISA HIV prevention in young women research agenda is a structured and systematic approach that includes:

I. advancing who is infecting who through understanding transmission dynamics;
II. why incidence rates in young women are so high despite coital activity being infrequent and heterosexual transmission of HIV being the least efficient mode of transmission, and
III. evaluation of novel strategies to prevent HIV infection.

Most research in women include those who are 18 years and older yet there is also a huge prevention need for young women <18 years. The CAPRISA 004 trial demonstrated an overall 39 % protective benefit of coitally linked use of tenofovir gel in women >18 years of age; there remain limited HIV prevention options for sexually active women younger than 18 years.

Most programmatic behavioural interventions targeting adolescents are delivered through schools and there are numerous HIV risk reduction interventions and life skills programmes currently being implemented. In addition, several school-based HIV prevention RCTs have been conducted where HIV incidence was the endpoint, but none to date have demonstrated an impact on reducing HIV [8–10]. Promising data from a conditional cash transfer intervention in Malawi to keep young girls in school [11], demonstrated a 61 % reduction in HIV prevalence and a 77 % reduction in HSV-2 prevalence in the intervention arm and has catalysed other studies to assess the impact of cash transfers on reducing incident HIV and HSV-2 infection. The RESPECT trial, conducted in Tanzania [12] in young women and men aged 18–30, established that STI incidence decreased most significantly in those receiving the highest value cash incentive (Adj RR: 0.73 95 % CI 0.47–0.99) when compared to the control arm.

The Reducing HIV Infection in Adolescents (RHIVA) program was designed to address several of the challenges faced by young girls and boys. These include poor internalisation of HIV risk; no sense of future and influence of peer pressure. It is a multi-component prevention intervention that includes the promotion of annual HIV testing, participation in a locally developed extra-curricular programme (My Life, My Future) that encourages future goal setting, provides information on HIV risk and sexually reproductive health issues, entrepreneurship and the importance of academic performance. Building on the experience in Malawi [11] the addition of a cash incentive to learners who had an annual HIV test, participated in the extra-curricular programme, and maintained 50 % pass rates in mid- and year-end examinations was included as a pilot programme in selected high schools in rural Kwazulu-Natal.

The purpose of the CAPRISA 007 study was primarily to assess the impact of the cash-linked RHIVA intervention on HSV-2 and HIV acquisition rates in high-school students in rural KwaZulu-Natal. Substance use and pregnancy rates were included as secondary objectives.

Intervening at a school level offers an efficient means of accessing a large cohort of adolescents that are still at lower risk of HIV but who are likely to experience sexual debut as they transition to older age, increasing their risk for HIV acquisition. High schools provide an opportunity and a key entry point for adolescent-focused interventions, which aim to enhance positive health outcomes and promote school retention and completion which are protective against HIV infection [13]. Individual schools are a large enough unit for cluster randomised controlled trials.

The CAPRISA 007 trial offered the opportunity to assess the impact of conditional cash transfers in promoting positive behaviours to potentially interrupt early risk pathways and reduce future HIV acquisition given the role of structural and behavioural factors contributing to these risk pathways. Incentivising behaviours conditional to achieving set milestones provides opportunities to potentially modify risk behaviours and interrupt causal pathways for reducing risk of HIV acquisition.

High quality evidence from randomised controlled trials is urgently needed to confirm the role for cash incentives to reduce HIV infection. The Vulindlela sub-district is located in one of the highest HIV burden districts in South Africa and globally and the CAPRISA pre-trial studies confirm the high HIV prevalence and incidence rates in this community. It provided an ideal location to implement and assess the impact of the RHIVA program. Given the variability between schools in terms of infrastructure, access to resources, quality of schooling and school retention rates, understanding the school context through an extensive situational analysis prior to implementing the RHIVA programme and impact assessment (CAPRISA 007) was critical to minimise variable and possibly biased outcomes. Therefore, prior to implementation of the program and impact assessment (CAPRISA 007), an audit of all high schools within the study area was conducted to provide a basis for selecting and matching schools to ensure comparability of paired schools in the intervention and control arms.

2 Situational Analysis/Audit of the Vulindlela High Schools

As part of the pre-program implementation and impact assessment preparatory activities, and in preparation of undertaking the school audit a spatial map was generated of all high schools in the Vulindlela School District. The audit was undertaken using a structured questionnaire and included all 42 high schools. The data collected included information which could be used to match schools such as number of students in each grade; geographical proximity of schools in order to minimise 'contamination' of learners crossing over in either direction between intervention and control schools; the grade 12 pass rate in the previous year; the physical condition of the school, number of teachers/educators to pupil ratio; accessibility of schools using public transport and availability of school social and health services. The data defined the context in which the trial would occur and assisted in making decisions on the design of the trial. The outcome of the schools audit highlighted several important factors:

- *Variability in quality of school environment*: the schools varied greatly in terms of the quality of their infrastructure, human resources, school retention rates, gender distribution and setting (deep rural versus rural versus peri-urban).
- *Geographic proximity of schools and possible contamination*: some schools were situated in closer proximity to one another than others, and with the need for a control and intervention arm, concerns of possible contamination was an important consideration.
- *The size of school population*: schools varied in overall population size as well as in distribution of gender. These variables, and the differential risk of young men versus young women needed to be taken into account for methodological issues and trial design in relation to number of clusters and sample size calculations.

The schools audit informed the selection of the matched school pairs for the cluster randomised controlled trial design. Schools whose Grade 9 and 10 learner populations were too small (less than 150 learners overall in Grade 9 and 10) were excluded. Schools that were too large were also excluded because no matching schools could be found. The remaining schools were matched based on criteria including, a minimum of 150 enrolled learners, Grade 12 exam pass rates, and ease of physical access to schools and school principal and school governing board acceptance of the intervention and impact assessment. The schools were matched in pairs and were the unit of randomisation for the cluster randomised design. To minimise possible contamination effects the schools audit was critical in selecting schools for comparable intervention and control arms, and minimising bias related to the schools.

3 The CAPRISA 007 Trial Design

The CAPRSA 007 trial, a proof-of-concept, matched pair, cluster randomised controlled trial (Panel 1) evaluated the impact of a cash-incentivised prevention intervention in reducing HIV and HSV-2 incidence rates in high-school learners. Grades 9 and 10 students from 14 selected secondary schools, regardless of age, gender or HIV status, were enrolled upon completion of all the necessary informed consent procedures. The trial had an open cohort, with enrolment taking place in 2010 and 2011.

Panel 1 CAPRISA 007 study schema

Purpose:	To assess the impact of a cash-incentivised prevention intervention on reducing HIV and HSV-2 incidence rates in high-school learners in rural KwaZulu-Natal
Primary objective:	To evaluate the efficacy of a cash-incentivised prevention intervention in reducing HIV and HSV-2 incidence rates in high-school learners
Secondary objectives:	To assess the impact of the intervention on: • academic performance • voluntary uptake of HIV testing • substance use patterns • pregnancy rates in female learners • contraceptive use patterns in female learners • participation in extra-curricular activities • HIV risk reduction behaviours including – condom use; – primary and/or secondary sexual abstinence rates; – sexually-transmitted infection rates; – intergenerational sexual coupling (age of sexual partner(s)); – age of sexual debut; – frequency of HIV testing; – number of concurrent sex partners; – frequency of partner change; – medical male circumcision rates; – anal sex rates
Study size:	Approximately 4000 eligible, consenting male and female learners
Study population:	Male and female learners in Grades 9 and 10 attending 14 selected secondary schools in Vulindlela School Circuit, KwaZulu-Natal
Study duration:	36 months
Intervention:	All eligibly enrolled learners in the intervention schools will receive a cash-incentivised prevention program delivered by MIET Africa and the KwaZulu-Natal Department of Education
Control:	No cash incentives for participation in the RHIVA programme

(continued)

Panel 1 (continued)

Impact assessment:	The impact of the cash-incentivised intervention will be assessed using a matched pair, cluster randomised controlled trial design. The 14 selected high schools in the Vulindlela School Circuit will be matched in pairs. The matched pairs of schools will be the unit of randomisation. Baseline measurements, using a standardised tool (structured questionnaire and biological specimens) will be undertaken simultaneously in each matched pair and will include all eligibly enrolled and consenting learners in the respective schools. On completion of baseline measurements in each matched pair of schools, the randomisation code for the pair will be revealed and the intervention will be implemented in the intervention school. All schools will receive the same prevention intervention but only the intervention school will receive the cash incentives. Follow-up measurements will be undertaken approximately 12 and 24 months after implementation of the intervention using a similar standardised assessment tool to that used at baseline. At baseline and during follow-up assessments in intervention and control schools, linked HIV and substance use testing will be undertaken in all learners and pregnancy testing in female learners. Other secondary endpoints will be assessed using a structured questionnaire
Primary endpoint:	HIV infection
Statistical considerations:	This is a proof of concept trial to demonstrate the efficacy of a cash-incentivised prevention intervention in reducing HIV incidence rates in high school learners in rural KwaZulu-Natal. Pairs of schools (matched on size and demography) will be used in randomising one to intervention and one to control. All measurements will be undertaken at an individual level within each unit of randomisation viz the school. Approximately 4000 learners in grades 9 and 10 from these 14 schools will be enrolled and followed for 24 months. The study will have 80 % power to measure a target effectiveness of 50 %. The sample size calculation is based on an overall trial HIV incidence rate of 3.8 per 100 person-years of follow-up (i.e. 5 per 100 person-years in the control arm). It is adjusted for an interim review after the 12 month assessment has been completed for all schools.
Ethical considerations:	Relevant assents, consents and permissions will be obtained prior to any study procedures being undertaken. The protocol will be reviewed by the University of KwaZulu-Natal Biomedical Research Ethics Committee (UKZN BREC). All consenting learners who test positive at baseline will be referred to the CAPRISA AIDS Treatment Programme (CAT) for ongoing care and support including access to antiretroviral treatment (ART) in accordance with the Department of Health ART Guidelines. Participants who become infected during the study will be referred to the CAT Programme for ongoing support and follow-up and initiated on ART when eligible. Any social harms experienced by participants in this impact assessment will be reported to the UKZN BREC and referred as appropriate to services within the community.
Study site:	Vulindlela School Circuit, KwaZulu-Natal

Learners were recruited following extensive community consultation. Informed consent was directly obtained from learners 18 years and older following literacy and comprehension assessments. For learners younger than 18 years, assent was obtained from the learner, and consent from the parent/guardian. If a parent/guardian or caregiver was unavailable (due to migrant labour, illness or death), a representative of the School Research Support Group (SRSG) assessed the participation of the relevant learner. The primary objective of the trial was incident HIV and HSV-2 infection, measured at annual follow-up visits. Secondary objectives were to assess the impact of the intervention on: academic performance, voluntary uptake and frequency of HIV testing, substance use patterns, pregnancies and contraceptive use patterns in female learners, participation in extra-curricular activities, HIV risk reduction behaviours including male and female condom use, primary and/or secondary sexual abstinence rates, sexually transmitted infections, age of sexual debut, intergenerational sexual coupling (age of sexual partner(s)), number of concurrent sex partners, frequency of partner change, medical male circumcision rates and anal sex practice.

Baseline measurements, using a standardised tool (structured questionnaire and biological specimens), were undertaken simultaneously for participants enrolled in the matched paired schools and pre-implementation of the RHIVA programme. On completion of baseline measurements, the randomisation code for the matched pair was revealed and the intervention was implemented for the school assigned to the intervention. All learners in the intervention and control schools received the same prevention intervention. The difference was learners from intervention schools received cash for achieving key study milestones. Follow-up measurements were undertaken approximately 12 and 24 months after implementation of the intervention using a similar standardised assessment tools used at baseline, and total study time was 36 months. HIV infection was assessed by measuring HIV antibodies in all learners at baseline and at each follow-up visit. The date of HIV acquisition was estimated as being the midpoint between the last negative and first positive HIV antibody test result. HSV-2 testing was performed using HerpeSelect® HSV-2 ELISA Kits, and urine pregnancy testing was performed. Secondary endpoints were assessed using a structured questionnaire. In addition to the procedures outlined, the following activities were completed:

- Confirmation of demographic data and locator information;
- Assessment of social harms; and
- Syndromic screening for sexually transmitted infections.

Only learners who tested HIV negative at the enrolment visit contributed to the final analysis. Participants with prevalent HIV infection and those who became infected during the study continued with study participation but were excluded during the analysis stage. The sample size for the trial was based on an HIV incidence rate of 5 per 100 person-years in the control schools with an expected 50 % reduction in HIV incidence rate in the intervention schools; with a 0.25 coefficient of variation between the clusters yielding a design effect of 1.6, alpha at

0.05 and power at 80 %. Thus the trial required in each arm a minimum of seven schools, with a minimum of 146 eligible students in each school.

To meet the ethical obligations and maintaining high-quality care for study participants, participants who seroconverted during the trial were referred for ongoing care and to access antiretroviral treatment and psychological support from organisations and primary healthcare clinics in the district. Those who chose not to participate in the CAPRISA 007 trial were still allowed to participate in the RHIVA programme.

3.1 Study Intervention

3.1.1 The Intervention Arm

The school as a unit randomised to the intervention arm received cash incentives for completing the required conditional behaviours or milestones. MIET Africa (a not-for-profit organisation who aims to improve the lives of children and youth by addressing barriers to learning and development) together with the KwaZulu-Natal Department of Education were responsible for the delivery of the RHIVA program and the cash incentives to students in the intervention arm who achieved the pre-specified milestones. Following the blinded baseline assessment undertaken in matched school pairs, the intervention and control school was revealed and the RHIVA team proceeded with delivery of the intervention to each school as per the random allocation.

Results from the laboratory testing were provided to learners off-site by select CAPRISA study staff either at the closest primary healthcare clinic or the CAPRISA Vulindlela Clinical Research Site on pre-set days. Transport was provided to learners to and from the school attended. All data linking learner personal identifiers and PID or study results were maintained securely with access to a limited number of study staff.

The behaviours that were cash incentivised were:

- ***Participation in a Sustainable Livelihood Programme (SLP) (My Life! My Future!)***
  The SLP was an extra-mural activity facilitated by trained peer/youth workers and comprised of weekly one hour sessions. The overall goal of the programme was, through increased engagement in relevant life skills, to foster a positive view of self and a greater sense of future. Payment for participation in the programme was linked to learner attendance; completing a portfolio which included a community audit report, business plan and evidence of having implemented a project. In order to receive the incentive, learners needed to:

(i) Attend 80 % of the My Life! My Future! SLP sessions;
(ii) identify a project and develop a business plan that included a community audit in terms of needs, existing resources and opportunities, and implement the identified project; and
(iii) Complete a portfolio showing evidence that the project was implemented. Attendance was assessed by the educators.

- ***Academic Performance***: To support learners in improving academic performance, attending school, completing schooling and improving their self-esteem, learners were incentivised to pass their midterm and end-of-year examinations for the duration of the study. In order to receive the cash incentive, learners were required to pass the examination with an average mark of at least 50 %.
- ***Voluntary uptake of Annual HIV testing services***: All learners were provided with the information on the knowledge of HIV status through regular testing and to access these services through all primary healthcare clinics in the districts and through several organisations that had been funded to provide these services in the community. Learners were required to provide the receipt from the clinic or the organisation that specified that the learner had taken an HIV test and received the results of the test. The class teacher received and maintained the records of the test results so that the learners could receive the cash incentive at each quarter on achieving this milestone.

Learners in the cash-linked RHIVA intervention school received R200 for having an annual HIV test, R50 every quarter for participating in 80 % of My Life My Future sessions, R150 for achieving a 50 % grade in each of the mid- and year-end academic assessments and R200 for the completion of a portfolio which includes implementing a business project in their community. Thus learners in intervention schools who met all of the conditionalities over the two-year period could receive a maximum of R1750.

3.1.2 The Control Arm

All eligibly enrolled learners in the control schools received the package of prevention programme as outlined for the intervention arm and delivered in the same manner except they received no cash for achieving the key milestones.

3.1.3 Baseline Characteristics

The total Grades 9 and 10 school learner population in the 14 schools sampled was 3781. In 2010, a total of 2675 (70.7 %) learners were enrolled. Of these, 1423 (53.2 %) were females and 1252 (46.8 %) were males. In 2011, a further 542 learners were enrolled of which 277 (51.1 %) were females and 265 (48.9 %) were males, with a total of 3217 of the 3781 learners enrolled (85 %).

Table 2 Baseline HIV and HSV-2 prevalence in high school students by age and sex

Age group (years)	Prevalence of HIV infection % (95 % confidence interval)		Prevalence of HSV-2 infection % (95 % confidence interval)	
	Male (1252)	Female (1423)	Male (1252)	Female (1423)
≤15	1.0	2.6	0.7	3.5
16–17	1.1	6.1	2.0	9.3
18–19	1.5	13.6	6.6	30.2
>20	1.8	24.7	3.5	43.3

Source Adapted from Abdool Karim et al. [15]

At baseline, 70.7 % learners provided consent or assent with parent/guardian or caregiver consent. The most common reason for non-enrolment was parental refusal of consent (653/1106, 59.0 %) with a small proportion of learners having insufficient cognitive ability to provide consent/assent (2/1106, 0.2 %). At follow-up, all 542 provided consent or assent with parental/guardian consent.

The baseline bio-behavioural assessments highlighted the risk of HIV and Herpes simplex-2 (HSV-2) infections amongst young people as well as the difference of risk per gender (Table 2). Factors associated with a higher prevalence of HSV-2 for female learners included being older than 18 years (aOR = 3.20, 95 % CI 2.33–4.38; $p < 0.001$), HIV-positive serostatus (aOR = 4.34,95 % CI 2.64–7.13; $p < 0.001$), previous pregnancy (aOR = 2.52, 95 % CI 1.58–4.03; $p < 0.001$), experience of or threat of violence for sex (aOR = 1.95, 95 % CI 1.30–2.95; $p = 0.001$) and living in a female-headed household (aOR = 1.68, 95 % CI 1.02–2.75; $p = 0.041$). Multivariate analysis indicated that experience of an adult death in the household (aOR = 1.36, 95 % CI 1.02–1.81; $p = 0.036$) was associated with increased risk of HSV-2 and an increase of risk of pregnancy in female learners (aOR = 2.27, 95 % CI 1.22–4.23; $p = 0.010$) [14].

4 Challenges and Lessons Learned

4.1 Challenges with Parental Consent

Ethical considerations are paramount when engaging adolescents. The need to protect them from possible exploitation was critical, but also created obstacles for undertaking research in this key vulnerable group. Obtaining informed consent for trial participation was confounded by four key factors:

- The high prevalence of child-headed households,
- Parent/legal guardians or caregivers were not easily accessible as many worked and were often away from home for extended period of time,
- Lack of formal establishment of guardianship, and
- Low levels of education or literacy in consenting adult parents/guardians or caregivers.

These factors played a key role in obtaining consent such that those who were considered to be most vulnerable were not able to participate in the study due to low levels of legal guardianship within the community. After extensive discussions with the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal (Federal-Wide Assurance number 678), it was agreed that the inclusion of this group of learners could potentially be beneficial. Therefore, the CAPRISA 007 trial was tasked with seeking surrogate parental consent when enrolling such individuals; to also waiver parental consent where a prospective participant did not wish to disclose trial participation, but only when the learner was deemed to have the cognitive ability to understand and was capable of consenting individually.

To overcome the absences of legal guardians, school research support groups (SRSGs) were established and permitted to (1) provide 'proxy' consent for a learner participating in the trial, (2) verify guardianship, and (3) oversee the comprehension assessments designed to establish literacy and comprehension prior to consent. SRSGs consisted of a body of community and parent representatives and included members from churches, women's groups, school governing body and community members. The SRSG members were trained on the study protocol and played a key role in being the intermediaries and successfully facilitating enrolment procedures for 23.9 % of assenting learners younger than 18 years.

4.2 Poor Literacy and Numeracy Skills

During the implementation of the CAPRISA 007 trial we found poor literacy and numeracy skills. The low levels of literacy and numeracy skills impacted the self-completed questionnaires, and the study had to move to a staff-guided method of completion, where staff read out the questions and were available to answer questions. In addition, for informed consent, a comprehension and literacy assessment tool was developed and implemented prior to the informed consent process in order to assess literacy, comprehension and to establish the need for a witness.

4.3 Importance of Meaningful Stakeholder Engagement

Stakeholder engagement plays a vital role in the process of research in communities. Ongoing updates were conducted during the CAPRISA 007 study. Stakeholders including the Department of Education, school managers and staff, facilities' managers of the Department of Health, community leadership, both traditional and democratically elected, school governing bodies (SGB) and learners' representatives were all regularly debriefed on the status of the study. Study updates to stakeholders were done at monthly and quarterly community and parents

meetings in each participating school. These sessions were also used as a platform to discuss challenges and possible solutions. Working with the Department of Health enabled easier referral for learner HIV testing. This process of regular feedback assisted in the identification of challenges and allowed open and mutually transparent communication between multiple stakeholders, essential for such a complex intervention that hinges on multi-stakeholder partnership co-operation.

4.4 Identifying the Need for Adolescent Sexual Reproductive Health Services

The implementation of the trial highlighted the need for adolescent friendly sexual reproductive health (SRH) services. We learned that adolescent girls had difficulty accessing SRH services, including knowing the people who work there, being shouted at by clinic staff, feelings of a lack of confidentiality, and long waiting times. It was evident from the conduct of the study that young women were sexually active and that a more nuanced approach to service provision was needed. CAPRISA has since piloted a mobile SRH service in several schools in the district, achieving high uptake of SRH services by schoolgirls using an innovative peer-led model.

5 Conclusion

To have an impact on the HIV pandemic, HIV prevention efforts have to include adolescent girls. The inclusion of adolescent boys is important for establishing positive gender norms at an early stage and whilst their HIV risk is low. The CAPRISA 007 trial, an open-label matched pair cluster randomised controlled trial was an important study for CAPRISA as it was the first large scale structural intervention evaluated by the organisation. It highlighted the complexities of undertaking a multi-component intervention in an under-resourced, high HIV burden district. An important consideration for conducting multi-component intervention studies is that pathways of risk remain complex and multi-faceted, and so the selection of conditionalities should be informed by a strong theoretical background, a strong knowledge of the epidemiology of the study context and incentives should focus on behaviours with clear links to HIV and that are within the students control.

The evidence and lessons learned from the CAPRISA 007 study may be useful to interventionists, researchers and policy-makers interested in understanding how incentivised, multi-component prevention interventions can be designed for adolescent populations.

References

1. Abdool Karim Q, Abdool Karim SS, Singh B, Short R, Ngxongo S. Seroprevalence of HIV infection in rural South Africa. AIDS. 1992; 6: 1535–9.
2. Gregson S, Nyamukapa CA, Garnett GP, Mason PR, Zhuwau T, Carael M, et al. Sexual mixing patterns and sex-differentials in teenage exposure to HIV infection in rural Zimbabwe. Lancet. 2002; 359(9321): 1896–903.
3. Pettifor AE, Rees HV, Kleinschmidt I, Steffenson AE, MacPhail C, Hlongwa-Madikizela L, et al. Young people's sexual health in South Africa: HIV prevalence and sexual behaviors from a nationally representative household survey. AIDS. 2005; 19(14): 1525–34.
4. UNAIDS. The gap report. Available from: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2014/UNAIDS_Gap_report_en.pdf [Accessed: 16 OCtober 2014]. Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS (UNAIDS); 2014.
5. Department of Health. The 2013 National Antenatal Sentinel HIV Prevalence Survey South Africa. Pretoria: Department of Health; 2015.
6. Abdool Karim Q, Kharsany AB, Frohlich JA, Werner L, Mlotshwa M, Madlala BT, et al. HIV incidence in young girls in KwaZulu-Natal, South Africa–public health imperative for their inclusion in HIV biomedical intervention trials. AIDS Behav. 2012; 16(7): 1870–6.
7. Kharsany AB, Frohlich JA, Yende-Zuma N, Mahlase G, Samsunder N, Dellar RC, et al. Trends in HIV Prevalence in Pregnant Women in Rural South Africa. J Acquir Immune Defic Syndr. 2015; 70(3): 289–95.
8. Cowan FM, Pascoe SJS, Langhaug LF, Mavhu W, Chidiya S, Jaffar S, et al. The Regai Dzive Shiri project: results of a randomized trial of an HIV prevention intervention for youth. AIDS. 2010; 24(16): 2533–44.
9. Ross DA, Changalucha J, Obasi AI, Todd J, Plummer ML, Cleophas-Mazige B, et al. Biological and behavioural impact of an adolescent sexual health intervention in Tanzania: a community-randomized trial. AIDS. 2007; 21(14): 1943–55.
10. Doyle AM, Ross DA, Maganja K, Baisley K, Masesa C, Andreasen A, et al. Long-term biological and behavioural impact of an adolescent sexual health intervention in Tanzania: follow-up survey of the community-based MEMA kwa Vijana Trial. PLoS Medicine. 2010; 7 (6): e1000287.
11. Baird SJ, Garfein RS, McIntosh CT, Ozler B. Effect of a cash transfer programme for schooling on prevalence of HIV and herpes simplex type 2 in Malawi: a cluster randomised trial. Lancet. 2012; 379(9823): 1320–9.
12. de Walque D, Dow WH, Nathan R, Abdul R, Abilahi F, Gong E, et al. Incentivising safe sex: a randomised trial of conditional cash transfers for HIV and sexually transmitted infection prevention in rural Tanzania. BMJ Open. 2012; 2: e000747.
13. Michielsen K, Chersich MF, Luchters S, De Koker P, Van Rossem R, Temmerman M. Effectiveness of HIV prevention for youth in sub-Saharan Africa: systematic review and meta-analysis of randomized and nonrandomized trials. AIDS. 2010; 24(8): 1193–202.
14. Abdool Karim Q, Kharsany ABM, Leask K, Ntombela F, Humphries H, Frohlich JA, et al. Prevalence of HIV, HSV-2 and pregnancy among high school students in rural KwaZulu-Natal, South Africa: a bio-behavioural cross-sectional survey. Sexually Transmitted Infections. 2014; 90(8):620–6.
15. Abdool Karim Q, Leask K, Kharsany A, Humphries H, Ntombela F, Samsunder N, et al. Impact of conditional cash incentives on HSV-2 and HIV prevention in rural South African high school students: results of the CAPRISA 007 cluster randomized controlled trial [Abstract TUAC0101LB]. Eighth International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention. Vancouver; 2015.

Chapter 7
HIV Vaccine and Passive Immunity Trials

Nigel Garrett, Kathryn Mngadi, Nivashnee Naicker and Lynn Morris

1 Background

Despite a trend of declining HIV incidence rates in many countries since 2005, UNAIDS estimates that worldwide up to 2 million people become newly infected with HIV each year [1]. While the increasing armamentarium of HIV prevention interventions is creating optimism for epidemic control, i.e. when new HIV infections and morbidity and mortality rates no longer pose a public health threat, safe and effective vaccines are needed to eliminate HIV. Mathematical modelling data have shown that an effective vaccine with broad coverage against circulating viruses could prevent more than 20 million infections by 2030. Importantly, the research showed that even a vaccine with low efficacy and limited coverage could play a crucial role in containing the epidemic (Fig. 1) [2, 3].

Advances in understanding HIV pathogenesis and the human immune system over the past three decades, continue to contribute to HIV vaccine development. However, several unique challenges remain. First, HIV attacks CD4+ T-cells, the very cells that orchestrate the immune system to combat intruding microbes. Second, this retrovirus continuously mutates and recombines resulting in an extensive diversity of viral strains. For a vaccine to be effective at a global level, it would have to protect against a large number of evolving and diverse strains of HIV. Third, there is not a single known case of an HIV positive person naturally

N. Garrett (✉) · K. Mngadi · N. Naicker · L. Morris
Centre for the AIDS Programme of Research in South Africa,
University of KwaZulu-Natal, Durban, South Africa
e-mail: Nigel.garrett@caprisa.org

L. Morris
Center for HIV and STIs, National Institute for Communicable Diseases,
Johannesburg, South Africa

Q. Abdool Karim et al. (eds.), *The CAPRISA Clinical Trials: HIV Treatment and Prevention*, DOI 10.1007/978-3-319-47518-9_7

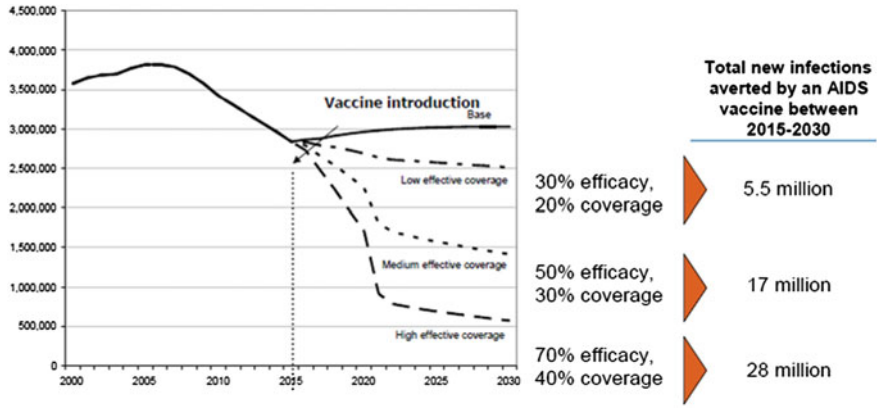

Fig. 1 The potential impact of an AIDS Vaccine

clearing the infection, which would enable scientists to study potential correlates of protection. The RV144 trial that demonstrated partial efficacy [4] has provided some new clues on what immune responses may be required and once better defined, will inform new immunogen designs that could accelerate the path to an effective vaccine.

The quest for a HIV vaccine started soon after the first cases of AIDS were reported in 1981. This evolving field has experienced many disappointments and some rare successes, underscoring the complex challenges in finding a safe and efficacious product. Early efforts focused on experiences in developing vaccines for other viral infections and included the use of attenuated forms of the virus; vector-based products; protein-based and nucleic acid-based vaccines. The initial focus on simple viral proteins to elicit an antibody response, not surprisingly with hindsight, had limited success. The focus then turned to vector-based products and eliciting an effective cellular immune response by stimulating anti-HIV CD8+ T-cells. The STEP/Phambili, AIDSVAX, and the HIV Vaccine Trials Network (HVTN) 505 trials [5–7] revealed in 2008, that cellular vaccine development would not be straightforward. In 2009, the RV144 trial demonstrated modest (31 %) preventive efficacy for an HIV vaccine regimen comprising ALVAC-HIV (vCP1521) and clade B/E gp120 Env protein (AIDSVAX B/E) in Thai volunteers, and while there was a lukewarm response to the initial findings, subsequent subgroup analysis of the data re-energised the vaccine field. Significantly, for the first time, correlates of protection in a study in humans were identified. The presence of IgG antibodies against the V1V2 region of the envelope offered protection, while plasma Env-specific binding IgA antibodies correlated with higher infection rates. These remarkable findings led to a strengthening of the HIV vaccine effort with scientists, governments, pharmaceutical companies, funders and community groups all joining to form the Pox-Protein Public-Private Partnership (P5) partnership, one of the most ambitious vaccine initiatives in history. A host of studies is

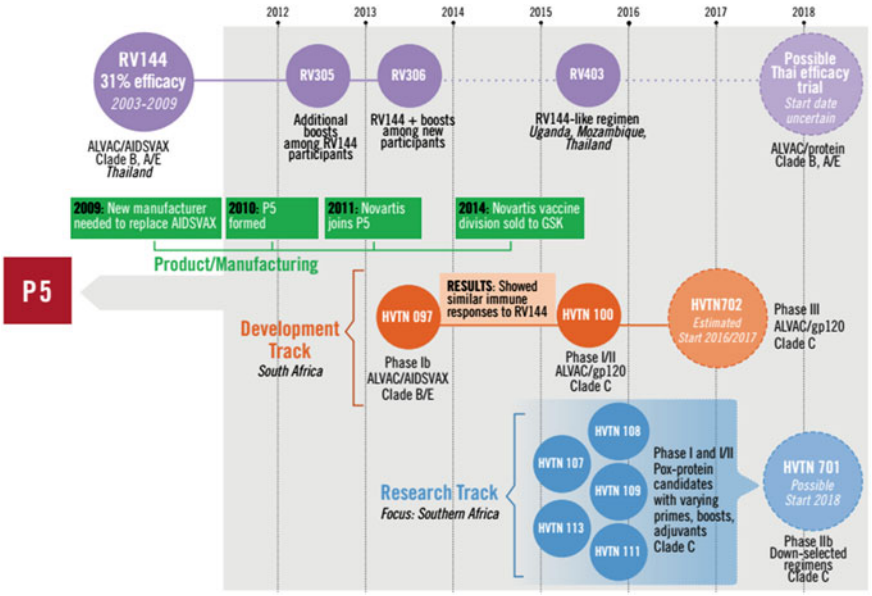

Fig. 2 Pox-Protein Public-Private Partnership (P5) partnership Vaccine Programme. *Source* http://www.avac.org reproduced with permission from AVAC

already underway or is about to be launched to improve on the RV144 results (Fig. 2). The discovery of broadly neutralising antibodies and protective antibodies found in the RV144 trial have now led to a consensus that an effective HIV vaccine would have to elicit both a strong humoral and cellular response.

In this chapter, we review CAPRISA's contribution to the clinical evaluation of HIV vaccine products over the past decade. We summarise CAPRISA's participation in the NIH-funded Phambili trial, the first phase IIB HIV vaccine study conducted in sub-Saharan Africa, and lessons learnt during its premature closure. We also discuss ongoing Vanguard vaccine studies underway at CAPRISA that will inform the next generation of efficacy trials. We conclude with a synopsis of CAPRISA's contributions to passive immunisation studies that could also inform vaccine development efforts.

2 Phase IIB Safety and Efficacy Trial: The HVTN 503 'Phambili' Study Experience

The HVTN 503 'Phambili' study (ClinicalTrials.gov, number NCT00413725) was the first vaccine efficacy trial undertaken in South Africa at the peak of the HIV/AIDS epidemic [6, 8, 9]. The trial was led by Dr. Glenda Gray in South Africa

and included the Perinatal Health Research Unit in Soweto, the Aurum Institute in Klerksdorp, the Desmond Tutu HIV Centre in Cape Town, the Medical University of Southern Africa (MEDUNSA) in Pretoria and CAPRISA in Durban. The prospect of a vaccine brought new hope of curbing HIV infections in the local South African HIV-1 clade C, high incidence, resource constrained setting. The trial was initiated in 2007 but was stopped early due to futility shown in the sister STEP trial. However, it provided an opportunity for many lessons to be gleaned on the conduct of vaccine clinical trials at the CAPRISA Research Clinic.

The trial was a phase IIB randomised placebo-controlled test-of-concept study of the MRKAd5 HIV-1 gag/pol/nef (Merck, Kenilworth, NJ, US) clade B-based 3-dose vaccine regimen that enrolled healthy, HIV-1 uninfected, sexually active volunteers aged between 18 and 35 years (Panel 1). Enrollment began on 24 January 2007 with 801 participants enrolled at all sites by 19 September 2007. The trial was prematurely halted [6] subsequent to the first interim efficacy analysis of the STEP trial of the same vaccine being tested in clade B populations in North and South America, the Caribbean and Australia, which showed futility overall and possible harm amongst a subgroup of male vaccine recipients with immunity to the adenovirus type 5 (Ad5) and those who were uncircumcised [5]. Consequently, further enrollments and vaccinations in the Phambili trial were immediately stopped at all sites in South Africa and participants were unblinded to product allocation and continued extended safety follow-up under a modified protocol (HVTN 503S) [8]. Primary analysis of the Phambili trial showed no evidence of vaccine efficacy [6]. Longer term follow-up of trial participants showed that a significantly higher number of vaccine recipients acquired HIV infection compared to placebo recipients, irrespective of the number of vaccinations received, gender, circumcision status or Ad5 serostatus [8]. In 2013, the HVTN 503S follow-up study recalled participants who tested HIV negative at HVTN 503 study exit to assess whether differences in risk behaviour or differential loss to follow up of placebo recipients could explain the higher rates of HIV infection observed among vaccinees; however, no differences were observed [8, 10]. Underlying immune activation due to Ad5 was hypothesised to be the reason for the increased risk and the HVTN decided not to use this vector in its vaccine development portfolio again.

At the CAPRISA eThekwini site, 53 volunteers met eligibility criteria and were enrolled into the Phambili study between July and September 2007. Participants were recruited from local sexually transmitted infection (STI) clinics, HIV testing centres, colleges and the general community. Following unblinding of the Phambili trial, participants were followed up quarterly. Two participants were subsequently lost to follow up and one withdrew consent, with the remaining 50 participants continuing follow-up until 2011. Participants who acquired HIV in the study were enrolled into the HVTN 802 protocol. The HVTN 503S sub-study followed up 22 of the 53 participants originally enrolled. Here, we discuss some of the operational and clinical challenges in undertaking a vaccine trial at our research site.

Panel 1 HVTN 503 Phambili study schema

Purpose:	To determine the safety, efficacy and tolerability of a three-dose regimen of an adenovirus-based HIV-1 vaccine in healthy South African adults
Study design:	A Multicenter Double-Blind Randomized Placebo-Controlled Phase IIB Test-of-Concept Study
Study population:	HIV negative men and women aged 18–35 years
Study duration:	This study will last about 42 months for HIV-uninfected participants; for those who become HIV infected, visits continue for 18 months after diagnosis
Study intervention:	Participants will be randomly assigned to receive three doses of either the MRKAd5 HIV-1 vaccine or placebo
Sample size:	3000 participants (study was halted early and 801 participants were enrolled in total)
Study procedures:	Participants will be randomly assigned to receive three doses of either vaccine or placebo. All participants will receive their injections at study entry and at Months 1 and 6. Participants will be asked to complete a post-vaccination symptom log for the 3 days following each vaccination to monitor body temperature and symptoms known to be associated with the vaccine. At all study visits, participants will be asked about any adverse events they may have experienced. There will be at least 14 study visits over the first 4 years of the study. A physical exam, medication history, risk reduction counselling and blood collection will occur at every visit. Participants will be asked to complete a social impact questionnaire at Weeks 12, 78 and 208; an outside testing and belief questionnaire at Weeks 30, 78, 130, 182 and 208; and a circumcision status assessment at Week 208. Participants will undergo HIV testing to check their HIV status approximately every 3 months Participants who become HIV infected during the study will have eight study visits at Weeks 4, 8, 12, 16, 20, 26, 52 and 78 post-diagnosis. A physical exam, risk reduction counselling, blood and urine collection and a pregnancy test will occur at all visits. Genital secretion collection may also occur at some visits. Participants who become HIV infected and need to begin anti-HIV therapy will be discontinued from this study, but encouraged to enroll in the HVTN 802 study
Primary outcome measures:	• Acquisition of HIV-1 infection • Viral load set point (HIV-1 RNA) in study participants who become HIV infected
Secondary outcome measures:	• Acquisition of HIV-1 infection among participants with baseline Ad5 neutralizing antibody titers of 200 or less • Viral load setpoint in such study participants • Durability of effect of vaccine on suppression of HIV-1 viral RNA and preservation of CD4 counts • One time questionnaire evaluating impact of discontinuation of vaccination on participants
Study sites:	Soweto HVTN Clinical Research Site (CRS), Johannesburg, Gauteng, MedCRU CRS, Pretoria, Gauteng, eThekwini CRS, Durban, KwaZulu-Natal, Emavundleni CRS, Cape Town, Western Cape Province, CAPRISA Aurum CRS, Klerksdorp

2.1 Lessons Learnt in the Conduct of the Phambili Trial and HVTN 503S Follow-on Study

Assembling the study team
Conducting an intended large-scale, multicenter vaccine trial required, as with other clinical trials, the assembly of a large multidisciplinary study team. In addition, the study team needed to undergo intensive protocol specific training. Prior to study start, the site was evaluated by study sponsors for site preparedness for the conduct of the trial. Appropriate staffing, training, pharmacy and laboratory infrastructure were some of the areas assessed for site preparedness for study implementation.

Regulatory Oversight
All studies of investigational products require review and approval from the local ethics committee and the South African Medicines Control Council prior to study start. The timeline for these reviews is unpredictable. An additional unanticipated delay of a vaccine import permit until May 2007 further delayed enrollment at the site.

Community engagement
Given the limited clinical trial participation experience in the most affected communities in our setting, community engagement and buy-in was critical to ensure that study participation was informed and voluntary. Additionally, HIV vaccine research was a relatively new concept in South Africa at the time. The team drew on experiences within CAPRISA in the conduct of other prevention and treatment trials to engage and educate the community on the purpose and value of vaccine research. This was done largely through the existing CAPRISA community advisory board (CAB), which comprised of representatives from various non-governmental organisations, religious leaders and community members, who met regularly to receive updates on ongoing and proposed research at CAPRISA. The CAB also provided feedback and input to and from the community. The community engagement activities extended to utilising the opportunity of sporting events and other HIV prevention campaigns within the community.

Breakthrough infections and access to care
A key reason for HIV prevention trials being undertaken in sub-Saharan Africa is the high incidence rates enabling studies to be undertaken very efficiently. Sites have an ethical obligation to provide information and access to known HIV prevention options prior to study enrollment and during follow-up study visits. Notwithstanding continued access to risk reduction counselling, which included condom provision and male medical circumcision, participants continued to acquire HIV infection during safety follow-up in the trial, underscoring the limitations of the current prevention options, the high risk of HIV acquisition in this setting, and the need for better prevention technologies. With seroconversion and breakthrough infections there is a need for ongoing access to care. At the time of the Phambili study, the public sector health facilities had begun their antiretroviral treatment

programmes. HIV-infected participants from the Phambili trial also had the option to access care, including ARV treatment, at the PEPFAR-funded CAPRISA AIDS treatment programme. Antiretroviral treatment initiation was based on prevailing HIV treatment guidelines being utilised in public sector health facilities.

Vaccine induced seropositivity

A unique challenge in the conduct of HIV vaccine trials is that of vaccine induced seropositivity (VISP), wherein participants who are assigned to the vaccine arm, test HIV positive on routine rapid antibody HIV tests if they develop antibodies to the vaccine being evaluated. The development of VISP also has implications for inadvertent unblinding of study participants who are assigned to the vaccine arm during the trial. In the Phambili trial once vaccinations were stopped, participants were unblinded, thus inadvertent unblinding was no longer a problem. At our site, 50 % of vaccine recipients developed VISP. Participants were rigorously counselled in this regard to avoid testing for HIV at outside health facilities. A long-term option of testing was made available to all participants affected by VISP following unblinding through the use of a VISP registry, which ensured that participants would have access to HIV testing at the HVTN site or appropriate facility long after the trial had ended. In the HVTN 503S study, the majority of participants who had initially tested positive for VISP at our site did not have VISP at their return visit. A particular concern with VISP may be that participants are mistakenly started on antiretroviral therapy, for example, when accessing antenatal care, and the potential for social harm given the high levels of stigma and discrimination experienced by HIV-infected persons in the workplace and community.

Co-enrollment into multiple studies

With time, we discovered that a proportion of trial participants was co-enrolled in other clinical trials at other research organisations in Durban. This problem was not unique to the Phambili study and measures were subsequently implemented to screen participants for co-enrollment prior to enrolment into new studies (see Chap. 4 for further details). Through the use of shared databases across clinical research organisations, participants are now assessed for co-enrollment into other studies by fingerprint scanning and by their South African identification number prior to joining a study.

Changing prevention landscape during trial and implications for standard of care

Following the results of three randomised controlled trials [11–13], undertaken in sub-Saharan Africa, which determined that male circumcision reduced HIV acquisition in men by 50–60 %, male medical circumcision (MMC) was offered to all male participants enrolled in the Phambili trial as part of risk reduction counselling, at a time when MMC was not routinely accessible at public health facilities. The uptake of circumcision in a traditionally non-circumcising region of South Africa was high with 79 % (22/28) uncircumcised male participants undergoing MMC, at a designated private service provider. The CAPRISA eThekwini site

contributed to almost 16 % of all post-enrollment circumcisions in Phambili, with the majority occurring prior to unblinding [10].

Despite the early closure of the Phambili trial, many important lessons were learnt about the conduct of vaccine trials in our setting that paved the way for CAPRISA to undertake current vaccine studies with the necessary research infrastructure and staff capacity in place. An important consideration for undertaking vaccine and other prevention trials is the need for long-term follow-up and care of trial participants who acquire HIV infection during the study. Specific to vaccine trials is the ongoing support for participants who acquire VISP.

3 Vanguard (Phase I/IIA) Vaccine Trials Underway at Caprisa

3.1 The HVTN 100 Trial

The P5 partnership developed a suite of clinical trials to deepen understanding of the mechanism of protection offered by RV144 and ultimately to develop a licensable product appropriate to regions with significant HIV burden (Fig. 2). HVTN 100 is a phase I/IIA randomised, double-blind, placebo-controlled clinical trial of clade C ALVAC-HIV (vCP2438) and Bivalent Subtype C gp120/MF59® in HIV-uninfected adults at low risk of HIV infection. The vaccine design and vaccination schedule for HVTN 100 were altered from the RV144 vaccine candidate with the aim of improving the magnitude and duration of vaccine-elicited immune responses, and to make the vaccine clade-specific to South Africa, hence the change in adjuvant (MF59 for alum), the addition of a 12 month protein boost, and the use of HIV inserts and proteins specific to clade C (Fig. 3).

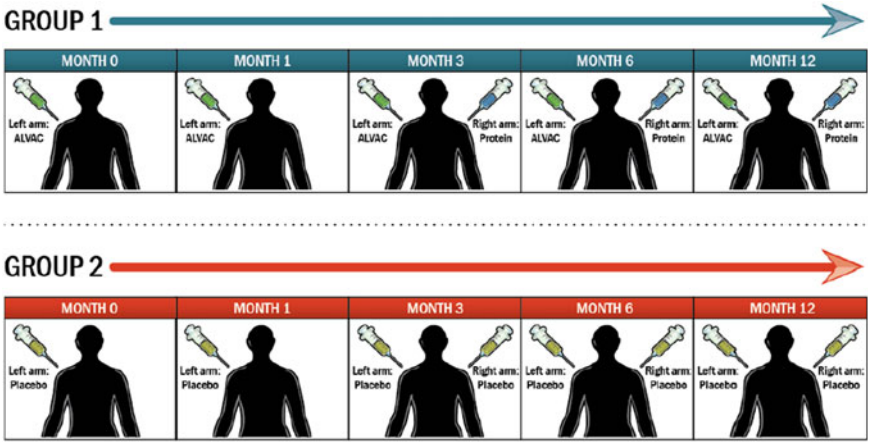

Fig. 3 Vaccination schedule in HVTN 100

HVTN 100 was preceded by HVTN 097 which tested the exact same regimen as the RV144 trial in a South African cohort of 100 participants due to a concern about the higher body mass index (BMI) of South Africans compared to the Thai population that could impact immunogenicity. To address the higher BMI, longer needles were used for vaccine administration for participants weighing over 90 kg to ensure that the vaccine was delivered intramuscularly. Preliminary results from HVTN 097 presented in October 2014 at the R4P Conference in Cape Town demonstrated equivalent immunogenicity in the South African cohort and in some cases better than that of the Thai cohort.

Preparations for HVTN 100 began in late 2014, with budget development and regulatory submissions. Staff from an existing CAPRISA microbicide implementation trial that was closing out was transitioned into HVTN 100. Community engagement and educational activities, CAB information sessions, development of regulatory files including standard operating procedures, source documentation and logs were undertaken in the run up to study activation. Key staff members attended protocol training in Durban together with staff from the five other South African sites, sharing experience and best practise, and providing support where possible. Between February and May 2015, 44 eligible participants were enrolled, exceeding the site allocated slots for the accrual period. To date, no serious adverse events related to study product have been reported, with one termination for a local reactogenicity reaction that recurred with subsequent vaccination. All other reactions have been mild to moderate and self-limiting. Two participants have been transferred to other sites when they relocated for employment opportunities; one of whom has since returned. Two other participants have been terminated: one based on PI discretion and one for loss to follow-up following relocation to a city that did not have a HVTN site conducting HVTN 100.

3.2 Lessons Learnt in Undertaking Vanguard Studies

Recruiting participants at low risk of acquiring HIV in a high HIV burden setting

A challenge in the conduct of Phase I studies in a high HIV disease burden setting is the recruitment of low-risk individuals. A new challenge for the CAPRISA site was the recruitment of male volunteers, given that the majority of CAPRISA's HIV prevention research had focused on women at high risk for acquiring HIV infection. Drawing on prior experience of risk assessment, the CAPRISA vaccine team developed a pre-screening protocol to assist with the identification of lower risk individuals that included the study specific inclusion/exclusion criteria and retention potential to minimise early withdrawal of enrolled participants or enrolment of participants who did not fully appreciate the longer term commitment needed in cohort studies and randomised controlled trials. Male involvement programmes developed for microbicide trials and HIV testing campaigns at tertiary institutions

were used to forge relationships with younger males <25 years who, based on epidemiological data, are known to be at lower risk. Older married women are another lower risk population targeted for education and recruitment. In summary, when recruiting low-risk participants in a high risk setting it is advisable to understand the local epidemic with all its nuances, and to consider use of additional tools such as a pre-screening protocol to target the right participants in the right risk category.

Retaining highly trained staff in between trials to ensure high quality study conduct

Maintaining a critical mass of experienced clinical trial staff is challenging when there are long gaps between trials. Extended gaps between trials reduces staff morale and motivation and often the best staff leave to seek other opportunities. Recruiting new and inexperienced staff requires more intense and frequent study monitoring to ensure high quality of study conduct. It is important to identify gaps in quality and to address these timeously. Root cause analysis by experienced senior staff and reaching out to other experienced sites and sharing best practise, goes a long way to pre-emptively address corrective and preventive action.

3.3 The HIV-V-A004 'APPROACH' Study

The HIV-V-A004 'APPROACH' study, sponsored by JANSSEN, a subdivision of the pharmaceutical company Johnson & Johnson is the first pharmaceutical industry study being undertaken by CAPRISA. It is an ongoing phase I/IIA study to evaluate the safety, tolerability and immunogenicity of Adenovirus 26 or Modified Vaccinia Ankara (MVA) vectored mosaic vaccine regimens with or without a clade C gp140 protein boost.

CAPRISA's participation in this study emanated from a long-standing collaboration with Dr. Dan Barouch and other scientists from the Ragon Institute at Harvard University and Massachusetts Institute of Technology in Boston who spearheaded the development of this vaccine. The ability to design so-called mosaic inserts that include components from different HIV subtypes, meant that this vaccine, if proven effective, could have a maximum global impact (Fig. 4). Dr. Barouch's non-human primate studies showed that prime-boost with vectors with mosaic inserts elicited protective immunity in stringent Simian Human Immunodeficiency Virus (SHIV) challenge models. Regimens with either of the two vectors reached up to 90 % per-exposure risk reduction at 1 year despite of the monkeys only receiving two vaccinations [14].

This multi-site study in low HIV risk individuals is being undertaken in the USA, South Africa, East Africa and Thailand. Enrollment in the US sites was initiated in February 2015 and in the non-US sites in July 2015. CAPRISA is contributing 29 of the 393 participants enrolled in this study and most participants have now received at least three of the four required vaccinations. A similar

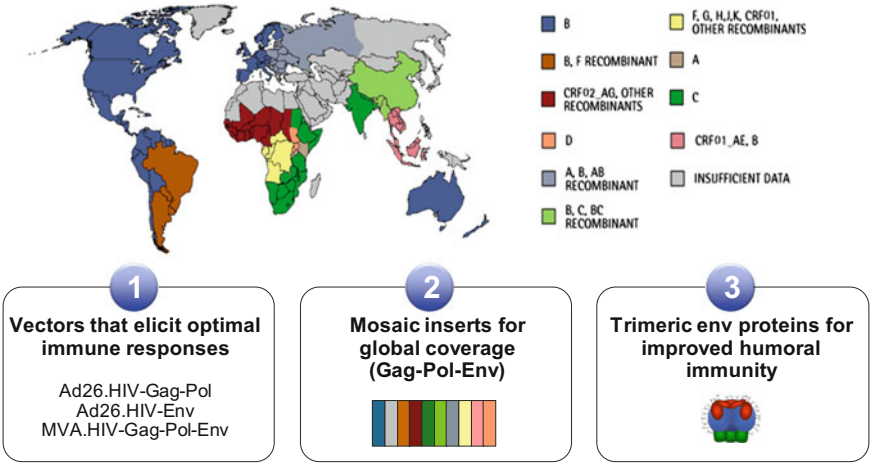

Fig. 4 Mosaic Vaccine components of the HIV-V-A004 trial. *Source* Reproduced with permission from Janssen Pharmaceuticals

approach to that used in HVTN 100 viz a pre-screening protocol was utilised to identify volunteers at lower risk of HIV infection. HIV-uninfected volunteers with no or only one partner in the previous year, and who were committed to using condoms consistently, were invited for screening, which included STI testing. In order to facilitate screening procedures, the CAPRISA team successfully piloted point-of-care STI testing using the GeneXpert® CT/NG (Cepheid, Sunnydale, CA, US) and OSOM® Rapid Trich (Sekisui Diagnostics, Lexington, MA, US) assays. This allowed for the rapid detection of screen failures, thereby avoiding costly procedures, and reducing unnecessary waiting times for participants.

A novel aspect of this study was the use of a web-based electronic data collection system, Medidata Rave® (Medidata, New York, US), in contrast to the hard copy case report form (CRF) and datafaxing system used to date in all the trials conducted at CAPRISA. This system enabled more rapid data capture, improved data quality through real-time monitoring and rapid communication with the sponsor's quality control team to resolve queries. It also assisted with generating financial reports.

4 Passive Immunisation Studies

The discovery and ability to manufacture large quantities of broad and potent antibodies isolated from HIV-infected individuals in the laboratory have opened up the possibility of using passive immunotherapy for HIV prevention. Unlike active immunisation, where the human immune system is stimulated to produce antibodies,

passive immunisation is the administration of pre-formed antibodies into the body. Animal studies have shown that HIV-specific broadly neutralising antibodies can prevent acquisition, but this important finding is yet to be corroborated in humans. Such evidence will not only provide important proof-of-concept that neutralising antibodies are an essential component of an HIV vaccine, but will also reveal the levels and frequency of antibody administration required for protection.

The first efficacy trial of a broadly neutralising antibody for HIV prevention, the HVTN 703 or AMP (antibody-mediated protection) study started enrolling participants in the USA and Africa in 2016. It uses an antibody called VRC01 that targets the CD4 binding site on the HIV envelope glycoprotein [15]. Since this antibody blocks a key step in the infection process it is active against the vast majority of global viruses, including those circulating in South Africa. VRC01 has already been shown to be safe in humans and to prevent mucosal transmission of simian immunodeficiency virus (SIV) in monkeys [16, 17].

The AMP trial will enroll 3900 participants globally, 2400 men who have sex with men and transgender subjects in North and South America, and 1500 healthy HIV negative women who are at high risk of HIV infection in sub-Saharan Africa. Participants will receive intravenous infusions of antibodies every 2 months for 20 months. In Africa, this randomised controlled trial will split women into three groups; 500 participants each will receive a high dose, a lower dose of VRC01 or placebo. The volunteers will be studied for over 2 years and monitored for HIV infection as an end point.

Both the CAPRISA eThekwini and Vulindlela Clinical Research sites are participating in this joint HVTN/HIV Prevention Trail Network (HPTN) protocol with each site contributing approximately 100 participants. The primary purpose of this trial is to evaluate the protective efficacy of an HIV neutralising antibody which will underscore the need for HIV vaccines to stimulate antibodies with broadly neutralising activity.

If VRC01 is shown to be efficacious, it will also open up the possibility of an additional prevention intervention for HIV-uninfected persons, similar to pre-exposure prophylaxis. Analogous to combination antiretroviral therapy for treatment, combinations of broadly neutralising antibodies could be prepared to enhance efficacy and longevity of protection. These could include amongst others PGT121, which targets the V3 glycan-rich epitope, as well as CAP256-VRC26.25.

The use of gene therapy is also currently being explored in the antibody field. In this technique, antibody genes are inserted into a vector which then becomes a local antibody-producing factory inside the body without the need for repeated injections.

As later discussed in Chap. 10, scientists at CAPRISA together with colleagues at the Vaccine Research Center isolated the broadly neutralising monoclonal antibody CAP256-VRC26.25 from the CAPRISA donor 256 [18, 19]. This antibody neutralises approximately 70 % of subtype C viruses and shows exceptional potency. A study designed to identify optimal combinations of 2, 3 or 4 broadly neutralising antibodies for the highest coverage always included CAP256-VRC26.25 [20]. In particular, combinations of two antibodies targeting the V3 glycan and the CD4 binding site neutralised 100 % of virus isolates. Importantly,

CAP256-VRC26.25 has been shown to protect monkeys from rectal challenge with a simianised HIV (Dan Barouch, personal communication) supporting clinical testing of this antibody in humans. As such, a large-scale manufacture of CAP256-VRC26.25.LS is underway with a development plan that is set to begin in mid-2017. The potency of CAP256-VRC26.25 favours the use of lower volumes of antibodies to reach an effective concentration. This may obviate the need for intravenous infusion allowing instead for a subcutaneous formulation which may be a more attractive delivery option. Currently, Phase I clinical trials using the antibodies VRC07-523.LS (that targets the CD4 binding site) and PGT121 (that targets the V3-glycan supersite) are in preparation.

5 Conclusions

Over the past decade, CAPRISA has been at the forefront of HIV prevention research and has made a significant contribution to HIV vaccine research. Much has been learned in the field of HIV Clade C pathogenesis through the CAPRISA 002 acute infection study (Chap. 10), not least the discovery of potent broadly neutralising antibodies. In partnership with HVTN and other sponsors, the CAPRISA vaccine team has garnered substantial experience in the conduct of early stage vaccine trials through to pivotal proof-of-concept studies and is well positioned as an important player in the vaccine development field in all stages of product development.

References

1. UNAIDS Factsheet 2015. Accessed 16 March 2016 at http://www.unaids.org/en/resources/campaigns/HowAIDSchangedeverything/factsheet.
2. Stover J, Bollinger L, Hecht R, Williams C, Roca E. The impact of an AIDS Vaccine in Developing Countries. Health Affairs 2007 Jul-Aug;26(4):1147–58.
3. Harmon TM, Fisher KA, McGlynn MG, Stover J, Warren MJ, Teng Y, Näveke A. Exploring the Potential Health Impact and Cost-Effectiveness of AIDS Vaccine within a Comprehensive HIV/AIDS Response in Low and Middle-Income Countries. PLoS One. 2016;11(1):e0146387.
4. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med. 2009;361(23):2209–20.
5. Buchbinder SP, Mehrotra DV, Duerr A, Fitzgerald DW, Mogg R, Li D, et al. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. *Lancet.* 2008;372(9653):1881–1893.
6. Gray GE, Allen M, Moodie Z, Churchyard G, Bekker LG, Nchabeleng M, et al. Safety and efficacy of the HVTN 503/Phambili study of a clade-B-based HIV-1 vaccine in South Africa: a double-blind, randomised, placebo-controlled test-of-concept phase 2b study. Lancet Infect Dis. Jul 2011;11(7):507–515.

7. Hammer SM, Sobieszczyk ME, Janes H, Karuna ST, Mulligan MJ, Grove D, et al. Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. N Engl J Med. 2013;369(22):2083–92.
8. Gray GE, Moodie Z, Metch B, Gilbert PB, Bekker L-G, Churchyard G, et al. The phase 2b HVTN 503/Phambili study test-of-concept HIV vaccine study, investigating a recombinant adenovirus type 5 HIV gag/pol/nef vaccine in South Africa: unblinded, long-term follow-up. Lancet Infect Dis. 2014; 14(5):388–396.
9. Gray GE, de Bruyn G, Slack C, Steel G, Williamson C. Preparing developing countries for efficacy trials. Curr Opin HIV AIDS. 2006;1(4):330–335.
10. Gray GE, Metch B, Churchyard G, Mlisana K, Nchabeleng M, Allen M, et al. Does participation in an HIV vaccine efficacy trial affect risk behaviour in South Africa? *Vaccine.* 2013;31(16):2089–2096.
11. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. PLoS Med. 2005;2(11):e298.
12. Bailey RC, Moses S, Parker CB, Agot K, Maclean I, Krieger JN, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet. 2007;369(9562):643–56.
13. Gray RH, Kigozi G, Serwadda D, Makumbi F, Watya S, Nalugoda F, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet. 2007;369 (9562):657–66.
14. Barouch DH, Stephenson KE, Borducchi EN, Smith K, Stanley K, McNally AG, et al. Protective efficacy of a global HIV-1 mosaic vaccine against heterologous SHIV challenges in rhesus monkeys. Cell. 2013;155(3):531–9.
15. Wu X, Yang ZY, Li Y, Hogerkorp CM, Schief WR, Seaman MS, et al. Rational design of envelope identifies broadly neutralizing human monoclonal antibodies to HIV-1. Science. 2010;329(5993):856–61.
16. Ledgerwood JE, Coates EE, Yamshchikov G, Saunders JG, Holman L, Enama ME, et al. Safety, pharmacokinetics and neutralization of the broadly neutralizing HIV-1 human monoclonal antibody VRC01 in healthy adults. Clin Exp Immunol. 2015;182(3):289–301.
17. Pegu A, Yang ZY, Boyington JC, Wu L, Ko SY, Schmidt SD, et al. Neutralizing antibodies to HIV-1 envelope protect more effectively in vivo than those to the CD4 receptor. Sci Transl Med. 2014;6(243):243ra88.
18. Doria-Rose NA, Schramm CA, Gorman J, Moore PL, Bhiman JN, DeKosky BJ, et al. Developmental pathway for potent V1V2-directed HIV-neutralizing antibodies. Nature. 2014 May 1;509(7498):55–62.
19. Doria-Rose NA, Bhiman JN, Roark RS, Schramm CA, Gorman J, Chuang GY, et al. New Member of the V1V2-Directed CAP256-VRC26 Lineage That Shows Increased Breadth and Exceptional Potency. J Virol. 2015;90(1):76–91.
20. Wagh K, Bhattacharya T, Williamson C, Robles A, Bayne M, Garrity J, et al. Optimal Combinations of Broadly Neutralizing Antibodies for Prevention and Treatment of HIV-1 Clade C Infection. PLoS Pathog. 2016;12(3):e1005520.

Part III
CAPRISA Clinical Trials for HIV–TB Treatment

Chapter 8
CAPRISA 003: Timing of Antiretroviral Initiation in HIV-TB Co-infected Patients—The SAPiT Trial

Nesri Padayatchi, Kogie Naidoo, Andy Gray, Salim S. Abdool Karim and Anneke Grobler

1 Background

1.1 Comprehensive International Program for Research on AIDS (CIPRA) and TB-HIV

The Centre for the AIDS Program of Research in South Africa (CAPRISA) and the CAPRISA eThekwini Research Clinic were established in 2002 under the CIPRA grant (described in detail in Chap. 2). From its inception, CAPRISA addressed a focused and strategic set of priorities based on the evolving HIV epidemic in South Africa and utilised the most appropriate but rigorous and robust approach to addressing these priority research areas.

This chapter will focus on CAPRISA's efforts to advancing understanding of treatment of HIV-TB co-infected patients and our contributions to addressing a key challenge of when to initiate antiretroviral treatment in HIV-TB co-infected patients.

N. Padayatchi (✉) · K. Naidoo · S.S. Abdool Karim · A. Grobler
Centre for the AIDS Programme of Research in South Africa,
MRC HIV-TB Pathogenesis and Treatment Research Unit,
University of KwaZulu-Natal, Durban, South Africa
e-mail: Nesri.padayatchi@caprisa.org

A. Gray
Division of Pharmacology, Discipline of Pharmaceutical Sciences,
School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa

S.S. Abdool Karim
Department of Epidemiology, Mailman School of Public Health,
Columbia University, New York, USA

Q. Abdool Karim et al. (eds.), *The CAPRISA Clinical Trials: HIV Treatment and Prevention*, DOI 10.1007/978-3-319-47518-9_8

1.2 Antiretroviral Initiation in HIV-TB Co-infected Patients

Between 1995 and 2005, South Africa experienced one of the largest and fastest growing HIV epidemics in the world [1] with almost 5.5 million people infected with HIV in South Africa during this period [2]. The World Health Organisation (WHO) recognised that fewer than 5 % of people in developing countries who needed ART were able to access them at that time, and called for at least 3 million people to be treated with antiretrovirals by 2005 [3]. The maturing HIV epidemic was accompanied by a substantial increase in the incidence of TB, the commonest first AIDS-defining condition. In southern Africa, almost two-thirds of TB patients were HIV positive, mostly with low CD4+ cell counts at the time of diagnosis. HIV testing and CD4+ cell count assays were considered to be cost-efficient in this group, since most TB patients were HIV positive and most HIV positive TB patients would have CD4+ cell counts below the threshold for ART initiation. The majority of HIV positive TB patients were therefore expected to fulfil the criteria for treatment initiation [4–6]. TB had also been shown to accelerate HIV disease progression, leading to higher case fatality rates, and HIV had been shown to have a negative impact on TB treatment outcomes [7–9]. It was common knowledge that there was a high case fatality amongst TB-HIV co-infected patients even with appropriate TB chemotherapy. There was however, no consensus even amongst experts on when to initiate antiretroviral treatment in HIV-TB co-infected patients —should HIV and TB treatment be initiated simultaneously or should antiretrovirals (ARVs) be introduced on completion of TB treatment was the dilemma.

At the time, WHO recommended that 'ART in patients with CD4 cell counts below 200/mm^3 be started between two weeks and two months after the start of TB therapy'. At the UN General Assembly Meeting on HIV/AIDS in September 2003, WHO declared that the lack of access to HIV treatment was a global health emergency [3]. Two years later, after the commencement of the START study, there was still no clarity on how and when to initiate ART in HIV-TB co-infected patients. WHO continued to call for evidence from prospective clinical trials to inform the development of suitable guidelines in this regard [10].

By the early 2000s, voluntary counselling and testing centres were readily available in South Africa, but less than 10 % of HIV infected people were aware of their HIV status, and fewer still knew their CD4+ cell count status and ARV treatment access was limited to those who could afford to pay for it. With limited resources available, and the discourse on ARV treatment access in resource limited settings changing following the XIIIth International AIDS conference hosted in Durban from should ARV treatment be provided to how it should be provided, an alternative approach was needed to efficiently identify those eligible for ART. During this period, two CAPRISA associated scientists, Kharsany [11], a Fogarty trainee, analysed data from a local TB clinic in Durban and described the changing

face of TB as a result of advancing HIV disease; and Wilkinson's research in rural KwaZulu-Natal also demonstrated the intertwining of the TB and HIV epidemics [12]. These, and other observations, laid the foundation for the prioritisation of HIV-TB co-infected patients in the CAPRISA CIPRA grant submission. Consultation with US-based infectious disease physicians, experienced in the provision of ART, including Drs El-Sadr, Hammer, Berkman, Hoos and others concurred that the timing of ART in TB-HIV co-infected patients was not known as TB was rare in most industrialised country settings. In contrast, in many developing countries TB was a major public health challenge and national TB treatment guidelines and infrastructure were already available and healthcare workers were trained to diagnose and manage TB. The question was therefore posed: should HIV care be integrated with TB care? There were opposing schools of thought: there were those that argued that the existing well-established TB infrastructure could play an important role in identifying those most in need of ART and that treating both conditions simultaneously would reduce the high mortality rates observed in TB and HIV co-infected patients; on the other hand, it was feared that integrating TB and HIV care would overburden an already fragile TB control program. At the individual patient level, there were concerns about the potential for significant drug–drug interactions, of high pill burdens and implications for adherence to both TB treatment and ART. The emergence of immune reconstitution reactions in patients on combined HIV-TB treatment was also of concern.

The focus on HIV and TB integration was also informed by chance encounters. After the IAS Conference in Durban in 2000, Dr. Gerald 'Jerry' Friedland, Professor of Medicine at Yale and a member of the IAS Governing Council, undertook a sabbatical in Africa, specifically focusing on this subject. At the 2001 Conference on Retroviruses and Opportunistic Infections (CROI) meeting in Chicago, Professor Salim 'Slim' Abdool Karim spotted a *New York Times* billboard with the headline: 'Indian Company Offers to Supply AIDS Drugs at Low Cost in Africa'. The article described how the chairman of Cipla, Yusuf K. Hamied, had offered generic antiretrovirals at markedly reduced prices to *Médecins Sans Frontières* in Africa. Fortuitously Jerry met Slim, at a hotel registration desk, and after exchanging 'niceties' about the winter weather, they became animatedly engaged in a discussion about a study to introduce ART in South Africa by integrating it with TB treatment. The withdrawal of the court action by several multi-national pharmaceutical manufacturers, which was blocking the implementation of the amendments to South African medicines law in April 2001, also provided new opportunities for access to generic medicines. The scene was set for the START study, the first randomised clinical trial to be conducted by the newly established CAPRISA.

2 When to Start Art in TB Patients?

2.1 START (Starting Tuberculosis and Antiretroviral Therapy)

Study overview

A key design feature of many TB control programmes has been the reliance on directly observed therapy for a defined course of treatment, referred to as DOTS. As both TB treatment success and continued viral suppression on ART relied on high levels of adherence to treatment, a DOT approach was considered appropriate for an integrated approach. The challenge, in 2002, was to find a once-daily combination ART regimen that was believed to be compatible with first-line TB treatment used in the intensive phase, including rifampicin. The START (**S**tarting **T**uberculosis and **A**nti**r**etroviral **T**herapy) trial (Panel 1) (CAPRISA001; NCT0091936) was therefore conceptualised to answer the following questions:

Panel 1 CAPRISA 001 START study schema

Study design:	This is a two-armed, randomized, open-label clinical trial evaluating whether the integration of HIV care into existing TB care services is feasible and practical in resource-poor settings. The study is conducted in two phases. The first phase represents the duration of TB therapy. The second phase represents the period after completion of TB therapy
Study population:	Men and women ≥18 years of age with documented HIV infection and smear-positive pulmonary TB
Study duration:	Study duration is 24 months after randomization
Sample size:	592 participants will be enrolled
Intervention:	Study participants will be randomized to one of the following arms stratified by CD4+ cell count, 50–200 cells/μL versus >200 cells/μL. Participants randomized into the integrated arm will receive antiretroviral therapy (ART) consisting of didanosine (ddI)/didanosine enteric coated (ddI-EC), lamivudine (3TC), and efavirenz (EFV) in conjunction with TB therapy upon randomization. Participants randomized to the sequential arm will complete TB treatment and then start ART consisting of ddI/ddI-EC, 3TC, and EFV. In instances where ddI/ddI-EC, 3TC, and EFV are contraindicated, an alternative regimen will be used
Treatment regimen:	At entry, participants will be randomized (1:1) to one of the following treatment arms: • **Integrated arm**: (ddI/ddI-EC) + 3TC + EFV once daily concurrently with standard TB treatment upon randomization • **Sequential arm**: (ddI/ddI-EC) + 3TC + EFV once daily initiated after completion of TB therapy

(continued)

Panel 1 (continued)

	ART substitution options will be available for participants who become pregnant, experience toxicities, or have treatment failure
Primary objective:	To assess the effectiveness of integrated TB and HIV care provision, including ART administered through a TB DOT program enhanced with an adherence support program (ASP), versus sequential treatment of TB and HIV, by comparing progression to AIDS-defining illnesses/mortality in participants with pulmonary TB and HIV co-infection during the first 18 months after enrollment in the study
Secondary objectives:	1. To assess the safety and tolerability as well as the drug interactions associated with combining anti-TB drugs with ART 2. To assess the impact of integrated TB and HIV care on adherence to anti-TB and ART 3. To assess the impact of integrated TB and HIV care on CD4+ cell counts and viral load 4. To determine and compare the incidence of IRIS/PR amongst TB/HIV co-infected participants who receive integrated versus sequential ART treatment and to examine the nature of the relationship between the incident PRs and potential immune markers of the immune reconstitution syndrome 5. To assess the impact of integrated TB and HIV care on TB and ART drug resistance 6. To assess the impact of integrated TB and HIV care on HIV risk-related behaviours and quality of life in co-infected participants 7. To assess the impact of integrating TB and HIV care on the TB outcomes (cure, successful completion, other non-specified TB outcomes, failure, and recurrence) 8. To assess the cost-effectiveness of integrated and sequential TB and HIV care 9. To assess the effectiveness of integrated TB and HIV care provision versus sequential treatment of TB and HIV by comparing progression to AIDS-defining illnesses/mortality during the entire study follow-up (approximately 2 years)
Study sites:	CAPRISA eThekwini Clinic in KwaZulu-Natal, South Africa

- Would integrated TB and HIV care reduce mortality and the rate of progression to subsequent AIDS-related conditions?
- When participants were treated with the combination of drugs used to treat both conditions, was this approach safe, well tolerated, and without negative pharmacologic interactions?
- Did this approach lead to improved HIV clinical outcomes?
- Did it lead to increased incidence of immune reconstitution events?
- Did the integration of HIV care into the TB program negatively impact TB outcomes?

The overall aim of the START study was therefore to assess whether the integration of HIV/AIDS care into existing TB care services was a feasible, practical approach to the implementation of ART in resource-constrained settings.

The study attempted to answer these questions through an operational health systems intervention design. A two-armed, randomised, open-label clinical trial was designed, in which participants were to be randomised into either the integrated arm, to receive ART in conjunction with TB therapy upon randomization, or the sequential arm, to receive ART only after completing TB treatment. Initially there was no lower limit to CD4 cell count as we did not want to make access to CD4 cell count a barrier to treatment initiation and importantly in keeping with a primary healthcare facility approach. During the review and protocol development process the NIH programme officer insisted on the CD4 cell count stratification, which in retrospect allowed us to understand this aspect better. Ultimately, randomisation in each arm was stratified by CD4+ count, into those with between 50 and 200 cells/μL and those with greater than 200 cells/μL.

However, there are challenges to combining an operational health research intervention and a randomised clinical trial. Operational research seeks to implement a real-world intervention, with all of the variability that is encountered in the field. However, clinical trials seek to eliminate as much variation as possible, and seek the cleanest possible design. Finalising the design of the START study therefore took almost two years. In addition to navigating the regulatory barriers to such research, the CAPRISA team also needed to satisfy the requirements of the newly established CIPRA programme at the NIH. Much effort was expended, for example, in creating the infrastructure to implement a sophisticated clinical trial, including the means to manage electronic case report forms. In most clinical trials, the trial medication is provided by the sponsor, usually the manufacturer of the medicine under investigation. However, in the case of the START trial, given that licensed drugs were being utilised, alternate sources of funding for the trial medication had to be established. Fortuitously, Professor Umesh Lalloo, a START study co-investigator was awarded a grant from the recently established Global Fund for AIDS, TB and Malaria to provide ARV treatment to AIDS patients in KwaZulu-Natal and provided the antiretrovirals for the START study through this mechanism.

Whilst navigating these complexities, it was decided to conduct a pilot study at the Prince Cyril Zulu Communicable Diseases Centre to address issues of safety of combining TB and ARV drugs, adequacy of the proposed efavirenz dose, feasibility, acceptability and adherence of combining antiretrovirals and TB medication. The pilot study demonstrated that TB programmes were feasible and acceptable sites for identifying those most in need of ART and integrating TB-HIV treatment [13]. However, what the pilot study could not identify was the many barriers created by the strict inclusion and exclusion criteria that had evolved for the START study. In the original protocol it was anticipated that a total of 592 participants would be enrolled in the study over a 24-months accrual period and that each participant would remain on study for a total of 24 months. A key requirement was that patients would be required to present daily during the work week for

directly observed dosing. Despite intensive recruitment strategies, and the presence of thousands of patients with TB, only 58 patients were enrolled in the stipulated 6-month period. A joint decision was made by the study sponsors and CAPRISA to prematurely close the trial. However, the 58 enrolled participants were followed-up to month 3 to collect data on the safety and pharmacokinetics of co-administered efavirenz and rifampicin. This decision also established an important principle for CAPRISA research, recognising the opportunities to maximise the benefits that could be obtained from a single large study by judicious use of ancillary projects that could answer important research questions. Nonetheless, the original question of the optimal timing of ART in TB patients remained unanswered. In the interim, PEPFAR was established and as a recipient of NIAID funding we were eligible to access PEPFAR funds through NIH to provide ART to AIDS patients. The original START study was revisited and the SAPiT study (described below) was initiated to answer the 'when to start ARTs in HIV-TB co-infected patients' question with an open-label trial design more in keeping with the original START proposal.

Efavirenz–Rifampicin Pharmacokinetic study

Based on the existing literature at the time of the design of the START study, the greatest concern was about the potential antagonistic interaction between rifampicin and the non-nucleoside reverse transcription inhibitor (NNRTI) component of the ART regimen. As a single daily dose was desired to allow for a DOT approach, the NNRTI chosen was efavirenz (EFV). It was also hoped at the time to procure a fixed-dose combination product containing the planned regimen of didanosine, lamivudine and efavirenz. The available evidence pointed to a reduction in peak and trough EFV concentrations when dosed together with rifampicin, at least in Caucasian populations [14]. Product labelling therefore included the recommendation to increase the dose of EFV in such settings. The START study provided a useful opportunity to gather more evidence in this data free terrain.

Efavirenz trough levels (before the next dose) and rifampicin peak levels (approximately 2.5 h post dose) were measured at months 1, 2 and 3 in the integrated arm. EFV trough levels were measured at the end of months 1, 2 and 3 after TB treatment was completed. Although the START study was prematurely closed, the 58 randomised participants contributed 209 steady-state EFV plasma concentrations, 83 of which were in the presence of rifampicin. When analysed using non-linear mixed effects modelling, the expected effect of rifampicin on EFV concentrations was not seen [15]. Instead, a decrease in apparent EFV clearance was shown, with a resulting increase in EFV exposure. In order to explain this observation, polymorphisms in the EFV-metabolising enzymes CYP2B6, CYP2A6 and UGT2B7 were subsequently sequenced. It was shown that polymorphisms were frequent in this population and were associated with elevated EFV levels [16]. Although no toxicity was associated with higher EFV levels, this study did provide evidence to support not adjusting EFV doses in patients on concomitant

rifampicin-containing TB treatment. Instead, the peak rifampicin levels measured at the same time showed lower than expected concentrations, especially in those with polymorphism in the SLCO1B1 (rs4149032) drug transporter gene [17]. It was therefore concluded that increased rifampicin doses might be warranted in African HIV-TB co-infected patients on integrated treatment for both conditions.

Transition from the START study to the SAPiT study

The key differences between the START and SAPiT study protocols related to the inclusion and exclusion criteria. These were less stringent, in order to enable faster, yet appropriate, enrolment into the study. In addition, by changing to a three-arm design, the study could answer the question as to whether TB and HIV treatment could be integrated, but also whether integration should occur early or late in TB treatment. Initially the desire was also to design a smaller study than START. However, despite considering other primary objectives, such as virological suppression rates at 12 months, it was finally decided to use the most relevant and definitive endpoint of mortality, even though this would lead to a larger study. With a sample size of 224 in each group, and an overall sample size of 672, the SAPIT study was thus not smaller than the START study.

2.2 SAPiT Trial (Starting Antiretroviral Therapy (ART) in Three Points in Tuberculosis Therapy)

In 2004, CAPRISA had established the CAPRISA AIDS Treatment programme (CAT). Funding for the development of necessary infrastructure was provided by PEPFAR programme, whilst the Global Fund covered the costs of antiretrovirals. The CAT Programme provided treatment and care primarily to a HIV-TB co-infected population. It was this treatment programme which provided the institutional basis for the SAPiT study.

SAPiT Study Outline

The primary objective of the SAPiT study (Panel 2) (Clinicaltrials.gov: NCT 398996) was to determine the optimal time to start ART in patients on TB treatment. A three-arm design was used, where patients were randomised to either start ART as soon as possible (within the first two months) after starting TB treatment (the early integrated treatment arm), to start ART after completing the 2-month intensive phase of TB treatment (the late integrated treatment arm) or to start ART as soon as possible after completing the entire course of TB treatment (the sequential treatment arm). In all three arms, the antiretrovirals used and the TB treatment regimens were the same.

Panel 2 CAPRISA 003 SAPIT study schema

Study Design:	This is a randomized, open-label pilot study comparing three existing treatment strategies of ART initiation in HIV/TB co-infected patients: Group 1: early initiation of ART with TB treatment, Group 2: initiation of ART upon completion of the intensive phase of TB treatment, Group 3: initiation of ART upon completion of the continuation phase of TB treatment
Study population:	Men and women ≥18 years of age with documented HIV infection and smear-positive pulmonary TB
Sample size:	Approximately 519 patients will be enrolled
Treatment regimen:	TB/HIV co-infected patients at the CDC are routinely offered ART in this treatment programme funded by PEPFAR and the Global Fund. The treatment programme includes extensive counselling and adherence support and detailed clinical and laboratory assessment for initiation of ART. At present, the clinicians arbitrarily decide when to start ART—this is the only aspect of the treatment programme which will be changed—patients will now be randomised into one of three ART starting points. All other care and monitoring received by all the patients in the treatment programme is standard
Primary objective:	To determine the optimal time to start ART in patients on TB treatment by comparing clinical status (CD4 count, viral load, mortality rates and Opportunistic Infections) at 18 months of HIV/TB co-infected patients who initiated ART with TB treatment, at the end of the intensive phase of TB treatment or upon completion of TB treatment
Secondary objectives:	1. To assess the impact of the three times of starting HIV care relative to TB treatment on the TB treatment outcomes (cure, treatment success, treatment interruption and treatment failure, other non-specified TB outcomes) 2. To assess the impact of the three times of starting HIV care relative to TB treatment on the emergence of ART or TB drug resistance 3. To assess the cost-effectiveness of TB and HIV care across the three arms
Study sites:	CAPRISA eThekwini Clinic in KwaZulu-Natal, South Africa

The primary outcome measure used was clinical status at 18 months after initial TB treatment initiation.

Safety Monitoring Committee

Approximately halfway through enrolment into the SAPiT study, the Safety Monitoring Committee reviewed the trial data as planned. The data showed that the mortality rate was 56 % lower in the early and late integrated treatment arms when

compared to the sequential treatment arm. The reduction in mortality in the integrated treatment arms was statistically significant both in patients with CD4 counts below 200 cells/μL and patients with CD4 counts from 200 to 500 cells/μL. This finding enhanced confidence in the results of the trial and the Safety Monitoring Committee decided that it would not be in the participants' best interests to continue the sequential arm of the trial and hence recommended the initiation of ART in this group as soon as possible. The Committee also recommended that the two integrated arms continue as per the original protocol.

Following the announcement of the Safety Committee findings

Even though one arm of the SAPiT study had been prematurely stopped, the interim results were considered of such significance that they justified a pre-publication announcement to key stakeholders. These interim results were presented in a scientific session at CROI in February 2009. In response to these findings, WHO issued a 'Rapid Advice', citing the SAPiT study, and stating that 'new and compelling evidence has become available, particularly concerning the earlier start of ART. The paper was published in the New England Journal of Medicine almost a year later [18]. Today there is a growing and compelling body of evidence of improved survival and reduced HIV-related illnesses with the earlier initiation of antiretroviral therapy in HIV-TB co-infected patients.

Major findings of the SAPiT study

The remaining arms of the SAPiT study were completed in 2010. As was shown by the interim result, co-administration of ART with TB therapy provided a 56 % survival benefit. Together with the results of other studies, this allowed for the WHO to issue global guidance that ART be provided to all co-infected patients together with their TB treatment, regardless of CD4 cell count. At the time, a rough estimate was that implementation of integrated TB and HIV treatment in South Africa could lead to an additional 100,000–150,000 patients (with TB and CD4 < 500) being initiated with ART and thereby prevent about 10,000 deaths each year.

The continuation of the integrated arms allowed for an important remaining question to be answered. A second set of analyses, first presented at CROI in February 2011, showed that early ART initiation (within 4 weeks of starting TB treatment) led to better survival rates in patients with CD4+ counts <50 cells/mm^3, but that ART initiation could be safely deferred to the first four weeks of the continuation phase of TB therapy in patients with CD4+ counts >50 cells/mm^3 [19].

Deferring ART initiation in those with higher CD4+ counts had two important benefits—lower incidence of paradoxical reactions and less frequent changes in ART regimens. Fear of precipitating a paradoxical immune reconstitution inflammatory syndrome (IRIS) had been a common reason to resist calls for integrating HIV and TB treatment. IRIS is defined as new onset or worsening symptoms, signs or radiographic manifestations that are temporally related to ART initiation in the presence of a treatment response. In order to study this phenomenon, a standardised case definition of IRIS had to be developed. A paradoxical reaction reporting

committee was created to independently and retrospectively evaluate whether each clinical case could be attributed to IRIS. SAPiT showed that the risk of IRIS was higher in patients initiating ART within the first 2 months after TB treatment initiation compared to later during TB treatment [20]. In the most severely immuno-compromised patients, with CD4+ counts <50 cells/mm^3, early ART integration was associated with an almost five-fold increased risk of IRIS. However, delaying ART initiation until after completion of the intensive phase of TB therapy was a safe option in those patients with CD4 cell counts ≥50 cells/mm^3. It was also shown that complete antiretroviral regimen shifts were more frequent in those with CD4+ cell counts <50 cells/mm^3 [21].

As with other CAPRISA studies, the SAPiT study was used to answer additional, non-clinical questions. A micro-costing study showed that initiation of ART after the completion of the intensive phase of TB treatment was cost-effective for patients with CD4+ counts >50 cells/mm^3 [22].

The SAPiT trial also provided an opportunity to conduct a secondary analysis of the 23 participants who were diagnosed with multi-drug resistant TB (MDR-TB). An 86 % reduction in mortality due to early initiation of ART was shown in patients diagnosed with MDR-TB. Despite the small sample size, the results were statistically significant due to the large effect size observed [23].

Ethical concerns raised with the SAPiT study

The first publication of the findings of the SAPiT study in the New England Journal of Medicine, several years after the public release of the of the SAPiT study findings raised some debate. Even though WHO guidance had emphasised the need for better evidence based on the pre-publication initial SAPIT findings from the sequential arm, questions were raised about the need for a study with a deferred treatment arm [24]. The authors of this critique were of the opinion that existing evidence from retrospective chart reviews was sufficient to guide clinical judgment. Whilst it was acknowledged that there was evidence to show that HIV-TB co-infected patients with low CD4+ counts had higher mortality, it had not at that stage been proven that early ART initiation in such patients improved morbidity and mortality [25]. The SAPiT study and others provided the data on which global guidance could be based, with greater confidence [26].

This ethical debate also underlined the value in publishing study findings simultaneously with conference presentations [27].

Impact on local and global policy

The findings of the SAPIT study have been incorporated into WHO, American (DHHS), British (BHIVA) and South African (SA TB and HIV*)* guidelines recommending that TB-HIV co-infected patients start TB treatment first, followed by ART as soon as possible within the first 8 weeks of treatment regardless of CD4 cell count. In those patients with severe immunosuppression (CD4 cell count <50 cells/mm^3), ART should, however, be initiated within the first 2 weeks of TB treatment start. It is important to note that patients with HIV-associated TB meningitis represent an important exception to the above recommendations. Data

from a randomised trial found no survival benefit from early ART in patients with TB meningitis, instead showing poor prognosis, with extremely high mortality rates of approximately 60 %, due largely to central nervous system associated TB-IRIS [28].

3 Challenges to Integration

Notwithstanding the compelling evidence from the SAPIT trial being validated by two independently conducted trials (CAMELIA and STRIDE) and national and global guidelines recommending integration of HIV and TB services, these services remain vertical and partly explain the continued high mortality rates in resource-constrained settings that have substantive HIV and TB epidemics. Translating evidence to policy and practice at a programmatic level requires a systematic and rigorous approach. The growing field of implementation science research is an attestation to this. To realise the full public health benefits of the SAPIT findings our team is currently undertaking the SUTHI trial (see Chap. 9) that has been carefully designed to test a practical, implementable and affordable strategy as one approach to improve HIV-TB treatment integration and thereby reduce deaths from the HIV-TB co-infection and maximise the survival benefits of ART and TB treatment provision.

References

1. UNAIDS. AIDS Epidemic Update. Geneva, Switzerland: Joint United Nations Program on HIV/AIDS; 2001.
2. National Department of Health. HIV & AIDS and STI Strategic Plan for South Africa 2007-2011. South Africa: National Department of Health; 2007.
3. World Health Organization. Scaling up antiretrovral therapy in resource-scarce settings: treatment guidelines for a public health approach. Geneva, Switzerland: World Health Organization; 2003.
4. Colvin M, Dawood S, Kleinschmidt I, Mullick S, Lallo U. Prevalence of HIV and HIV-related diseases in the adult medical wards of a tertiary hospital in Durban, South Africa. International Journal of STD & AIDS. 2001; 12(6): 386–9.
5. Mukadi YD, Maher D, Harries A. Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa. AIDS. 2001; 15(2): 143–52.
6. Whalen C, Horsburgh CR, Hom D, Lahart C, Simberkoff M, Ellner J. Accelerated course of human immunodeficiency virus infection after tuberculosis. American Journal of Respiratory and Critical Care Medicine. 1995; 151(1): 129–35.
7. Elliott AM, Halwiindi B, Mwinga AG. Treatment of tuberculosis in HIV-infected patients in Zaire. The New England Journal of Medicine. 1995; 333(8): 519–20.
8. Schluger NW. Issues in the treatment of active tuberculosis in human immunodeficiency virus-infected patients. Clinical Infectious Diseases. 1999; 28(1): 130–5.

9. Whalen C, Okwera A, Johnson J, Vjecha M, Hom D, Wallis R, et al. Predictors of survival in human immunodeficiency virus-infected patients with pulmonary tuberculosis. The Makerere University-Case Western Reserve University Research Collaboration. American Journal of Respiratory and Critical Care Medicine. 1996; 153(6 Pt 1): 1977–81.
10. World Health Organization. TB/HIV research priorities in resource-limited settings: Report of an expert consultation. Geneva, Switzerland: World Health Organization; 2005 2005.
11. Kharsany A, Connolly C, Olowolagba A, Abdool Karim S, Abdool Karim Q. Increasing burden of pulmonary tuberculosis in young women. S Afr Med J. 2006; 96(6): 524–5.
12. Wilkinson D. High-compliance tuberculosis treatment programme in a rural community. Lancet. 1994; 343(8898): 647–8.
13. Jack C, Lalloo U, Abdool Karim Q, Abdool Karim S, El-Sadr W, Cassol S, et al. A pilot study of once-daily antiretroviral therapy integrated with tuberculosis directly observed therapy in a resource-limited setting. Journal of Acquired Immune Deficiency Syndromes. 2004; 36(4): 929–34.
14. Gengiah TN, Gray AL, Naidoo K, Abdool Karim Q. Initiating antiretrovirals during tuberculosis treatment: a drug safety review. Expert opinion on drug safety. 2011; 10(4): 559–74.
15. Gengiah TN, Holford NH, Botha JH, Gray AL, Naidoo K, Abdool Karim SS. The influence of tuberculosis treatment on efavirenz clearance in patients co-infected with HIV and tuberculosis. European Journal of Clinical Pharmacology. 2012; 68(5): 689–95.
16. Gengiah TN, Botha JH, Yende-Zuma N, Naidoo K, Abdool Karim SS. Efavirenz dosing: influence of drug metabolizing enzyme polymorphisms and concurrent tuberculosis treatment. Antiviral Therapy. 2015; 20(3): 297–306.
17. Gengiah TN, Botha JH, Soowamber D, Naidoo K, Abdool Karim SS. Low rifampicin concentrations in tuberculosis patients with HIV infection. Journal of Infection in Developing Countries. 2014; 8(8): 987–93.
18. Abdool Karim SS, Naidoo K, Grobler A, Padayatchi N, Baxter C, Gray A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. New England Journal of Medicine. 2010; 362(8): 697–706.
19. Abdool Karim SS, Naidoo K, Grobler A, Padayatchi N, Baxter C, Gray AL, et al. Integration of antiretroviral therapy with tuberculosis treatment. New England Journal of Medicine. 2011; 365(16): 1492–501.
20. Naidoo K, Yende-Zuma N, Padayatchi N, Naidoo K, Jithoo N, Nair G, et al. The immune reconstitution inflammatory syndrome after antiretroviral therapy initiation in patients with tuberculosis: findings from the SAPiT trial. Annals of Internal Medicine. 2012; 157(5): 313–24.
21. Naidoo A, Naidoo K, Yende-Zuma N, Gengiah TN, Padayatchi N, Gray AL, et al. Changes to antiretroviral drug regimens during integrated TB-HIV treatment: results of the SAPiT trial. Antiviral Therapy. 2014; 19(2): 161–9.
22. Naidoo K, Grobler AC, Deghaye N, Reddy T, Gengiah S, Gray A, et al. Cost-Effectiveness of Initiating Antiretroviral Therapy at Different Points in TB Treatment in HIV-TB Coinfected Ambulatory Patients in South Africa. Journal of Acquired Immune Deficiency Syndromes. 2015; 69(5): 576–84.
23. Padayatchi N, Abdool Karim SS, Naidoo K, Grobler A, Friedland G. Improved survival in multidrug-resistant tuberculosis patients receiving integrated tuberculosis and antiretroviral treatment in the SAPiT Trial. The International Journal of Tuberculosis and Lung Disease. 2014; 18(2): 147–54.
24. Boulle A, Clayden P, Cohen K, Cohen T, Conradie F, Dong K, et al. Prolonged deferral of antiretroviral therapy in the SAPIT trial: did we need a clinical trial to tell us that this would increase mortality? South African Medical Journal. 2010; 100(9): 566, 8, 70–1.
25. Abdool Karim Q, Abdool Karim SS, Baxter C, Friedland G, Gengiah T, Gray A, et al. The SAPIT trial provides essential evidence on risks and benefits of integrated and sequential treatment of HIV and tuberculosis. South African Medical Journal. 2010; 100(12): 808–9.

26. World Health Organization. Rapid advice: antiretroviral therapy for HIV infection in adults and adolescents. Geneva, Switzerland: World Health Organization; 2009.
27. Abdool Karim SS, Abdool Karim Q, Friedland G, Lalloo U, El-Sadr WM. Implementing antiretroviral therapy in resource-constrained settings: opportunities and challenges in integrating HIV and tuberculosis care. AIDS. 2004; 18(7): 975–9.
28. Török ME, Yen NTB, Chau TTH, Mai NTH, Phu NH, Mai PP, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)–associated tuberculous meningitis. Clinical Infectious Diseases. 2011; 52(11): 1374–83.

Chapter 9
Scaling up TB-HIV Integration in Public Health Clinics: Translating Research Findings into Practice

Kogieleum Naidoo, Santhanalakshmi Gengiah, Nesri Padayatchi and Salim S. Abdool Karim

1 Introduction

Tuberculosis (TB) is a global public health crisis with an estimated 9.6 million people infected with TB and, of these, 1.5 million died from the disease in 2014 alone [1]. An estimated 12 % were co-infected with HIV and 400,000 TB-related deaths were among HIV-infected individuals [1]. HIV is the strongest risk factor for TB, with the escalation in TB incidence rates as a consequence of the intertwining of the two epidemics [2]. According to the WHO *Global Tuberculosis Report 2015*, South Africa alone contributes to almost a quarter of the world's new and relapse TB cases [1]. South Africa's TB burden ranks third highest in the world, with rates of HIV co-infection estimated to be as high as 70 % [3]. TB is a curable disease provided it is detected early and treated effectively. Statistics South Africa ranked TB as the number 1 cause of death in HIV-infected patients for the last 10 years [4]. South Africa is also home to 18 % of all people infected with HIV globally despite having <1 % of the global population. There are an estimated 6 million people living with HIV in South Africa giving it the dubious ranking of number 1 globally in terms of HIV disease burden. As a United Nations member state, South Africa was a participant in meeting the Millennium Development Goals (MDGs). MDG 6

K. Naidoo (✉) · S. Gengiah · N. Padayatchi · S.S. Abdool Karim
Centre for the AIDS Programme of Research in South Africa,
University of KwaZulu-Natal, Durban, South Africa
e-mail: Kogie.naidoo@caprisa.org

S.S. Abdool Karim
Department of Epidemiology, Mailman School of Public Health,
Columbia University, New York, USA

Q. Abdool Karim et al. (eds.), *The CAPRISA Clinical Trials: HIV Treatment and Prevention*, DOI 10.1007/978-3-319-47518-9_9

was to combat HIV/AIDS Malaria and other Diseases including TB, specifically relating to halting TB incidence, and halving both TB prevalence and HIV-TB associated death rates. The 2014 WHO Global TB Report ranked South Africa among the 22 high burden TB countries, which did not meet their MDGs [1]. The inability to meet these goals is largely due to poor coordination between HIV and TB programmes and the lack of a best-practice model to achieve optimal HIV-TB service integration [1].

One of the greatest challenges to integrating TB and HIV services was determining the optimal time to initiate ART in TB patients. On the one hand, early ART was associated with higher rates of drug interactions, drug toxicity, immune reconstitution inflammatory syndrome and higher pill burden, while on the other hand deferring ARTs in TB patients was associated with higher rates of AIDS disease progression and mortality. Empiric evidence from randomised controlled trials (RCT) was not available to guide clinical decision-making in the use of ART in TB patients. The CAPRISA 003 SAPiT trial provided RCT evidence for the integration of TB and HIV care through the demonstration of 56 % lower mortality among patients on the integrated TB and HIV treatment arm compared to the ARV treatment deferred arm [5] (see Chap. 8). Several RCTs subsequently provided clear evidence of the survival benefits of integrating TB and HIV, especially for patients with low CD4+ cell counts [6–8]. These findings were incorporated into local and international guidelines and have informed TB-HIV integration policy aimed at improved outcomes for both patients and programmes. Evidence on various additional strategies and interventions that benefit TB and HIV co-infected patients has also been accumulating in recent years. Despite this, HIV-associated TB mortality still dominates as the most common cause of premature mortality in HIV and TB endemic resource limited settings. It is important to be cognisant of the existing operational and implementation challenges that impede adaptation of evidence from these clinical trials into practice. Clear operational guidelines exist for TB care provision and for ARV treatment provision. The key steps for care provision for each of these diseases are also referred to as the care cascade. As we have learnt from the success in reducing mother-to-child transmission of HIV, these cascades are critical for implementation success. There is no available cascade that integrates HIV and TB services. Traditionally, TB and HIV services exist as two vertical independent programmes that are in some instances co-located. Referrals between the HIV and TB programmes is often inadequate leading to high HIV-associated TB mortality in ART programmes and suboptimal HIV screening and ART initiation within TB programmes. TB-HIV integration should encompass screening for HIV and TB among all patients, streamlined clinic procedures and patient flow supporting TB treatment and prevention activities among HIV-infected patients, clinically skilled staff to co-manage both diseases, a single appointment, data management and patient filing system and an efficient patient retention strategy. However, there has been no collation of evidence to date that can be used to produce a package of readily implementable HIV-TB services translatable at the

primary healthcare (PHC) level, where most TB and HIV service delivery occurs. While there is an urgent need for effective integration of TB and HIV services, little information is available on how best to achieve this. Additionally, co-located services do not necessarily address comprehensive care provision, especially if TB and HIV care remains fragmented.

Research findings, investments and gains made in the field of HIV-TB research aimed at impacting mortality in co-infected patients will be futile if they cannot be translated into everyday practice. We designed the CAPRISA 013 trial to address this vast disconnect between tested TB-HIV interventions and the mechanisms to operationalise these interventions in clinics, to maximise efforts in reducing HIV-associated TB mortality through TB-HIV integration.

2 Translating Evidence to Policy and Practice

Implementation science research aimed at identifying and addressing barriers and bottlenecks at each stage of the TB and HIV service integration cascades is the key to effective adaptation of evidence in support of integration within real-world healthcare settings. Now that the research community has established effective interventions for HIV-TB co-infected patients, it is logical to shift focus to implementation of service integration. Questions relating to programmatic scale-up of integrated services such as demand creation, acceptability from user and provider perspectives of integrated HIV-TB cascades, logistical challenges to implementation, scalability and sustainability of these interventions in existing health facilities, remain unanswered. Limitations of the current approach to training Health care workers (HCWs) when new services are introduced need to be considered. Currently, the best delivery model of integrated HIV-TB services in a 'real world' setting is unknown but is likely to vary at a local level based on the existing disease burden, healthcare delivery infrastructure including staffing, supply chains and acceptability of service integration by users and providers. Implementing evidence-based knowledge in 'real life' clinical care settings is complex and influenced by a combination local context, health system inputs (e.g. health worker knowledge and availability of commodities), monitoring and evaluation with clear targets and goals, but even when these inputs are not a barrier, the care delivery system rarely replicates results achieved under controlled clinical study conditions. In some instances the outcomes are better and in others it could be worse. Goal setting with ongoing monitoring linked to iterative cycles of improvement as captured in the quality improvement (QI) methods, are increasingly being used as one approach to systematically test and incorporate local ideas into strategies for reliable implementation and scale-up. More details on the QI strategy have been provided in Chap. 5 in relation to CAPRISA 008 and the integration of a microbicide into sexual reproductive health services.

3 CAPRISA 003: Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPIT)—Addressing Barriers to TB-HIV Integration

3.1 Addressing TB-HIV Integration Policy and Guidelines

The CAPRISA 003 SAPiT (Starting Antiretroviral Therapy at Three Points in Tuberculosis) trial made national and international headlines in 2009 [9] and impacted World Health Organization (WHO) treatment policy in 2010 [10]. As a result of the SAPiT trial, in 2009, President Jacob Zuma announced that TB-HIV co-infected patients would be treated under one roof [9], signifying the call for integrated TB and HIV services within South African Department of Health facilities.

SAPiT was one of three key RCTs providing essential evidence to inform the optimal timing of antiretroviral therapy (ART) initiation in HIV-infected TB patients. Prior to the release of SAPiT results, guidelines on timing of ART initiation in TB co-infected patients rested largely on recommendations from observational studies and expert opinion [5]. The SAPiT trial provided robust empirical evidence that integrating ART and TB treatment significantly improves survival in co-infected patients [5]. In addition to the SAPiT trial, the CAMELIA and STRIDE studies supported the integration of ART and TB treatment as improving survival of HIV-TB co-infected patients [7, 8]. The WHO and the South African Department of Health quickly incorporated and adopted the SAPiT trial recommendations into treatment guidelines and policies (Fig. 1) however, the true public health impact of these findings on survival benefits for HIV-TB co-infected patients at a population level is yet to be realised and underscores the importance of bridging the gap between clinical trial evidence and implementation at a programmatic level.

3.2 Understanding Barriers to TB-HIV Integration Implementation

While South Africa has been successful in rapid scale-up of ART, and despite high levels of co-infection, TB and ART services continue to be delivered in separate facilities or services where even screening for TB in AIDS patients or HIV in TB patients is not taking place. Several studies have assessed operational challenges in delivering integrated services [11–15]. A major barrier is how new services are introduced into existing facilities and includes little attention to demand creation or preparedness of HCWs to deliver the new service or integrate the new service into existing services. Improved preparedness of facilities and frontline HCWs to integrate TB-HIV treatment for both conditions within a single facility is a good starting point for operational success including minimising delays in ART initiation among TB patients referred from other services or facilities [12].

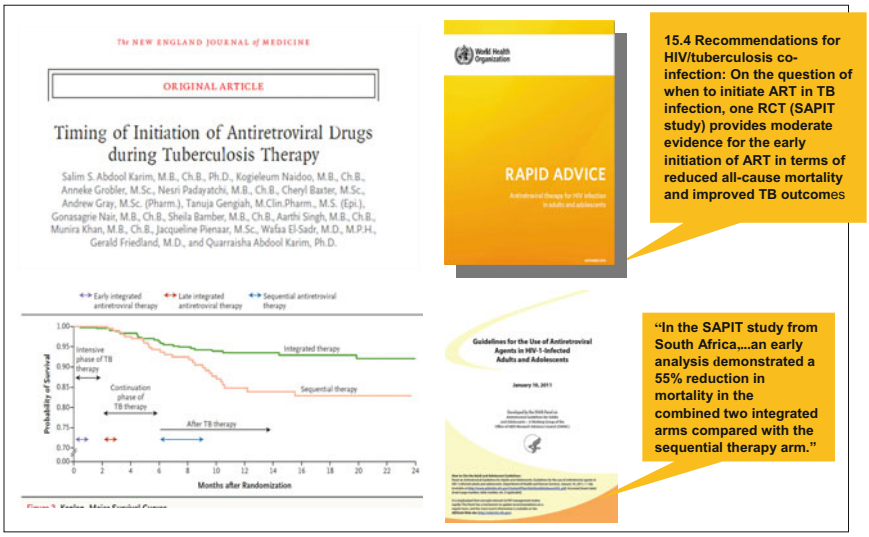

Fig. 1 SAPiT trial impact on treatment policy and guidelines

Service integration is defined as 'a coordinated provision of healthcare services', which includes 'several models ranging from locating two services in one facility, to a one-stop-shop model that provides a complete package of services delivered by one health-care team' (Fig. 2) [15]. The obvious benefit of integration to the patient includes fewer health facility visits, and receipt of a more comprehensive and complete service that meets their health needs. Integrated service provision also benefits clinics through optimal use of trained staff, decongestion of patient waiting areas, reduced pharmacy visits and lower administrative burden [16]. An additional weakness within the current vertical HIV and TB programmes is lack of oversight in programme coordination and data management. ART service delivery is the mandate of doctors and a cadre of trained professional nurses, the NIMART (Nurse Initiated and Managed ART) nurses. In contrast, TB has for the last two decades, been the responsibility of TB nurses, who are enrolled nursing assistants that provide the day-to-day management of TB, including the recording and reporting. While effort has been invested into establishing common process indicators, data systems remain separate with patient and programmatic outcomes recorded and reported separately. Furthermore, the absence of referral and linkage to care processes between HIV and TB programmes and vice versa indicates that this activity is unmonitored and remains external to both programmes, with its success dependent on patients' resources and health seeking behaviour.

One of the major criticisms of how integration is being conducted in resource limited settings is that it is disjointed [13], largely because HIV and TB programmes have not been co-located. To understand the operational challenges of

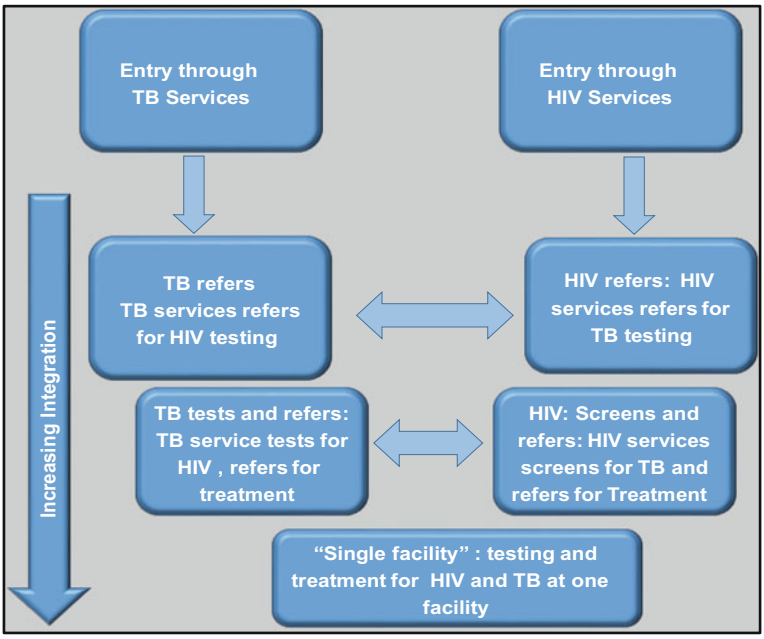

Fig. 2 Models of HIV-TB Integration [14]

integrating HIV and TB treatment, we reviewed the published literature on integration of services and then derived an optimal package of HIV-TB service delivery. There is strong support that the ideal model of HIV-TB service integration is a 'one-stop-shop' approach where patients can be managed at one facility, by one healthcare worker on one appointment for both HIV and TB.

QI methods provide a rigorous framework for the development of local strategies that overcome barriers to implementation of evidence-based interventions [17, 18]. QI methodology addresses the 'how' of program implementation, and is increasingly being promoted for large-scale improvements in health systems performance. Technically, QI improves process performance through a framework based on an understanding of the psychology of system change. QI processes include developing a common simplified view of the components and linkages of integrated care, use of real-time data feedback to track and improve system performance, and crucially, iterative testing and incorporation of ideas for performance improvement from the frontline practitioners, managers, and customers in the local context. The role of QI in optimising healthcare delivery designs and improving outcomes on a large scale is now well established and has been demonstrated in the public-sector health system of South Africa [17], notably in improving delivery of prevention of mother-to-child transmission (PMTCT) services [19–21]. This approach has not been applied to TB-HIV integration.

3.3 The Study Hypothesis

We hypothesise that QI methodology to implement TB-HIV integrated care will achieve comprehensive and reliable delivery of integrated HIV and TB care with better clinical outcomes than clinics utilising standard support for existing clinical protocols. The primary aim of the CAPRISA 013 SUTHI trial is to test the effectiveness of a peer mentor-led, QI model of service delivery of integrated HIV-TB treatment on mortality in HIV-TB co-infected patients treated in rural primary healthcare clinics in KwaZulu-Natal.

4 Study Design

The SUTHI trial (NCT02654613) is a cluster randomised trial (Panel 1). Typically, the CAPRISA studies, such as SAPiT, have focused on testing clinical interventions at an individual patient level to establish safety and efficacy under strict trial conditions and at a well-resourced research clinic. This is also referred to a 'proof-of-concept' study which is an important first step to inform policy or licensure of investigational products. However, translating policy to practice or programmatic scale-up requires a different set of considerations. Understanding how TB-HIV service integration should be embedded in a busy Department of Health clinic requires a more pragmatic research design. A cluster randomised trial has the advantage that control and intervention clinics are balanced on all aspects other than the intervention, thus removing confounding factors. This requires randomisation of a sufficient number of clinics, to ensure balance between the two treatment arms. If clinics are merely assigned to the two arms there is a chance that study staff could choose clinics where it is easier to work, thereby resulting in a bias in assigning clinics as intervention or control clinics.

Panel 1 CAPRISA 013 SUTHI study schema

Purpose:	To develop, implement and evaluate an integrated TB-HIV primary care model of service delivery aimed at improving HIV and TB outcomes in co-infected patients accessing services in primary healthcare clinics
Design:	Cluster randomised control trial where clinics, with all their HIV-TB patients, are randomised as a group but the trial outcome is measured in individual patients at each of these clinics
Population:	HIV or TB infected suspects and cases attending primary healthcare facilities located in rural, South Africa
Duration:	Each clinic will be included in the study for an 18 month period

(continued)

Panel 1 (continued)

Intervention:	A quality improvement model of service delivery for integrated HIV-TB treatment: a peer-led, mentored and supported comprehensive model of integrated TB and HIV services at a primary healthcare level aimed at improving TB and HIV outcomes at a programmatic level and individual patient based level
Sample Size:	40 primary healthcare facilities in the Ugu and uThungulu Districts
Primary Objective:	The aim of this study is to test the effectiveness of a peer mentor-led, quality improvement model of service delivery of integrated HIV-TB treatment on mortality in HIV-TB co-infected patients treated in rural primary healthcare clinics in KwaZulu-Natal
Primary Endpoints:	TB-HIV service integration, Mortality
Secondary Objectives:	• To determine the impact of a QI-mediated HIV-TB services integration on patient mortality • To determine the effectiveness of peer-led Quality Improvement (QI) to integrate HIV-TB services • To identify clinic-level factors that impact on integrated HIV-TB services • To determine the cost-effectiveness of implementing HIV-TB services using Quality Improvement methodology (Intervention Clinics) versus the control clinics implementing HIV-TB services independently • To identify a set of interventions, change ideas, tools and approaches that can be used to scale up adoption, implementation and sustainability of integrated HIV-TB services across South Africa
Sites:	Primary Health Care clinics in 2 rural districts in KwaZulu Natal

Since the intervention is being conducted at the clinic level, clinics are the unit of randomisation. Furthermore, there are ethical and logistical constraints to randomise patients within a clinic, as the aim is to evaluate the effect of integrating services at a clinic level. There are certain disadvantages of cluster randomised trials compared to individual randomised trials, such as lower power with the same number of participants, chance of contamination between clinics and influence of ecological variables on the results. Despite these limitations, a cluster randomised trial design is the most appropriate to answer the question at hand. Mortality was the chosen endpoint of the study, as the goal of the intervention is to determine the population-level impact of the intervention on reducing mortality.

5 Study Methodology

5.1 The Intervention Arm

5.1.1 TB-HIV Integration Interventions Selected

Based on the most recent evidence and guidelines, the study intervention will focus on implementation of the HIV-TB integration package contained in Panel 2.

Panel 2 The full package of integrated HIV-TB services

• Intensified case finding for TB in HIV-infected patients
• Isoniazid preventative therapy for HIV-positive patients that screen TB negative
• Testing and counselling for HIV in all patients with TB, including children and pregnant women
• Cotrimoxazole therapy for TB-HIV co-infected patients
• ART initiation for all co-infected patients
• Adopting a one patient, one appointment, one file, and one data management system approach
• Enhanced retention in care strategies
• Enhanced ART and TB treatment adherence strategies

5.1.2 Implementation Science Research and the QI Approach

Despite the large evidence base of successful strategies in averting morbidity and mortality in TB-HIV co-infected patients, public health impact has been small due to inadequate uptake in routine clinical care and the separation of HIV and TB services [22, 23]. An implementation science approach will be used to understand how these evidence-based interventions can be embedded in a real-life setting, with the above-mentioned TB-HIV Integration interventions expanding beyond just the patient level but to also incorporate interventions at the health system environment level. It is with these considerations, that a multidisciplinary research team has been assembled that includes QI mentors, frontline healthcare workers, behavioural scientists, epidemiologists, data managers, health systems strengthening experts and scientists [22].

Using the Model for Improvement (Fig. 3) and QI principles, we aim to achieve new ways of using evidence-based interventions known to reduce morbidity and mortality in TB-HIV co-infected patients within primary healthcare clinics. The QI intervention for this study will entail mentoring and coaching key clinic staff to identify gaps in performance in key areas of TB-HIV service delivery and

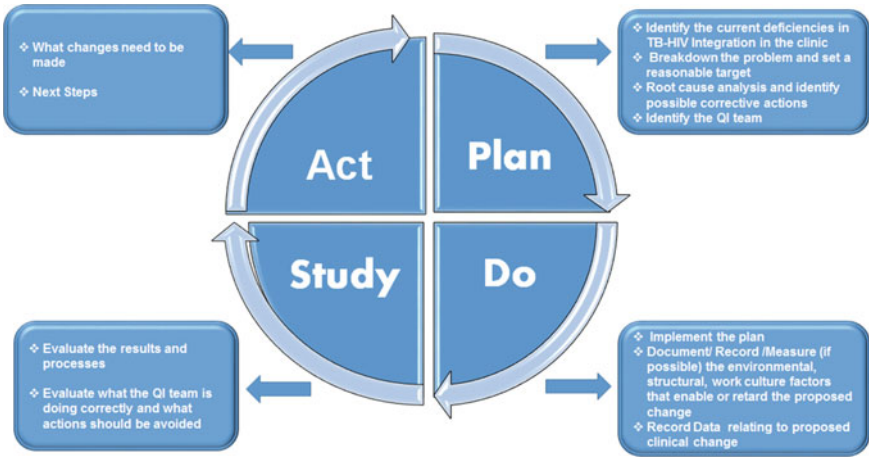

Fig. 3 The Quality Improvement Model for Healthcare Improvement [24]

systematically test change ideas to close performance gaps. They will also examine patient flow, systems and processes. The QI approach will be engaged within PHC facilities in building institutional capability among frontline HCWs in adapting the eight identified TB-HIV integration interventions through:

1. Using facility data to critically evaluate gaps in implementation of each component of the core TB-HIV integration activities
2. Using problem-solving skills and local peer-to-peer knowledge exchange, to generate new ideas for improvement and to test these ideas and review performance and progress in TB-HIV integration
3. To embed changes to systems and processes that improves performance in TB-HIV integration
4. Ongoing review and problem solving for sustained optimal levels of TB-HIV integration.

Performance will be tracked through routinely collected indicators. The effectiveness of the change ideas generated will be assessed by study staff, who will collate a set of successful interventions and tools that could be made generalizable for scalability.

5.2 The Control Arm

The current Department of Health standard of care will prevail in PHCs assigned to the control arm. All clinic processes, systems and functions will be documented by the study team, without any active intervention. Data systems will, however, be enhanced to ensure that data collected accurately reflects clinic performance.

6 Study Outcomes

The SUTHI study has the potential to demonstrate the impact of TB-HIV QI integration interventions on district level morbidity and mortality in HIV-TB co-infected patients. The demonstration of an optimised 'change package' aimed at assisting PHC clinics in improving HIV-TB services would address several key questions. First, the study will provide much needed guidance on 'how' to translate clinical trial evidence on which TB-HIV integration guidelines are based, into practice at the PHC clinic level where most service delivery occurs. Second, it will help define a model of QI for TB-HIV integration that is both scalable and sustainable, which has the potential to improve quality of care, clinical and programmatic outcomes in high TB and HIV burden settings. Third, this study will generate a set of QI principles that will help entrench data driven decision-making, and a culture of continuous improvement of services that is not limited to TB and HIV within facilities, with the potential to impact overall performance of the health system.

7 Innovation

7.1 Translating Evidence

The current design of the care delivery system has stymied TB-HIV treatment integration within the services, preventing the translation of clinical trial evidence into improved clinical outcomes at the population level. The SUTHI trial uses implementation science research to address the translation gap to obtain evidence-based practices on TB-HIV service integration.

7.2 Collaboration Between Key Role Players

In this study, CAPRISA is partnering with BroadReach Healthcare (BRHC) Africa, the Institute for Healthcare Improvement (IHI) and the South African Department of Health. Each collaborating partner brings a unique perspective to the study and addresses an important area in TB-HIV service integration. The BRHC team has health systems strengthening experience in local and national facilities and has good knowledge of the organisational structure, operational challenges and data management systems within the health department. The IHI is a leader in the field of QI and health management science and in taking evidence-based interventions to scale [25]. IHI's demonstrated expertise in the South African PMTCT [19] of HIV programme will be adapted to the TB-HIV Integration context, aimed at generating a set of innovative scalable intervention strategies (a 'change package') developed

from local knowledge of frontline health workers and managers. The South African Department of Health staff involved in this study will be active participants and this will strengthen the potential adoption, implementation and sustainability of the study.

7.3 Engagement at PHC Level

The randomisation at the PHC level allows for local frontline QI collaboratives to be formed, thereby facilitating idea generation, learning sessions and implementation enhancing sustainability of translating TB-HIV integration evidence. In addition, the ability of taking the QI intervention to scale will be enhanced as PHC coordinators have a wide reach through the multiple PHC clinics under their purview.

8 Anticipated Impact of the Study

There is strong support that the ideal model of HIV-TB service integration is the single facility or 'one-stop-shop' approach where patients can be tested, treated and cared for at one facility, by one healthcare worker and given one clinic appointment for both HIV and TB services. The major weakness in the current vertical HIV and TB programmes is the unmonitored referral and linkage to care process between HIV and TB programmes and vice versa. In addition, the lag between health policy and TB-HIV integration implementation implies that the true population-level impact of clinical trial evidence that supports integration would not be realised in the near future. This study will demonstrate how reduced morbidity and mortality in TB-HIV co-infected patients can be achieved through readily implementable strategies suitable at a PHC level that bridge the gap between science, policy and implementation with a potential to maximise the success and sustainability of the ART rollout in South Africa.

References

1. WHO. Global Tuberculosis Report 2015. Geneva http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf WHO, 2015.
2. Suthar AB, Lawn SD, del Amo J, Getahun H, Dye C, Sculier D, et al. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis. PLoS Med. 2012;9(7): e1001270.
3. Friedland G, Harries A, Coetzee D. Implementation issues in tuberculosis/HIV program collaboration and integration: 3 case studies. J Infect Dis. 2007;196 (Suppl 1): S114–23.

4. StatsSA. Mortality and causes of death in South Africa, 2011: Findings from death notifications Pretoria StatsSA, 2014.
5. Abdool Karim SS, Naidoo K, Grobler A, Padayatchi N, Baxter C, Gray A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. N Engl J Med. 2010;362(8): 697–706.
6. Abdool Karim SS, Naidoo K, Grobler A, Padayatchi N, Baxter C, Gray AL, et al. Integration of antiretroviral therapy with tuberculosis treatment. N Engl J Med. 2011;365(16): 1492–501.
7. Havlir DV, Kendall MA, Ive P, Kumwenda J, Swindells S, Qasba SS, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. N Engl J Med. 2011;365(16): 1482–91.
8. Marcy O, Laureillard D, Madec Y, Chan S, Mayaud C, Borand L, et al. Causes and determinants of mortality in HIV-infected adults with tuberculosis: an analysis from the CAMELIA ANRS 1295-CIPRA KH001 randomized trial. Clin Infect Dis. 2014;59(3): 435–45.
9. SAnews.gov.za. Address by President Jacob Zuma on the occasion of World AIDS Day http://www.sanews.gov.za/south-africa/address-president-jacob-zuma-occasion-world-aids-day. 2009. http://www.sanews.gov.za/south-africa/address-president-jacob-zuma-occasion-world-aids-day (accessed 01 February 2016 2016).
10. WHO. Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a public health approach Geneva: WHO; 2010.
11. Lawn SD, Campbell L, Kaplan R, Boulle A, Cornell M, Kerschberger B, et al. Time to initiation of antiretroviral therapy among patients with HIV-associated tuberculosis in Cape Town, South Africa. J Acquir Immune Defic Syndr. 2011;57(2): 136–40.
12. Lawn SD, Campbell L, Kaplan R, Little F, Morrow C, Wood R, et al. Delays in starting antiretroviral therapy in patients with HIV-associated tuberculosis accessing non-integrated clinical services in a South African township. BMC Infect Dis. 2011;11: 258.
13. Legido-Quigley H, Montgomery CM, Khan P, Atun R, Fakoya A, Getahun H, et al. Integrating tuberculosis and HIV services in low- and middle-income countries: a systematic review. Trop Med Int Health. 2013;18(2): 199–211.
14. Nglazi MD, Bekker LG, Wood R, Kaplan R. The impact of HIV status and antiretroviral treatment on TB treatment outcomes of new tuberculosis patients attending co-located TB and ART services in South Africa: a retrospective cohort study. BMC Infect Dis. 2015;15(1): 536.
15. Uyei J, Coetzee D, Macinko J, Guttmacher S. Integrated delivery of HIV and tuberculosis services in sub-Saharan Africa: a systematic review. Lancet Infect Dis. 2011;11(11): 855–67.
16. Baddeley AD, M.; Kanchar, A.; Matteelli, A.; Timimi, H.; Getahun, H. Missed opportunities in the TB/HIV cascade of care in 14 high burden TB/HIV African countries, 2012. International AIDS Conference 2015; 2015; Vancouver, Canada; 2015.
17. Berwick DM. The science of improvement. JAMA. 2008;299(10): 1182–4.
18. Deming WE. Out of the crisis: Cambridge, Mass. Massachusetts Institute of Technology, Center for Advanced Engineering Study, ©1986.; 1986.
19. Mate KS, Ngubane G, Barker PM. A quality improvement model for the rapid scale-up of a program to prevent mother-to-child HIV transmission in South Africa. Int J Qual Health Care. 2013;25(4): 373–80.
20. Mphatswe W, Mate KS, Bennett B, Ngidi H, Reddy J, Barker PM, et al. Improving public health information: a data quality intervention in KwaZulu-Natal, South Africa. Bull World Health Organ. 2012;90(3): 176–82.
21. Youngleson MS, Nkurunziza P, Jennings K, Arendse J, Mate KS, Barker P. Improving a mother to child HIV transmission programme through health system redesign: quality improvement, protocol adjustment and resource addition. PloS One. 2010;5(11): e13891.
22. Bauer MS, Damschroder L, Hagedorn H, Smith J, Kilbourne AM. An introduction to implementation science for the non-specialist. BMC Psychol. 2015;3: 32. Printed and On File
23. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care. 2012;50(3): 217–26.

24. HRSA. Quality Improvement http://www.hrsa.gov/quality/toolbox/methodology/qualityimprovement/index.html U. S. Department of Health and Human Services Health Resources and Services Administration, 2011 09 August 2014.
25. Colbourn T, Nambiar B, Bondo A, Makwenda C, Tsetekani E, Makonda-Ridley A, et al. Effects of quality improvement in health facilities and community mobilization through women's groups on maternal, neonatal and perinatal mortality in three districts of Malawi: MaiKhanda, a cluster randomized controlled effectiveness trial. Int Health. 2013;5(3): 180–95.

Part IV
Experiences and Lessons Learnt from Clinical Trials in CAPRISA

Chapter 10
From Bench to Bedside: Lessons from HIV Natural History Cohort Studies

Carolyn Williamson, Lynn Morris, Nigel Garrett, Penny Moore, Wendy Burgers and Koleka Mlisana

1 Rationale for the CAPRISA 002 Acute Infection Study (AI Study)

The CAPRISA 002 Acute Infection study is an open cohort that started recruiting in 2004 and continues to enrol and follow up participants 12 years later. The study recruits women very soon after HIV infection and follows them throughout infection and treatment. As the epidemic in South Africa disproportionally affects young women, and prevention of HIV infection of women was a primary goal of CAPRISA, this study only recruited women. Prevention of HIV infection in ado-

C. Williamson (✉) · W. Burgers
Division of Medical Virology, Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, Cape Town, South Africa
e-mail: Carolyn.Williamson@uct.ac.za

L. Morris · P. Moore
Center for HIV and STIs, National Institute for Communicable Diseases, Johannesburg, South Africa

C. Williamson · L. Morris · N. Garrett · P. Moore · W. Burgers
Centre for the AIDS Programme of Research in South Africa, University of KwaZulu-Natal, Durban, South Africa

K. Mlisana
Department of Medical Microbiology, School of Laboratory Medicine and Medical Sciences, Inkosi Albert Luthuli Central Hospital Academic Complex, University of KwaZulu-Natal, Durban, South Africa

K. Mlisana
National Health Laboratory Services, Johannesburg, South Africa

Q. Abdool Karim et al. (eds.), *The CAPRISA Clinical Trials: HIV Treatment and Prevention*, DOI 10.1007/978-3-319-47518-9_10

lescent girls and young women is considered critical to altering the course of the HIV epidemic and the study originally proposed to include both adolescents and young adults. However, due to ethico-legal challenges with enrolling adolescents the protocol was amended to only include adults from the age of 18 years and older [1].

At the time of study initiation, there was a limited understanding of how disease progression was affected by viral subtype, early immune responses, host genetics, socio-economic conditions and the environment. Furthermore, candidate HIV vaccines being considered for efficacy trials in the 2000s were likely to act principally by reducing viral load, and there was a lack of data on clinical predictors of disease progression in African cohorts. Events in acute infection contribute disproportionally to subsequent disease progression, and it was reasoned that studying how people initially control the virus would help design vaccines that elicited T cell responses. The high incidence of HIV in the country provided CAPRISA researchers with a unique opportunity to identify these individuals in very early infection. As the cohort matured and the field evolved, the study changed its focus from cellular to humoral immunity. Identifying women in the Acute Infection Study (or AI study) who naturally developed broadly neutralising antibodies allowed us to investigate antibody development, which will help to design strategies to elicit these types of responses through vaccination.

Established by South African scientists, the AI Study was one of the first of its kind in Africa to interrogate, in great depth, HIV natural history of disease (Fig. 1), and to translate these findings into discovery of interventions including the identification of a highly potent broadly neutralising antibody that will be evaluated for the prevention of HIV infection.

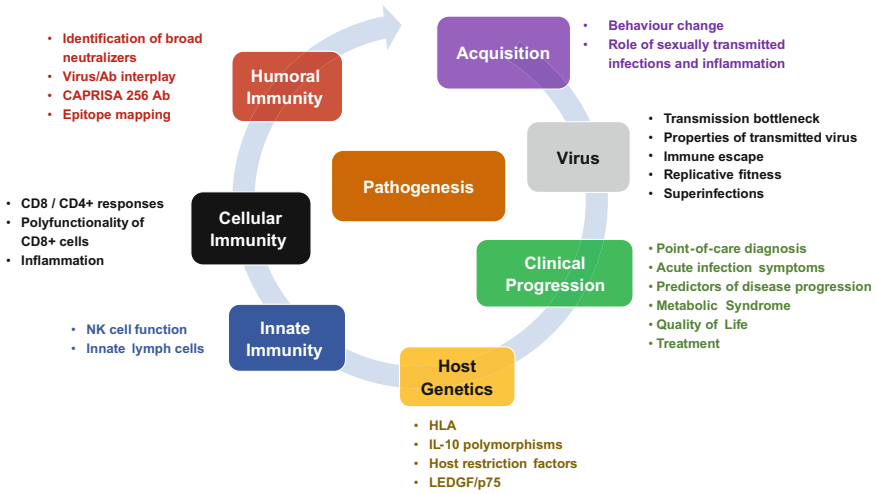

Fig. 1 Continuum of CAPRISA 002 acute infection studies

1.1 Establishment of CAPRISA 002 Acute Infection Cohort

Between August 2004 and May 2005, we enrolled an HIV uninfected cohort of women at high risk for HIV acquisition, as evidenced by self-reported sex work or having more than three sexual partners in the three preceding months [2]. Table 1 outlines some of the key areas to consider when setting up research cohorts. One of the key successes of the AI cohort was the initial reliance on Community Liaison Persons (CLPs) who were familiar with the networks and were therefore able to recruit these high risk women. This HIV negative cohort was followed for 24 months with monthly HIV antibody testing, and RNA-PCR performed on all antibody negative samples using a pooling algorithm [3]. To increase numbers, we also recruited women within three months of a previous HIV-negative diagnosis from other prevention cohorts, including women who became infected while participating in the CAPRISA 004 microbicide trial [4]. Following identification of acute HIV infection, women were followed every week for a month, every two weeks up to 3 months post infection, monthly for a year and quarterly thereafter (Fig. 2).

Establishing observational cohorts in resource poor environments provides unique challenges which will differ between locations and populations. These challenges include poor access to health infrastructure; social, cultural and logistical hurdles; retaining study participants, who tended to be highly mobile, for an extended period of time; and difficulties in contacting individuals using conventional means. The initial funder, the US National Institute of Allergy and Infectious Diseases (NIAID) does not support provision of drugs, and the lack of South African government support for antiretroviral (ARV) provision at the time of protocol development posed an ethical dilemma to the AI team. Fortunately, in late 2003 the government reversed its policy, and ARV roll-out started, albeit slowly. To ensure women had access to treatment while the government ARV programme was being developed, in 2004 CAPRISA established the CAPRISA AIDS Treatment programme (CAT), funded by the PEPFAR programme, with the Global Fund supporting the costs of ARVs. Over time, the requirement for a CAPRISA dedicated programme diminished, and by 2013 all women had been transitioned from CAT to government clinics for treatment.

Table 1 Key areas to consider when setting up research cohorts

• Adequate community engagement
• Intensive training of the research and clinical staff
• Development of an extensive manual of operations with clear standard operating procedures (SOPs) for consistency
• Creation of a safe and participant friendly atmosphere in the research clinic with provision of good medical care
• Detailed quality management plan that ensures collection of good quality data
• Constant monitoring of study procedures, participant accrual and retention

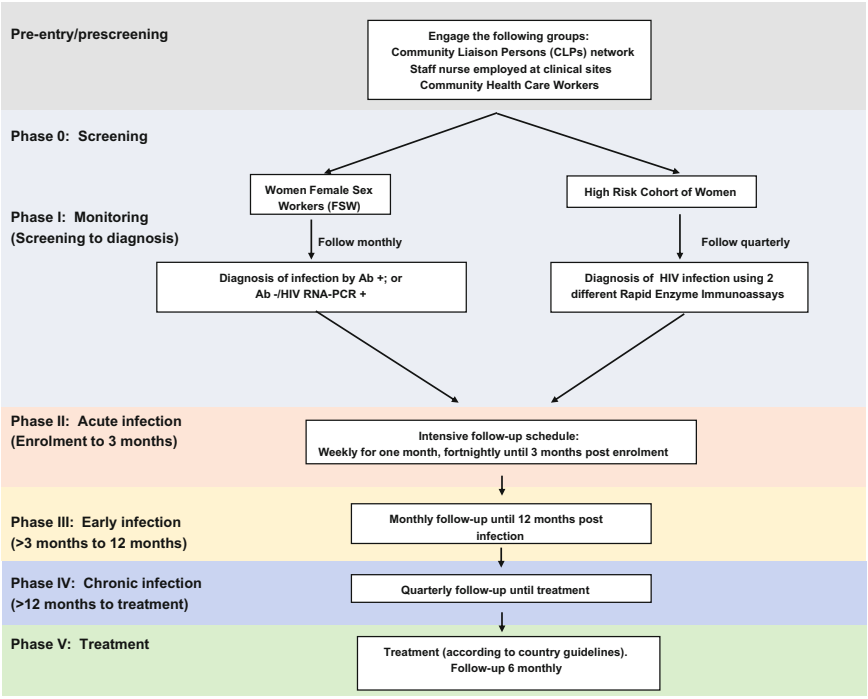

Fig. 2 Study schema

To date, 233 recently HIV-infected women have been recruited into the AI cohort. Despite the low socio-economic status and high mobility of these women, the retention has remained extremely high, at 95 % after 12 years. We attribute this success in retaining the cohort to a combination of factors, including strong relationships between participants and experienced staff members, a structured engagement with the community supported by the CAPRISA Community Advisory Board, and the dedication of these women to continue to participate in an important project. Other contributing factors are benefits for the women in the study who have access to good medical care and sexually transmitted infection (STI) screening, monetary reimbursement and experienced counsellors and trackers who would call or send text messages to participants before appointments and conduct home visits if visits are missed.

1.2 HIV Subtype C Disease Progression: Informing Treatment Programmes

The majority (98 %) of CAPRISA participants were infected with HIV subtype C based on gag and/or env sequencing. Following infection, we observed a significant

loss of CD4 cells, with women losing almost 50 % of their pre-infection CD4 cells by 6 months post infection, and little CD4 count rebound following acute infection. Nearly half of women progressed to a CD4 count <350 cells/μL (previous SA and WHO guidelines for initiation of therapy) within 2 years of infection, and delineating by CD4 count <500 cells/μL, nearly 70 % of individuals would be eligible to start antiretroviral therapy (ART) within one year of HIV infection (current South African guidelines) (Fig. 3). Both early CD4 count (3 months post infection) and viral load set point (12 months post infection) were predictive of disease progression [5].

The infrastructure established for CAPRISA 002 enabled us to recruit women who seroconverted while participating in other HIV prevention cohorts. One example is the CAPRISA 004 1 % Tenofovir gel (TFV) microbicide trial [4]. An unexpected finding from this trial was the higher viral load set point in women who were enrolled in the TFV compared to the placebo arm [6]. This observation demonstrates the importance of having epidemiological and basic science infrastructure to support clinical trials. Although we found no differences in the number of transmitted variants nor gag-protease replication capacity between viruses breakthrough infections in the TFV compared to placebo arm [7, 8], individuals in the TFV arm had slower antibody avidity maturation.

The rapid disease progression observed in this cohort highlights the importance of identifying individuals with acute HIV infection, and supports the 'Test and Treat' approach when managing the disease (latest WHO guidance and to be implemented in South Africa). To support this, one recent project in CAPRISA evaluated the GeneXpert HIV-1 viral load point-of-care test [9], an assay that could assist in diagnosing people with acute infections in the clinic setting [10]. Expanding the number of individuals on ART poses serious challenges to the country in terms of drug costs, concomitant cost of viral load monitoring and resistance testing, and ensuring long-term ART adherence. However, earlier treatment confers many benefits, not just to the patient, but also by reducing community viral load and preventing subsequent transmission.

Since 2015, the AI participants have been offered treatment at diagnosis, because of the overwhelming evidence for an individual [11, 12] and a public health benefit [13] of starting therapy early. The uptake of early treatment has been high, with more than 90 % of AI participants now on treatment. Viral load suppression rates

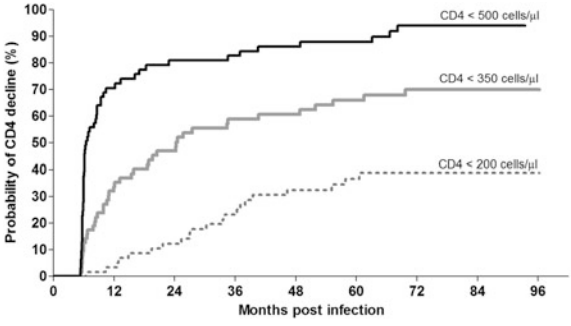

Fig. 3 Superimposed Kaplan–Meier graphs of time to CD4 count <200 cells/μl, <350 cells/μl and <500 cells/μl since estimated date of infection. Figure from Mlisana et al. [5]

have been consistently above 85 % up to 3 years after treatment initiation. Another objective of the study was to assess quality of life of participants from diagnosis, and it was interesting to observe that quality of life scores increased steadily from diagnosis, and continued to rise once treatment was commenced [14, 15].

1.3 HIV Pathogenesis: The Transmitted Virus and Immune Escape

The intense follow up of the AI cohort enabled us to undertake studies to understand the HIV transmission event at a molecular level. Generation of viral sequences from the first time point following infection elucidated the characteristics of the transmitted virus and demonstrated that in 80 % of subtype C infected Africans, only one viral variant caused infection, despite the exposure to hundreds of millions of variants in the sexual inoculum [16]. This result is critical for vaccine and microbicide development as it suggests that there is a severe bottleneck associated with transmission and that biomedical interventions only have to block a minimal dose.

The ability to clone these viruses that initiate infection—so-called transmitted/founder (t/f) viruses—is key to the field as these are the targets that vaccines need to block. These t/f viruses that cross the mucosal barrier may have a phenotype that distinguishes them from viruses sampled during chronic infection [17]. CAPRISA has contributed significantly to a large panel of subtype C envelope clones that has provided valuable information for vaccinologists. First, viruses collected pre-seroconversion were shown to be more resistant to neutralisation compared to post-seroconversion viruses, in part due to key glycans relevant to immune recognition by broadly neutralising antibodies that are present at a lower frequency on t/f viruses [18]. Second, these studies provided evidence of antigenic drift with viruses becoming more neutralisation resistant as the epidemic matured, suggesting that vaccines may need to be updated occasionally to track the evolving epidemic. This panel provides valuable reagents to the field when screening for and assessing vaccine responses and cross-reactive monoclonal antibodies.

The extraordinary variability of HIV-1 enables the virus to rapidly escape immune responses. Escape mutations located in functionally important regions can attenuate viral replication resulting in lower viral load, although this may be marginal and this benefit is not necessarily sustained [19, 20]. The AI cohort was one of the first to show that people infected with viruses harbouring attenuating immune escape mutations have a survival advantage. Future vaccine strategies have the potential to drive the virus down an evolutionary pathway, which would result in a less fit virus. While this approach may only provide temporary benefit to the individual, lowering viral load may provide a community benefit by reducing the risk of transmission.

1.4 HIV Pathogenesis: Cellular Immunity

Following the failure of early vaccine trials that had aimed to elicit protective antibodies, efforts in the early 2000s were refocused on elucidating adaptive cellular immunity. It was thought that eliciting these responses through vaccination would control, or even eliminate, the early foci of infection; or, lower viral loads and thus halt or slow disease progression and lower transmission. To inform vaccine design, early studies in CAPRISA focused on identifying cellular immune responses associated with viral control. The frequent sampling of the cohort during early HIV infection enabled a detailed description of the emergence of HIV-specific CD8 T cell responses within the first year of infection, with HIV Nef responses being detectable as early as three weeks post infection [21]. The loss of these responses coincided with viral escape, whereas persistence of responses was associated with slower disease progression. An important additional result was that simple analysis of IFN-γ production to measure the magnitude of the HIV-specific CD8 T cell response was a poor predictor of viral set point [22].

Following disappointing results in vaccine trials testing the T cell vaccine concept (HVTN505 and STEP/Phambili), a key concept that emerged in the field was that single measures of cellular immune function were limited in predicting viral control. Rather, multiple measures of the quality of the T cell response to HIV may be important, including the magnitude (size), specificity (which HIV regions are targeted), polyfunctionality (ability to secrete multiple antiviral cytokines) and the memory differentiation status (a measure of longevity of the response). Thus, in order to dissect the relative contribution to viral control of the quantity versus quality of the CD8+ T cell response, we analysed the influence of a combination of these factors, and found that a high magnitude of polyfunctional CD8+ T cells targeting HIV Gag and Nef were associated with lower viral set point, as well as a central memory differentiation phenotype [23, 24]. These data highlighted the importance of eliciting such cells by vaccination to enable the best outcome following breakthrough infection.

As the cohort evolved and participants initiating ART increased, it became clear that there was value in continuing to study HIV infection in the context of viral suppression. Although the clinical benefit of ART is undeniable, and CD4+ T cell numbers recover with successful therapy, we do not have a good understanding of whether functional aspects of the immune system are restored fully when viral load is suppressed, or whether some immune abnormalities persist despite the absence of virus. It is of particular importance to define the factors that associate with successful pathogen-specific CD4+ T cell recovery upon ART, as limited normalisation of functional CD4+ T cell responses could account for sustained incidence of opportunistic infections. We demonstrated that the memory differentiation phenotype of CD4+ T responses to common co-pathogens such as *Mycobacterium tuberculosis* or Cytomegalovirus dictated their replenishment, and can substantially limit restoration of immunity that was depleted during untreated HIV infection [25].

Studying treated HIV infection also gives us the opportunity to ask questions about the HIV reservoir during long-term successful ART. Understanding the size and dynamics of the HIV reservoir is a critical question in HIV cure research, and we can retrospectively examine early factors that may influence the size of the reservoir over the course of HIV infection.

1.5 Neutralising Antibodies and Their Targets

The identification of individuals during acute HIV-1 infection made it possible to study the timing and kinetics of the neutralising antibody response. An analysis of the sensitivity of t/f viruses from CAPRISA participants to their own serum antibodies showed that everyone develops strain-specific neutralising antibodies within the first five months of HIV-1 infection [26]. These antibodies predominately target the variable regions of the envelope explaining their strain-specificity and the ability of the virus to escape rapidly with minimal impact on viral load [27]. The importance of these early antibody responses in shaping viral populations that stimulate later antibodies with more cross-neutralising activity has now become apparent. We were the first to show that shifting sugar molecules on the viral envelope in order to escape strain-specific antibodies created a new epitope that became the target of later broadly neutralising antibodies [18, 28].

The storage of longitudinal samples in the CAPRISA cohort has proved to be an extremely valuable resource, enabling important scientific findings. As broadly neutralising antibodies only develop in some individuals and take between 2 and 4 years to appear [29], it was this long-term repository of samples that enabled intensive retrospective studies of women who eventually developed broadly neutralising antibodies, to map their targets on the HIV Env protein, define how they developed and characterise the associated changes in viral populations.

Monoclonal antibodies from a number of research groups have helped to define the targets of broadly neutralising antibodies on the HIV-1 envelope glycoprotein [30]. These sites of vulnerability cluster to five regions: the CD4 binding site (CD4bs), the V1V2 region on the apex of the trimer, the V3 glycan supersite, the linear MPER region in gp41 and a trimer-specific target in the gp120-gp41 interface. Mapping of the plasma responses in the CAPRISA cohort has shown the presence of antibodies targeting all five sites (Fig. 4). Monoclonal antibodies that target all sites of vulnerability have been isolated and, although not all are broadly neutralising, they represent the broadly neutralising lineage, potentially enabling the isolation of related members through large-scale sequencing of single sorted B cells.

Comparative studies using samples from CAPRISA participants who did not develop broadly neutralising antibodies have also provided important insights. In particular, one such study showed that the germline antibody gene repertoires do not differ between people who develop broadly neutralising antibodies and those

who do not [31]. This study was prompted by the observation that HIV antibodies, particularly those to the CD4bs, show restricted germline gene usage, in other words, they only use particular genes to make anti-HIV antibodies. One possibility was that the absence of these genes may explain why some individuals fail to make broadly neutralising antibodies. However, this was not found to be the case, which is encouraging for vaccine design, as it suggests that everyone has the same genetic potential to make broadly neutralising antibodies to HIV.

Samples from sites other than blood have also been collected from women in the CAPRISA cohort and proven to be very useful. This includes samples collected via a cervicovaginal lavage or placement of a menstrual cup which allowed us to demonstrate that the antibody specificities in the female genital tract, including those associated with broad neutralising activity, were similar to those found in blood [32, 33]. This is important for vaccines and passive immunisation since both rely on systemic antibodies reaching the sites of transmission, namely the genital mucosa. Another important finding was that the HIV-specific antibodies were almost exclusively IgG rather than IgA, which is more typically found in mucosal secretions.

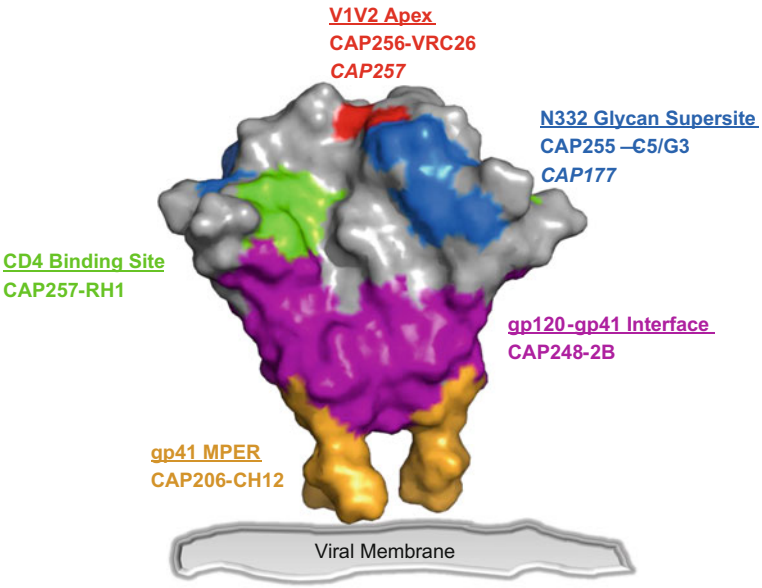

Fig. 4 Broadly neutralising antibodies identified in CAPRISA study participants. The trimeric HIV envelope spike with each of the five targets of broadly neutralising antibodies shown in a different colour. Monoclonal antibodies isolated from 5 CAPRISA participants are indicated below each target with the donor identifier included as a prefix. The plasma specificity for 2 participants is shown in italics. CAP257 was found to have at least 2 specificities. Figure drawn by Constantinos Kurt Wibmer

2 Translational Science, from Bench-to-Bedside: The Story of CAP256

The exceptional potency and breadth of the neutralising antibodies in the plasma of one participant, CAP256, was recognised early on [29, 34]. This donor was super-infected in 2005 with two distinct HIV-1 subtype C viruses and developed broadly neutralising antibodies as early as one year after infection, which increased in neutralisation breadth by three years (Fig. 5).

In collaboration with Dr John Mascola and Dr Peter Kwong of the Vaccine Research Center at the National Institutes of Allergy and Infectious Diseases (USA), we isolated a family of related monoclonal antibodies that recapitulated the plasma neutralisation breadth [35, 36]. Like the serum, the CAP256-VRC26 antibody lineage targets the V1V2 epitope on the HIV-1 envelope glycoprotein [34]. The value of having samples from acute infection through to the development of breadth has been most evident in this participant, where we could trace the evolution of the heavy and light chain antibody genes and showed that the long CDRH3 that is characteristic of antibodies targeting this region was present in the original progenitor B cell [35]. This was a major insight for vaccines as it suggests

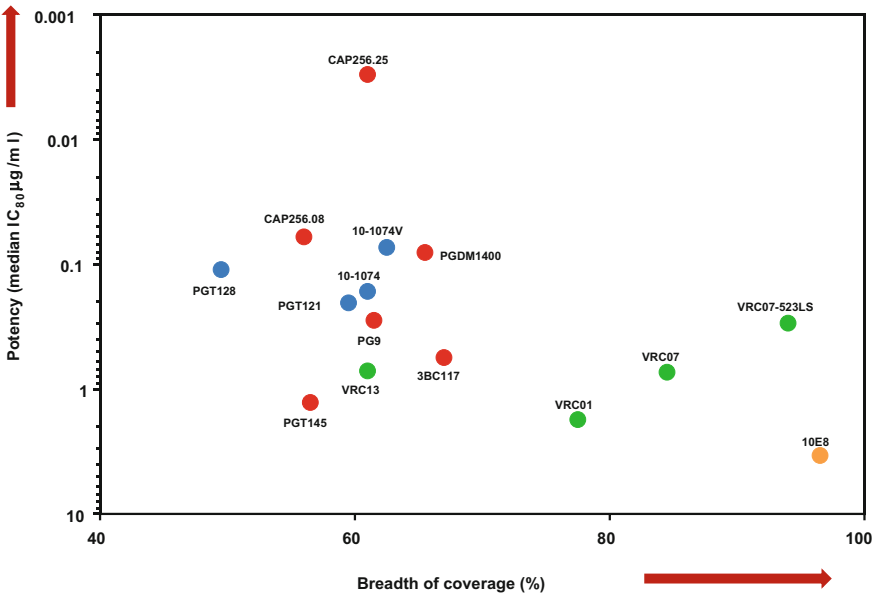

Fig. 5 Potency and breadth of CAP256-VRC26.25. Potency-breadth plot of 15 broadly neutralising antibodies targeting four distinct epitopes on the HIV-1 envelope glycoprotein. Percentage breadth was measured against a panel of 200 acute/early clade C HIV-1 Env pseudoviruses. IC_{80} is the concentration required to inhibit viral entry by 80 %. CAP256-VRC26.25 showed the highest potency against this panel. Figure drawn by Jinal Bhiman using data from Wagh et al. PLoS Pathogens, [38]

that an immunogen needs to engage rare B cells that harbour long CDRH3 regions. Screening of large numbers of viruses identified a small number of special strains including the CAP256 virus that are able to bind these progenitor antibodies [36]. The availability of monoclonal antibodies, together with well characterised viral clones, allowed us to definitively show that viral diversity drives neutralisation breadth. We found that the broadest antibodies are able to neutralise the myriad of escaped variants by tolerating variation in the epitope [37]. We have designed envelope immunogens incorporating these features, which will be tested to determine if they can elicit anti-V1V2 antibodies.

One antibody, called CAP256-VRC26.25, was shown to be one of the most potent antibodies identified to date, and is now under development for passive immunisation studies (Chap. 7).

3 Enablers of Success

The CAPRISA 002 Acute Infection Study was established to address major South African research priorities: first to aid in the development of a cost-effective prophylactic vaccine that could control the HIV epidemic; and second to inform HIV clinical management and treatment policy. It later broadened its mandate to support microbicide research, and more recently cure research. Differences in the virus, host and environment required these studies to be conducted in South Africa and the network of South African investigators who implemented the AI study, were uniquely placed to do this research. Furthermore, the high incidence of HIV enabled the recruitment of adequate numbers of participants to address these scientific questions.

To maximise impact, scientists with varying expertise from four academic centres around South Africa were assembled to write the original project proposal, including Universities of KwaZulu-Natal, Cape Town, Witwatersrand and Western Cape. This had a multiplier effect as it harnessed the best talent, across multiple disciplines, from around the country irrespective of institutional affiliation. The dispersed model required special attention to communication and the development of a common vision, which was essential as it provided a foundation for trust resulting in free discussion and exchange of data within a transparent agenda. The inclusion of researchers with complementary expertise in clinical, behavioural, virological, immunological and bioinformatics research provided a greater critical mass to achieve high quality research with great impact. Active mentorship and development of younger scientists, together with this model of multiple principal investigators, provided greater long-term sustainability.

At the time of establishing CAPRISA, many of the investigators were internationally linked through, for example, the WHO, African AIDS Vaccine Programme, International AIDS Vaccine Initiative, South African AIDS Vaccine Initiative and HIV Vaccine Trials Network. Through these scientific collaborations, key researchers in the field, such as Ron Swanstrom, James Mullins, David Montefiori

and Julie McElrath provided early assistance in study design and grant writing. However, the major foundation of success was the early funding and expertise provided by CIPRA (NIAID, NIH, USA), which resulted in the establishment of a high quality cohort, repository and data management system. This paved the way for high quality specimens (despite long-term storage), and data—a cornerstone to all science—and provided leverage for future funding.

The AI study objectives were also aligned to those of the global funders, enabling the group to build on this initial investment. CAPRISA was well placed to become partners with two highly collaborative consortia that had an interest in elucidating mechanisms of transmission and developing reagents for vaccine trials, including the NIAID-funded Centre for HIV/AIDS Vaccine Immunology (CHAVI), established in 2005 and led by B. Haynes (Duke University); as well as the Collaboration for AIDS Vaccine Discovery (CAVD) funded by the Bill and Melinda Gates Foundation and led by D. Montefiori (Duke University). In addition to greater funding, being part of these consortia provided CAPRISA 002 investigators with greater access to scientific expertise and reagents, and ultimately enabled research that had a greater impact.

The AI team has a highly collaborative approach to research and as such, supports the principle of data and reagent sharing as a mechanism to accelerate the development of an HIV vaccine. This is done under standard approaches of material transfer agreements for clinical material, and a more lenient approach to sharing through the provision of reagents and data directly to other scientists, and to HIV/AIDS repositories [38, 39]. This approach has facilitated a global focus on subtype C infections. It has also enabled the establishment of collaborations which have allowed CAPRISA researchers to access cutting edge technologies, reagents and resources. These collaborations have also provided training to South African scientists.

A key aspect of the success of CAPRISA has been the training of young scientists funded for many years through the Columbia University-Southern African Fogarty AIDS Training Programme, and more recently the Collaboration for AIDS Vaccine Discovery (CAVD). The approach of sending students to collaborating laboratories with CAPRISA samples to answer a defined question (and often to learn new techniques) proved to be very productive. In addition to enhancing skills and enabling technology transfer, these student training trips initiated or strengthened collaborations between CAPRISA and international laboratories. This produced many Ph.D. graduates, more than 100 publications (Table 2) and led to new sources of funding.

While largely a basic and clinical science project, the CAPRISA 002 Acute Infection study has informed policy, and there are plans to translate some of these bench findings into clinical trials. The CAPRISA 002 study has transitioned a critical stage in the history of HIV research: funded in 2002 when treatment was not available in the public sector, up to today when we are implementing a ‘Test and Treat’ approach. It will not be possible to perform pathogenesis studies in the absence of treatment in the future, making the repository of high scientific value. The AI study is based firmly within the community and decisions are anchored within the long-term goal of benefitting the community and South Africa through the

Table 2 Ten top impact findings from the CAPRISA 002 Acute Infection Cohort (google citations >50 indicated, as of March 2016)

1. Establishing a cohort at high risk of HIV infection in South Africa (von Loggerenberg et al. Plos One 2008; 101 citations), and elucidation of rapid disease progression (Mlisana et al. CID. 2014)
2. Symptomatic vaginal discharge is a poor predictor of sexually transmitted infections suggesting syndromic management is suboptimal (Mlisana et al. JID. 2012, 50 citations)
3. 80 % of individuals are infected with a single virus suggesting a severe transmission bottleneck and a low viral dose for vaccines to block (Abrahams et al. JV. 2009; 258 citations)
4. Identification of virological and immunological factors associated with HIV-1 differential disease progression; and observation that viruses containing certain CTL escape variants provided HLA-mismatched recipients with a survival advantage (Chopera et al. JV. 2011); (Chopera et al. Plos Path. 2008; 124 citations)
5. HIV-specific and total CD8+ T memory phenotypes associated with viral set (Burgers et al. JI. 2009; 60 citations)
6. Timing of neutralising antibody responses in acute infection (Gray et al. JV. 2007; 234 citations); elucidation of their targets (Moore et al. JV. 2008; 134 citations); (Moore et al. Plos Path. 2009; 150 citations)
7. Identification of neutralisation breadth in ~20 % of individuals over four years provides foundation for studies aimed at identifying factors associated with broadly neutralising antibodies (bNAbs) for translation to vaccine design (Gray et al. JV. 2011, 234 citations)
8. Viral escape from autologous neutralising antibodies creates new epitopes that are the target for bNAbs, shows for the first time, how viral factors influence bNAb development (Moore et al. Nat Med. 2012, 140 citations); and how escape drives increased plasma neutralisation breadth through sequential recognition of multiple epitopes and immunotypes (Wibmer et al. Plos Path. 2013; 50 citations)
9. Viral diversity is needed for bNAb development suggesting that a cocktail of sequential immunogens that mimic viral evolution may need to be part of a vaccination strategy (Bhiman et al. Nat Med. 2015)
10. Isolation of a highly potent monoclonal antibody from CAP256, which targets the V1V2 region and is derived from rare B cell precursors suggesting a vaccine will require special features to engage them (Doria-Rose et al. Nature. 2014, 136 citations)

development of effective biomedical interventions. The national, African and global alignment of the CAPRISA 002 model enabled access to both funding and expertise. The cooperative, collaborative, multi-institutional, multi-principal investigator model facilitated high quality, high impact research, as well as sustainability.

References

1. Singh JA, Abdool Karim SS, Abdool Karim Q, Mlisana K, Williamson C, Gray C, et al. Enrolling adolescents in research on HIV and other sensitive issues: Lessons from South Africa. PLoS Med. 2006; 3: 0984–8.
2. van Loggerenberg F, Mlisana K, Williamson C, Auld SC, Morris L, Gray CM, et al. Establishing a cohort at high risk of HIV infection in South Africa: Challenges and experiences of the CAPRISA 002 acute infection study. *PLoS One* 2008; 3. DOI:10.1371/journal.pone.0001954.

3. Abdool Karim SS, Mlisana K, Kharsany ABM, Williamson C, Baxter C, Abdool Karim QA. Utilizing nucleic acid amplification to identify acute HIV infection. *AIDS* 2007; 21: 653–5.
4. Abdool Karim Q, Abdool Karim SS, Frohlich J, Grobler AC, Baxter C, Mansoor LE, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women.[Erratum appears in Science. 2011 Jul 29;333(6042):524]. *Science (80-)* 2010; 329: 1168–74.
5. Mlisana K, Werner L, Garrett NJ, McKinnon LR, van Loggerenberg F, Passmore JA, et al. Rapid disease progression in HIV-1 subtype c-infected South African women. *Clin Infect Dis* 2014; 59: 1322–31.
6. Garrett NJ, Werner L, Naicker N, Naranbhai V, Sibeko S, Samsunder N, et al. HIV disease progression in seroconvertors from the CAPRISA 004 tenofovir gel pre-exposure prophylaxis trial. *J Acquir Immune Defic Syndr* 2015; 68: 55–61.
7. Valley-Omar Z, Sibeko S, Anderson J, Goodier S, Werner L, Arney L, et al. CAPRISA 004 tenofovir microbicide trial: No impact of tenofovir gel on the HIV transmission bottleneck. *J Infect Dis* 2012; 206: 35–40.
8. Chopera DR, Mann JK, Mwimanzi P, Omarjee S, Kuang XT, Ndabambi N, et al. No Evidence for Selection of HIV-1 with Enhanced Gag-Protease or Nef Function among Breakthrough Infections in the CAPRISA 004 Tenofovir Microbicide Trial. *PLoS One* 2013; 8. DOI:10.1371/journal.pone.0071758.
9. Garrett NJ, Drain P, Werner L, Samsunder N, Abdool Karim SS. Diagnostic Accuracy of the Point-of-care Xpert® HIV-1 Viral Load Assay in a South African HIV clinic. *J Acquir Immune Defic Syndr* 2016; published online March 8. DOI:10.1097/QAI.0000000000000978.
10. Sanders EJ, Wahome E, Powers KA, Werner L, Fegan G, Lavreys L, et al. Targeted screening of at-risk adults for acute HIV-1 infection in sub-Saharan Africa. *AIDS* 2015; 29 Suppl 3: S221–30.
11. INSIGHT START Study Group. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. *N Engl J Med* 2015; 373: 1–13.
12. Danel C, Moh R, Gabillard D, Badje A, Le Carrou J, Ouassa T, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *N Engl J Med* 2015; 373: 808–22.
13. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011; 365: 493–505.
14. Tomita A, Garrett N, Werner L, Burns JK, Mpanza L, Mlisana K, et al. Health-related quality of life dynamics of HIV-positive South African women up to ART initiation: Evidence from the CAPRISA 002 acute infection cohort study. *AIDS Behav* 2014; 18: 1114–23.
15. Tomita A, Garrett N, Werner L, Burns JK, Ngcobo N, Zuma N, et al. Impact of antiretroviral therapy on health-related quality of life among South African women in the CAPRISA 002 acute infection study. *AIDS Behav* 2014: 1801–7.
16. Abrahams M-R, Anderson JA, Giorgi EE, Seoighe C, Mlisana K, Ping LH, et al. Quantitating the multiplicity of infection with human immunodeficiency virus type 1 subtype C reveals a non-poisson distribution of transmitted variants. *J Virol* 2009; 83: 3556–67.
17. Ping L-H, Joseph SB, Anderson JA, Abrahams MR, Salazar-Gonzalez JF, Kincer LP, et al. Comparison of viral Env proteins from acute and chronic infections with subtype C human immunodeficiency virus type 1 identifies differences in glycosylation and CCR5 utilization and suggests a new strategy for immunogen design. *J Virol* 2013; 87: 7218–33.
18. Moore PL, Gray ES, Wibmer CK, Bhiman JN, Nonyane M, Sheward DJ, et al. Evolution of an HIV glycan-dependent broadly neutralizing antibody epitope through immune escape. *Nat Med* 2012; 18: 1688–92.
19. Chopera DR, Mlotshwa M, Woodman Z, Mlisana K, de Assis Rosa D, Martin DP, et al. Virological and immunological factors associated with HIV-1 differential disease progression in HLA-B 58:01-positive individuals. *J Virol* 2011; 85: 7070–80.
20. Ntale RS, Chopera DR, Ngandu NK, de Assis de Rosa D, Zembe L, Gamieldien H, et al. Temporal association of HLA-B*81:01- and HLA-B*39:10-mediated HIV-1 p 24 sequence evolution with disease progression. *J Virol* 2012; 86: 12013–24.

21. Mlotshwa M, Riou C, Chopera D, de Assis Rosa D, Ntale R, Treunicht F, et al. Fluidity of HIV-1-specific T-cell responses during acute and early subtype C HIV-1 infection and associations with early disease progression. *J Virol* 2010; 84: 12018–29.
22. Gray CM, Mlotshwa M, Riou C, Mathebula T, de Assis Rosa D, Mashishi T, et al. Human immunodeficiency virus-specific gamma interferon enzyme-linked immunospot assay responses targeting specific regions of the proteome during primary subtype C infection are poor predictors of the course of viremia and set point. *J Virol* 2009; 83: 470–8.
23. Burgers WA, Riou C, Mlotshwa M, Maenetje P, de Assis Rosa D, Brenchley J, et al. Association of HIV-specific and total CD8+ T memory phenotypes in subtype C HIV-1 infection with viral set point. *J Immunol* 2009; 182: 4751–61.
24. Riou C, Burgers WA, Mlisana K, Koup RA, Roederer M, Abdool Karim SS, et al. Differential impact of magnitude, polyfunctional capacity, and specificity of HIV-specific CD8+ T cell responses on HIV set point. *J Virol* 2014; 88: 1819–24.
25. Riou C, Tanko RF, Soares AP, Masson L, Werner L, Garrett NJ, et al. Restoration of CD4 + Responses to Copathogens in HIV-Infected Individuals on Antiretroviral Therapy Is Dependent on T Cell Memory Phenotype. *J Immunol* 2015; 195: 2273–81.
26. Gray ES, Moore PL, Choge IA, Decker JM, Bibollet-Ruche F, Li H, et al. Neutralizing antibody responses in acute human immunodeficiency virus type 1 subtype C infection. *J Virol* 2007; 81: 6187–96.
27. Moore PL, Ranchobe N, Lambson BE, Gray ES, Cave E, Abrahams MR, et al. Limited neutralizing antibody specificities drive neutralization escape in early HIV-1 subtype C infection. *PLoS Pathog* 2009; 5: e1000598.
28. Wibmer CK, Bhiman JN, Gray ES, Tumba N, Abdool Karim SS, Williamson C, et al. Viral escape from HIV-1 neutralizing antibodies drives increased plasma neutralization breadth through sequential recognition of multiple epitopes and immunotypes. *PLoS Pathog* 2013; 9: e1003738.
29. Gray ES, Madiga MC, Hermanus T, Moore PL, Wibmer CK, Tumba NL, et al. The neutralization breadth of HIV-1 develops incrementally over four years and is associated with CD4+ T cell decline and high viral load during acute infection. *J Virol* 2011; 85: 4828–40.
30. Wibmer CK, Moore PL, Morris L. HIV broadly neutralizing antibody targets. *Curr Opin HIV AIDS* 2015; 10: 135–43.
31. Scheepers C, Shrestha RK, Lambson BE, Jackson KJ, Wright IA, Naicker D, et al. Ability to develop broadly neutralizing HIV-1 antibodies is not restricted by the germline Ig gene repertoire. *J Immunol* 2015; 194: 4371–8.
32. Archary D, Seaton KE, Passmore JS, Werner L, Deal A, Dunphy LJ, et al. Distinct genital tract HIV-specific antibody profiles associated with tenofovir gel. *Mucosal Immunol* 2016; 9 (3): 834. DOI:10.1038/mi.2016.21.
33. Mkhize NN, Durgiah R, Ashley V, Archary D, Garrett NJ, Abdool Karim Q, et al. Broadly neutralizing antibody specificties detected in the genital tract of HIV-1 infected women. *AIDS* 2016; 30(7): 1005–14.
34. Moore PL, Gray ES, Sheward D, Madiga M, Ranchobe N, Lai Z, et al. Potent and broad neutralization of HIV-1 subtype C by plasma antibodies targeting a quaternary epitope including residues in the V2 loop. *J Virol* 2011; 85: 3128–41.
35. Doria-Rose NA, Schramm CA, Gorman J, Moore PL, Bhiman JN, DeKosky BJ, et al. Developmental pathway for potent V1V2-directed HIV-neutralizing antibodies. *Nature* 2014; 509: 55–62.
36. Gorman J, Soto C, Yang MM, Davenport TM, Guttman M, Bailer RT, et al. Structures of HIV-1 Env V1V2 with broadly neutralizing antibodies reveal commonalities that enable vaccine design. *Nat Struct Mol Biol* 2016; 23: 81–90.

37. Bhiman JN, Anthony C, Doria-Rose NA, Karimanzira O, Schramm CA, Khoza T, et al. Viral variants that initiate and drive maturation of V1V2-directed HIV-1 broadly neutralizing antibodies. *Nat Med* 2015; 21: 1332–6.
38. Wagh K, Bhattacharya T, Williamson C, Robles A, Bayne M, Garrity J, et al. Optimal Combinations of Broadly Neutralizing Antibodies for Prevention and Treatment of HIV-1 Clade C Infection. *PLoS Pathog* 2016; Mar 30: e1005520.
39. Bures R, Morris L, Williamson C, Ramjee G, Deers M, Fiscus SA, et al. Regional clustering of shared neutralization determinants on primary isolates of clade C human immunodeficiency virus type 1 from South Africa. *J Virol* 2002; 76: 2233–44.
40. Mlisana K, Naicker N, Werner L, Roberts L, van Loggerenberg F, Baxter C, et al. Symptomatic vaginal discharge is a poor predictor of sexually transmitted infections and genital tract inflammation in high-risk women in South Africa. *J Infect Dis* 2012; 206: 6–14.
41. Chopera DR, Woodman Z, Mlisana K, Mlotshwa M, Martin DP, Seoighe C, et al. Transmission of HIV-1 CTL escape variants provides HLA-mismatched recipients with a survival advantage. *PLoS Pathog* 2008; 4. DOI:10.1371/journal.ppat.1000033.
42. Moore PL, Gray ES, Choge IA, Ranchobe N, Mlisana K, Abdool Karim SS, et al. The c3-v4 region is a major target of autologous neutralizing antibodies in human immunodeficiency virus type 1 subtype C infection. *J Virol* 2008; 82: 1860–9.

Chapter 11
Advancing Understanding of HIV Infection in Women Through Mucosal Immunology Studies

Jo-Ann S. Passmore, Lenine L. Liebenberg, Nonhlanhla N. Mkhize, Derseree Archary and Lindi Masson

1 Building a Mucosal Immunology Program at CAPRISA to Understand HIV Acquisition in Women

1.1 Introduction

By the late 1990s, it emerged that HIV activated the immune system and that this chronic immune activation played an important role in HIV disease progression [1–3]. It had been shown that T cell activation, even during early HIV infection, was associated with more rapid disease progression [4].

By 1994, the HIV epidemic had hit South Africa hard and was well-established and generalised, with a faster progressing clinical course than observed internationally [5]. Adolescent girls and young women (AGYW) in eastern and southern Africa were acquiring HIV infection 5–7 years earlier than their male peers and had up to eightfold higher burden of HIV infection. This underscored the need to determine who these AGYW were acquiring HIV from and why there was such a

J.S. Passmore (✉) · L. Masson
Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, Cape Town, South Africa
e-mail: Jo-ann.Passmore@uct.ac.za

J.S. Passmore
National Health Laboratory Services, University of KwaZulu-Natal, Cape Town, South Africa

L.L. Liebenberg · D. Archary
Centre for the AIDS Programme of Research in South Africa, University of KwaZulu-Natal, Durban, South Africa

N.N. Mkhize
Center for HIV and STIs, National Institute for Communicable Diseases, Johannesburg and Centre for the AIDS Programme of Research in South Africa, Durban, South Africa

Q. Abdool Karim et al. (eds.), *The CAPRISA Clinical Trials: HIV Treatment and Prevention*, DOI 10.1007/978-3-319-47518-9_11

higher rate of HIV acquisition in this group, while simultaneously evaluating new technologies to prevent HIV infection in AGYW. Understanding and defining immune correlates of protection or risk for HIV at the point of exposure viz the female genital tract is a key toward developing more targeted prevention, treatment and/or cure strategies.

A priority of CAPRISA is to prevent HIV infection in AGYW, in a very structured and systematic way by focusing on the "Who? Why? and What?" questions relating to acquisition, understanding increased susceptibility and evaluating novel prevention strategies. From the inception of CAPRISA in 2002, the acute infection study has been centrally important for understanding clinical, virological and immunological events following early HIV infection in women and monitoring how these events evolve with time (see Chap. 10).

The CAPRISA 002 study, other vanguard cohort studies in preparation for HIV prevention trials and the prevention trials conducted by CAPRISA, created opportunities to study events that precede HIV acquisition. The CAPRISA 002 cohort is the first study in the world where extensive systemic and cervicovaginal lavage (CVL) samples were collected from women prior to HIV infection and intensively post-HIV acquisition, linked to detailed epidemiological, virological and immunological data (see Chap. 10). This provided a unique opportunity to investigate the inter-relationships in greater detail. The mucosal immunology research program within CAPRISA was established in 2006, to advance understanding of mucosal events around HIV acquisition, and factors associated with enhancing HIV risk in women in CAPRISA studies.

1.1.1 Genital Inflammation During Acute HIV Infection and Disease Progression

In rhesus macaques, Wang et al. showed that induction of vaginal inflammatory cytokine responses prior to challenge with Simian Immunodeficiency Virus (SIV) in the same compartment was associated with increased plasma viral load set-point [6]. To interrogate this in humans, the earliest study on mucosal responses at CAPRISA studied cytokines and innate responses in CVLs collected during acute HIV infection from the CAPRISA 002 cohort, testing the hypothesis that inflammatory responses at mucosal surfaces following HIV-1 transmission influenced disease outcome [7, 8]. We compared CVL concentrations of key inflammatory cytokines including interleukin (IL)-1β, IL-6, tumour necrosis factor (TNF)-α, IL-8, IL-10 and IL-12 in acutely HIV-infected women (at their earliest time point post-infection), in a subset of women prior to seroconversion and to controls who remained HIV negative. We found that acutely HIV-infected women had elevated CVL concentrations of IL-6, IL-10 and IL-12 compared to HIV-negative controls, and that acute cervicovaginal IL-1β, IL-6 and IL-8 concentrations correlated inversely with blood CD4 counts, suggesting that genital inflammation was

associated with lower CD4 counts during acute HIV infection [7]. We then evaluated whether genital inflammation during these very early time-points influenced the rate of disease progression and showed that higher genital inflammatory cytokine concentrations during early HIV infection (6 and 17 weeks post-infection) were associated with higher plasma viral load set-point and lower CD4 counts 12 months post-infection [8]. Additionally, the relationship between early infection genital cytokine concentrations and disease progression was independent of blood CD4 counts and plasma viral loads measured at the same time as cytokine concentrations, suggesting that increased genital inflammation was not due to HIV disease status. We did, however, show that the main drivers of genital inflammation appeared to be sexually transmitted infections (STIs) and bacterial vaginosis (BV). The findings of this study suggest that the inflammatory environment in the genital tracts of women around the time of sexual HIV acquisition may influence disease outcome, and that strategies to reduce genital inflammation may slow disease progression. In CAPRISA 002, ~80 % of infections were the result of infection with a single HIV subtype C variant (see Chap. 10; [9]), with dual infections accounting for the other 20 % of infections and all viruses isolated during acute infection were CCR5 tropic. We were interested to evaluate whether women infected with single or multiple HIV variants had differing genital tract cytokine profiles, potentially providing insight into the mechanism associated with multiple transmissions. However, we did not find any difference between genital inflammation in those women infected with single versus multiple variants. We hypothesised that genital inflammation would contribute to the detection of HIV in genital secretions. In CAPRISA 002 women over the first year of infection, HIV viral loads were measured in CVLs at 6, 17, 30 and 55 weeks post-infection as an indicator of HIV shedding. We found CVL viral loads did not correlate between time-points, indicating that different women were shedding HIV at different times. Elevated cytokine concentrations in CVL were associated with higher CVL viral loads at all time-points. Importantly, in the CAPRISA 002 cohort, we showed that inflammatory cytokine levels pre-infection correlated with those post-infection and in fact were not significantly elevated during early HIV infection, suggesting that pre-existing inflammation may influence disease progression.

We learnt two lessons from conducting this study: (1) inflammatory responses at the site of HIV acquisition determined long term disease prognosis; and (2) being able to match pre- versus post-infection mucosal samples from the same women was one of the most valuable resources to shed light on factors associated with HIV infection.

1.1.2 Inflammatory Responses in the Genital Tract Were Independent of Those in Blood

In addition to finding that genital inflammation during acute HIV infection influenced subsequent disease progression, this early study from the CAPRISA Mucosal Immunology Research Team suggested distinct responses during acute HIV

infection in the genital tract and blood, leading us to ask whether blood biomarkers of activation and disease progression in women following infection overlapped with those detected in the genital tract. Through a collaboration with CHAVI (PI: J. Passmore), we measured a large panel of cytokines in plasma samples collected from women in the CAPRISA 002 cohort. We found that acute infection plasma cytokine concentrations were indeed strongly predictive of disease outcome [10], with concentrations of five inflammatory and T cell-regulating cytokines being highly predictive of viral load set-point 12 months post-infection. IL-12p40, IL-12p70, IFN-γ, IL-7 and IL-15 predicted 66 % of the variation in viral load set-point. Plasma concentrations of IL-12p40 and GM-CSF during acute infection were associated with maintenance of CD4 counts above 350 cells/μl while IL-1α, eotaxin and IL-7 were associated with more rapid CD4 loss. These two clusters of cytokines were more strongly predictive of viral load set-point and CD4+ T cell loss than either acute infection CD4 counts, viral loads or both combined. We demonstrated the potential to use plasma cytokine concentrations as easily measurable biomarkers during acute HIV infection to predict subsequent disease progression, with potential to be utilised to manage HIV disease progression and evaluate the ability of therapeutic HIV vaccines to control HIV infection. However, we found no correlation between genital tract and plasma cytokines, and markers of disease progression differed between the genital tract and plasma, suggesting that differing immune mechanisms may be at play in these distinct immunological compartments [8].

1.1.3 Overlap Between HIV-Specific Antibody Responses in the Genital Mucosa and Blood

Given compartmentalization of cytokine responses and cellular activation between the female genital tract and blood, we were interested to investigate whether the well-characterised neutralising antibody responses against HIV described in Chap. 10 were available in secretions from the lower reproductive tract. Broadly neutralising antibodies (bNAbs) are able to inhibit the majority of HIV strains and, if elicited by an HIV vaccine, are likely to be effective at blocking infection at the site of entry. In a close collaboration between CAPRISA-associated scientists at the National Institute for Communicable Diseases (NICD) and the CAPRISA Mucosal Laboratory, we isolated HIV-specific IgG, but not IgA, from genital secretions (CVLs) from women in CAPRISA 002, and found that the ratio of total IgG to HIV-specific IgG was similar to plasma [12]. HIV-specific IgG reacted with multiple envelope antigens, including V1V2, gp120, gp140 and gp41 [11, 12] and had neutralising activity against both Tier 1 and Tier 2 primary HIV-isolates [12]. Antibodies targeting well-known glycan epitopes and the membrane proximal region of gp41 were detected in genital secretions, and matched specificities in plasma. These data show that women with HIV-specific plasma bNAbs have overlapping specificities in their genital secretions, indicating that these

predominantly IgG isotype antibodies may transudate from blood to the genital tract. This study of natural HIV infection provides evidence that induction of systemic HIV-specific bNAbs can lead to antiviral immunity at the portal of entry. Therefore, antibodies elicited by systemic vaccination (or transferred through passive immunisation) are likely to reach mucosal surfaces and could contribute to preventing the sexual transmission of HIV.

1.1.4 Female Genital Tract Inflammation and Risk of HIV Acquisition

There is a large degree of heterogeneity in susceptibility to sexual HIV acquisition in women, with some remaining uninfected despite high levels of exposure [13]. In macaques, production of pro-inflammatory cytokines and chemokines that are involved in recruitment of HIV target cells to the female genital tract were found to be essential for a productive SIV infection [14]. In vitro studies also demonstrated other potential mechanisms for the relationship between inflammatory cytokines and HIV, showing that inflammatory cytokines and chemokines not only recruit and activate HIV target cells [15], but also reduce epithelial barrier function [16] and activate HIV transcription [17]. However, a direct relationship between genital inflammation and risk of HIV acquisition in humans had not yet been demonstrated.

The completion of the CAPRISA 004 tenofovir microbicide trial in 2010 [18], and collection of an array of genital specimens during the study pre-HIV infection, gave us the unique opportunity to investigate this possible relationship. We measured a panel of cytokine biomarkers of inflammation, selected based on our studies, showing a relationship between these cytokines and HIV disease or inflammatory genital conditions in CAPRISA 002 [8, 19]. From the CAPRISA 004 mucosal specimens, we found a striking relationship between pre-infection genital inflammation and HIV risk, showing that women with inflammation were at 3.2-fold greater odds of acquiring HIV than women who did not have inflammation. We further showed that chemokines responsible for recruiting HIV target cells, macrophage inflammatory protein (MIP)-1a, MIP-1ß and interferon gamma-induced protein 10 (IP-10), were increased in women who later became HIV infected compared to those who did not [20]. MIPs are also the major macrophage protein produced in response to bacterial endotoxins [21] while IP-10 is a major chemotactic cytokine for macrophages and T cells [22]. Genital cytokine concentrations were also higher in younger women than older women, suggesting that biological factors may indeed contribute to the higher rates of HIV acquisition observed in young African women. These results highlighted the importance of biological factors in HIV transmission and suggested that biological factors may have a significant impact on the success of HIV prevention strategies. This study also motivated a renewed interest in mucosal immunology in the context of HIV prevention, as a better understanding of the causes of genital inflammation and mechanisms to address this inflammation are urgently needed.

1.2 Causes of Genital Inflammation that Underlie HIV Risk in Women

We found that women from the CAPRISA 002 cohort, with STIs and/or BV before they became HIV infected, had elevated concentrations of inflammatory cytokines in their genital tracts [23] and that these conditions were highly prevalent in certain high-risk populations of South African women [19]. Furthermore, most of the women with these inflammatory conditions lacked clinical signs and they would thus have remained untreated in the South African setting, where STIs/BV are only treated if women present with clinical signs or symptoms (syndromic management), as per the South African STI treatment guidelines. Of particular concern was that women with asymptomatic infections had comparably high levels of genital inflammation as women with symptomatic infections [19]. Many women in resource-limited settings are thus likely to have STI/BV-related inflammation that remains unresolved, placing them at increased risk of HIV infection and reproductive complications. These studies highlighted an important gap in the South African healthcare system, and the need to revisit STI and BV management strategies in order to identify commonly asymptomatic infections more effectively.

McKinnon et al. [24] showed that human IL-17 producing T cells [T helper 17 (Th17) cells] preferentially expressed mucosal homing receptors, including the major HIV co-receptor CCR5, enabling them to move to the genital tract. Furthermore, they showed that these CCR5+ Th17 cells were also more permissive to binding to gp120 of HIV. In macaques, Stieh et al. [25] showed that the primary targets for HIV infection following SIV challenge were Th17-like cells (defined by their expression of CCR6 but lack of CCR10 expression). Within the CAPRISA 002 cohort, this led us to investigate the influence of STIs and BV at the cellular level in the female genital tract, focusing specifically on Th17 cells because of their importance in HIV infection [26]. Women with bacterial STIs, specifically chlamydia and gonorrhoea, had higher genital IL-17 concentrations than women with no STI, while women with candidal pseudohyphae or spores had lower IL-17 concentrations compared to women without candidal infections. Viral STIs (HSV-2 and HIV) were not associated with significant changes in genital IL-17 concentrations. Cervical Th17 cell frequencies, however, were not associated with STIs or candida.

Although genital inflammation was strongly associated with HIV risk in the CAPRISA 004 cohort, we found that STIs only accounted for 20 % of the inflammation observed, with *Trichomonas vaginalis* being identified as the most common infection driving inflammation [20]. We are actively pursuing other possible non-STI causes of the inflammation observed in CAPRISA 004.

There are several mechanisms by which genital tract inflammation could increase HIV risk. Inflammation may impair mucosal barrier integrity by increasing epithelial permeability [27–29]. Alternatively, genital inflammation may be involved in the recruitment and/or activation of target cells required for HIV replication [30, 31]. Studies in macaques have shown that genital tract inflammation

and target cell recruitment to the mucosa are necessary precipitous events for productive SIV infection following vaginal exposure [14]. MIP-3α and IL-8 were critical for this effect, and IL-8 overlapped with the CAPRISA 004 data on genital tract inflammation and HIV risk [20]. Recruitment of immune cells to tissues typically requires inflammation [32], and these cells are critical for HIV to establish infection in the first few days of transmission.

2 Can We Define Genital Inflammation Using Cytokine Biomarkers Alone?

In our study of prediction of HIV risk in CAPRISA 004, using the definition of genital tract inflammation where more than half of the cytokines and chemokines (5/9) that we measured where elevated (top 75th percentile of the cohort), was debated broadly during the peer review process, leading us to strongly defend the robustness of this definition of inflammation through several alternate analyses [20]. This led us to debate whether we could define inflammation by a specified sum of inflammatory cytokines, and whether this reflects true inflammation. The medical dictionary defines inflammation 'as a localised protective response elicited by injury or destruction of tissues, which serves to destroy, dilute, or wall off both the injurious agent and the injured tissue' (http://medical-dictionary.thefreedictionary.com/Inflammation). Inflammation is part of the complex host response to harmful stimuli, involving immune cells, blood vessels and molecular mediators, including cytokines, to eliminate the initial cause of cell injury, clear dead cells and repair tissues damaged from the original insult and the inflammatory process. In the context of the female genital tract, we argue that selected chemokines and inflammatory cytokines are a valuable and non-invasive mucosal specimen, giving insight into the innate environment associated with inflammation. While cellular trafficking within the vagina and migration to draining lymph nodes would give alternate insight into mechanisms associated with HIV risk, biopsy samples from the lower reproductive tract (LRT) of women in a setting of high HIV burden would be considerably more invasive and possibly even unethical to collect, given the rate of wound healing in the LRT.

3 Does Inflammation Undermine Topical Microbicide Efficacy?

Compelling data from the CAPRISA 004 trial demonstrated that mucosal inflammation is an independent predictor of HIV acquisition [20]. The CAPRISA Mucosal Immunology Laboratory based much of its subsequent work on expanding

this observation by investigating potential causes of genital inflammation, a mechanism for the relationship between genital inflammation and increased HIV risk, and on testing the hypothesis that a certain threshold of mucosal inflammation in the genital tract is required for HIV to establish infection. The outcomes of these investigations will have important implications for HIV prevention strategies that block genital inflammation.

In 2014, the CAPRISA Mucosal Immunology Laboratory was awarded an NIH R01 grant based on their response to the RFA 'Mucosal Environment and HIV Prevention (MEHP) (R01)' with their research proposal entitled 'Inflammation and HIV Risk: Understanding Partial Tenofovir Efficacy in CAPRISA 004' (PI: Passmore). The proposed research would conduct a comprehensive cohort study of clinical samples from the completed CAPRISA 004 trial, with a focus on understanding the mechanisms associated with the partial efficacy of 1 % tenofovir (TFV) gel from that trial. Further, the study would also include a combination of prospective clinical trial samples from the CAPRISA 008 tenofovir gel implementation trial, and in vitro and in vivo models to define a mechanism for the observed relationship between genital inflammation and HIV risk. CAPRISA 004 trial participants with TFV drug levels >1000 ng/ml had significantly higher levels of protection [33], indicating potentially that intracellular deoxyadenosine triphosphate (dATP), the source of phosphates necessary for TFV's antiviral activity, within activated HIV target cells was competing with TFV and undermining its activity. We hypothesised that in the placebo arm, a theoretical threshold of genital tract inflammation results in HIV infection, with women having both medium and high levels of inflammation becoming infected. However, in the setting of TFV gel, only women who become HIV infected display high levels of inflammation. Hence, TFV increases the inflammation threshold required for the virus to establish infection. The ongoing study also tests the hypothesis that inflammation alters TFV efficacy through recruitment of activated target cells and/or competition between intracellular TFV (TFV-diphosphate; TFV-DP) and dATP in activated cells. Anticipated outcomes of the study include information on strategies to improve the efficacy of topical TFV: either through administration of higher doses of TFV to protect the women with high levels of inflammation, or better management of genital tract inflammation.

We have previously shown that endocervical cytobrush-derived T cells collected from the female genital tract were more activated than matched blood samples [24, 34]. Others had also demonstrated that competition for intracellular dATP, which is elevated in activated cells, might account for the reduced efficacy of TFV in activated cells [35]. Because T cells present in the female genital tract are significantly more activated than those circulating in blood, we speculated that TFV's ability to block HIV replication may be compromised at mucosal sites in some individuals due to a higher threshold of activation.

4 Did Tenofovir Change Genital Tract or Plasma Antibody Responses?

In an era where combination prevention strategies, including PrEP and HIV vaccines, are being used together to prevent HIV infection, understanding the impact of antiretroviral drugs on the immune system is crucial. The impact of topical antiretrovirals for pre-exposure prophylaxis on humoral responses following HIV infection is unknown. Women who became HIV infected despite using TFV gel were shown to have preserved CD4 T cell responses to HIV earlier following infection than seroconverters from the placebo arm [36]. Since development of B cell responses is dependent on CD4 T cell help during maturation [37], we hypothesised that this preservation of CD4 T cells during acute HIV infection may influence subsequent B cell antibody production. In support of this, we showed that women assigned to TFV gel had higher IgG responses to several antigens, including the major envelope protein gp120 Env, HIV major capsid protein p24 and HIV reverse transcriptase p66 in both plasma and the genital tract compared to women assigned to the placebo gel at multiple time-points post-infection [11]. Notably, p66 IgA titres in the genital tract and plasma were significantly higher in the TFV compared to the placebo arm. Plasma titres for nine of the ten HIV-IgG specificities predicted genital tract levels, suggesting broad overlap between concentrations in plasma and the genital tract. Our data suggest that humoral immune responses are increased in blood and the genital tract of women who acquire HIV infection in the presence of TFV gel [11]. We are in the process of extending these findings to understand whether the antibody responses are functionally superior in TFV gel exposed women compared to the women in the placebo arm.

5 Standardising Mucosal Sampling: Does Collection Method Matter?

Optimising methods for genital specimen collection to accurately characterise mucosal immune responses is a priority for the CAPRISA Mucosal laboratory and for the HIV prevention field at large, and CAPRISA has contributed to these efforts since its inception. We recognised quite early on that there were significant gaps in the field regarding optimal methods of mucosal sampling, where methods are not standardised [38, 39]. To address this gap, we undertook a cross-sectional randomised study to understand what the qualitative and quantitative differences were between two different mucosal sample collection methods: the current gold standard, the CVL versus the more recent Softcup, marketed as a menstrual fluid collection device, which was repurposed in our study as an intravaginal mucosal fluid collection device [40]. HIV-infected, antiretroviral therapy-naïve women from the CAPRISA 002 acute HIV infection cohort study were randomised to have

Table 1 The SCCIPT considerations when sampling from the mucosa

• **Standardised**: across clinical sites and between individuals
• **Comfortable**: to the participant
• **Concentrated**: High concentrations of biomarkers when determining appropriateness of mucosal sample
• **Impact**: of sampling on the immune environment under investigation
• **Practical**: convenient, and easy
• **Time**: for mucosal sampling and impact on participant visit duration

genital fluid collected using the menstrual cup (MC) with subsequent CVL, or by CVL alone. HIV-specific IgG against multiple gene products and cytokines were measured in genital sample sets from these women. IgG responses against HIV and cytokines were detected more prevalently in MCs compared to CVLs and at higher concentrations; although both total IgG and cytokine concentrations correlated strongly between MC and corresponding post-MC CVL. We concluded that MCs may therefore represent an ideal tool to assess immunological parameters in genital secretions, without interfering with concurrent collection of conventional CVL samples. This study has provided important data for collection of genital samples from female participants in HIV prevention trials, and led to the adoption of a standardised approach (the SCCIPT considerations) within CAPRISA for specimen collection from the female genital mucosa (Table 1).

6 Translation of Research to Improve Mucosal Health

Findings from immunological research in the CAPRISA studies underscore the importance of identifying, comprehensively, the causes of inflammation and evaluating the impact that their control, or elimination, might have on genital epithelial barrier integrity and HIV target cell availability at the predominant site of heterosexual transmission of HIV in women. Our pivotal data identifying a similar contribution of asymptomatic and symptomatic STI infection to genital inflammation [19] is central to current studies investigating the feasibility of implementing diagnostically driven STI treatment over syndromic management of STI in order to reduce genital inflammation. The finding that STIs contributed to only 20 % of the observed genital inflammation in CAPRISA 004 study participants led us to expand the scope of research in the Mucosal laboratory to investigate other biological causes of genital inflammation (including other bacterial, viral, nematode and fungal pathogens) and factors that facilitate their presence (hygiene and sexual practices, vaginal product and contraception use). Unpublished data from the CAPRISA Mucosal Immunology Laboratory has identified a strong relationship between Human papillomavirus (HPV) and increased risk of HIV infection

(Liebenberg et al., unpublished), as well as suggesting a cytokine-mediated cellular mechanism for this association (Liebenberg et al., unpublished). Further, we have shown in women from the CAPRISA 002 cohort that injectable hormonal contraception use (including DMPA and Net-EN) may also influence genital tract cytokine responses [41], highlighting the potential impact to HIV risk by popular hormonal contraception choices in South Africa.

Data from CAPRISA 004, VOICE, FACTS001 and ASPIRE trials highlight the importance of product adherence to effective protection from HIV infection. Tenofovir-based products can confer protection against HIV infection if used as and when instructed correctly. In addition to new modalities that women will use to provide protection against HIV infection, and potentially pregnancy, data from the CAPRISA 004 trial demonstrates the importance of also controlling genital inflammation in efforts to prevent HIV infection. Further studies are required to determine the impact that the control of inflammatory agents would have on the permissiveness of the female genital tract to HIV infection; or to optimise methods to fortify the genital epithelial barrier against HIV entry, to repel immune factors that promote infection or to retain effective anti-HIV immunity at the genital tract. In the absence of an effective vaccine against HIV infection, mucosal-targeted approaches to prevent HIV infection are critical to controlling the epidemic, particularly in young women.

Collectively, data from the CAPRISA 002 and CAPRISA 004 studies suggested the importance of genital inflammation in determining HIV infection risk [20], that STIs and BV are important causes of genital inflammation, and that these genital conditions are mostly asymptomatic [19, 23]. From these observations, we are exploring whether cytokines would be useful biomarkers to identify women with asymptomatic STIs and BV [20] that could be used to develop an inexpensive point-of-care test to screen women for an inflammatory genital condition in resource-limited settings, complementing and improving syndromic management.

Table 2 Five top impact findings from the CAPRISA Mucosal Group as of March 2016

1. Plasma cytokines during acute HIV-1 infection predict HIV disease progression. Roberts et al. AIDS 2010. Cited 102 times, Google Scholar [10]
2. Inflammatory cytokines in the genital tract are associated with lower CD4+ cell counts during acute HIV-1 infection. Bebell et al. JID (2009). Cited 58 times [7]
3. Symptomatic vaginal discharge is a poor predictor of sexually transmitted infections suggesting syndromic management is suboptimal (Mlisana et al. JID. 2012, 51 citations) [5]
4. Genital inflammation increases the risk of HIV acquisition in women. Masson et al. CID (2015). Cited 10 times [20]
5. Genital tract inflammation during early HIV-1 infection predicts worse disease outcome. Roberts et al. JID. 2012. Cited 37 times [8]

7 Conclusion

Through a series of key studies from the CAPRISA Mucosal Laboratory (summarised in Table 2), we have systematically investigated both the causes and consequences of inflammation around HIV infection of the female genital tract. Working within the CAPRISA 002 and then CAPRISA 004 cohorts, we have shown that genital inflammation was an important determinant of HIV risk in South African women, driven partly by known and controllable STIs and BV; and that infection against the backdrop of inflammation can have disease accelerating effects seen up to 1 year of infection. Defining the major drivers of mucosal inflammation will give invaluable insight into combination strategies to prevent HIV infection and provide clues to ways of improving existing prevention methods.

References

1. Sheppard HW, Ascher MS, McRae B, Anderson RE, Lang W, Allain JP. The initial immune response to HIV and immune system activation determine the outcome of HIV disease. Journal of Acquired Immune Deficiency Syndromes. 1991; 4(7): 704–12.
2. Gougeon ML, Lecoeur H, Dulioust A, Enouf MG, Crouvoiser M, Goujard C, et al. Programmed cell death in peripheral lymphocytes from HIV-infected persons: increased susceptibility to apoptosis of CD4 and CD8 T cells correlates with lymphocyte activation and with disease progression. J Immunol. 1996; 156(9): 3509–20.
3. Liu Z, Cumberland WG, Hultin LE, Prince HE, Detels R, Giorgi JV. Elevated CD38 antigen expression on CD8+ T cells is a stronger marker for the risk of chronic HIV disease progression to AIDS and death in the Multicenter AIDS Cohort Study than CD4+ cell count, soluble immune activation markers, or combinations of HLA-DR and CD38 expression. J Acquir Immune Defic Syndr Hum Retrovirol. 1997; 16(2): 83–92.
4. Deeks SG, Kitchen CM, Liu L, Guo H, Gascon R, Narvaez AB, et al. Immune activation set point during early HIV infection predicts subsequent CD4+ T-cell changes independent of viral load. Blood. 2004; 104(4): 942–7.
5. Mlisana K, Werner L, Garrett NJ, McKinnon LR, van Loggerenberg F, Passmore JA, et al. Rapid disease progression in HIV-1 subtype C-infected South African women. Clinical Infectious Diseases. 2014; 59(9): 1322–31.
6. Wang Y, Abel K, Lantz K, Krieg AM, McChesney MB, Miller CJ. The Toll-like receptor 7 (TLR7) agonist, imiquimod, and the TLR9 agonist, CpG ODN, induce antiviral cytokines and chemokines but do not prevent vaginal transmission of simian immunodeficiency virus when applied intravaginally to rhesus macaques. Journal of Virology. 2005; 79(22): 14355–70.
7. Bebell LM, Passmore JA, Williamson C, Mlisana K, Iriogbe I, van Loggerenberg F, et al. Relationship between levels of inflammatory cytokines in the genital tract and CD4+ cell counts in women with acute HIV-1 infection. Journal of Infectious Diseases. 2008; 198(5): 710–4.
8. Roberts L, Passmore JA, Mlisana K, Williamson C, Little F, Bebell LM, et al. Genital tract inflammation during early HIV-1 infection predicts higher plasma viral load set point in women. Journal of Infectious Diseases. 2012; 205(2): 194–203.
9. Abrahams MR, Anderson JA, Giorgi EE, Seoighe C, Mlisana K, Ping LH, et al. Quantitating the multiplicity of infection with human immunodeficiency virus type 1 subtype C reveals a non-poisson distribution of transmitted variants. Journal of Virology. 2009; 83(8): 3556–67.

10. Roberts L, Passmore JA, Williamson C, Little F, Bebell LM, Mlisana K, et al. Plasma cytokine levels during acute HIV-1 infection predict HIV disease progression. AIDS. 2010; 24(6): 819–31.
11. Archary D, Seaton KE, Passmore JS, Werner L, Deal A, Dunphy LJ, et al. Distinct genital tract HIV-specific antibody profiles associated with tenofovir gel. Mucosal Immunol. 2016; 9 (3): 821–33.
12. Mkhize NN, Durgiah R, Ashley V, Archary D, Garrett NJ, Karim QA, et al. Broadly neutralizing antibody specificities detected in the genital tract of HIV-1 infected women. AIDS. 2016; 30(7): 1005–14.
13. Kaul R, Cohen CR, Chege D, Yi TJ, Tharao W, McKinnon LR, et al. Biological factors that may contribute to regional and racial disparities in HIV prevalence. American Journal of Reproductive Immunology. 2011; 65(3): 317–24.
14. Li Q, Estes JD, Schlievert PM, Duan L, Brosnahan AJ, Southern PJ, et al. Glycerol monolaurate prevents mucosal SIV transmission. Nature. 2009; 458(7241): 1034–8.
15. Wira CR, Fahey JV, Sentman CL, Pioli PA, Shen L. Innate and adaptive immunity in female genital tract: cellular responses and interactions. Immunol Rev. 2005; 206: 306–35.
16. Nazli A, Chan O, Dobson-Belaire WN, Ouellet M, Tremblay MJ, Gray-Owen SD, et al. Exposure to HIV-1 directly impairs mucosal epithelial barrier integrity allowing microbial translocation. PLoS Pathog. 2010; 6: e1000852.
17. Osborn L, Kunkel S, Nabel GJ. Tumor necrosis factor alpha and interleukin 1 stimulate the human immunodeficiency virus enhancer by activation of the nuclear factor kappa B. Proc Natl Acad Sci U S A. 1989; 86(7): 2336–40.
18. Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010; 329(5996): 1168–74.
19. Mlisana K, Naicker N, Werner L, Roberts L, van Loggerenberg F, Baxter C, et al. Symptomatic vaginal discharge is a poor predictor of sexually transmitted infections and genital tract inflammation in high-risk women in South Africa. Journal of Infectious Diseases. 2012; 206(1): 6–14.
20. Masson L, Passmore JA, Liebenberg LJ, Werner L, Baxter C, Arnold KB, et al. Genital inflammation and the risk of HIV acquisition in women. Clinical Infectious Diseases. 2015; 61(2): 260–9.
21. Sherry B, Tekamp-Olson P, Gallegos C, Bauer D, Davatelis G, Wolpe SD, et al. Resolution of the two components of macrophage inflammatory protein 1, and cloning and characterization of one of those components, macrophage inflammatory protein 1 beta. J Exp Med. 1988; 168 (6): 2251–9.
22. Dufour JH, Dziejman M, Liu MT, Leung JH, Lane TE, Luster AD. IFN-gamma-inducible protein 10 (IP-10; CXCL10)-deficient mice reveal a role for IP-10 in effector T cell generation and trafficking. J Immunol. 2002; 168(7): 3195–204.
23. Masson L, Mlisana K, Little F, Werner L, Mkhize NN, Ronacher K, et al. Defining genital tract cytokine signatures of sexually transmitted infections and bacterial vaginosis in women at high risk of HIV infection: a cross-sectional study. Sexually Transmitted Infections. 2014; 90(8): 580–7.
24. McKinnon LR, Nyanga B, Chege D, Izulla P, Kimani M, Huibner S, et al. Characterization of a human cervical CD4+ T cell subset coexpressing multiple markers of HIV susceptibility. J Immunol. 2011; 187(11): 6032–42.
25. Stieh DJ, Matias E, Xu H, Fought AJ, Blanchard JL, Marx PA, et al. Th17 Cells Are Preferentially Infected Very Early after Vaginal Transmission of SIV in Macaques. Cell host & Microbe. 2016; 19(4): 529–40.
26. Masson L, Salkinder AL, Olivier AJ, McKinnon LR, Gamieldien H, Mlisana K, et al. Relationship between female genital tract infections, mucosal interleukin-17 production and local T helper type 17 cells. Immunology. 2015; 146(4): 557–67.

27. Hillier SL, Moench T, Shattock R, Black R, Reichelderfer P, Veronese F. In vitro and in vivo: the story of nonoxynol 9. Journal of Acquired Immune Deficiency Syndromes. 2005; 39(1): 1–8.
28. Fichorova RN, Tucker LD, Anderson DJ. The molecular basis of nonoxynol-9-induced vaginal inflammation and its possible relevance to human immunodeficiency virus type 1 transmission. Journal of Infectious Diseases. 2001; 184(4): 418–28.
29. Arnold KB, Burgener A, Birse K, Romas L, Dunphy LJ, Shahabi K, et al. Increased levels of inflammatory cytokines in the female reproductive tract are associated with altered expression of proteases, mucosal barrier proteins, and an influx of HIV-susceptible target cells. Mucosal Immunol. 2016; 9(1): 194–205.
30. Grossman Z, Feinberg MB, Paul WE. Multiple modes of cellular activation and virus transmission in HIV infection: a role for chronically and latently infected cells in sustaining viral replication. Proc Natl Acad Sci U S A. 1998; 95(11): 6314–9.
31. Zhang Z, Schuler T, Zupancic M, Wietgrefe S, Staskus KA, Reimann KA, et al. Sexual transmission and propagation of SIV and HIV in resting and activated CD4+ T cells. Science. 1999; 286(5443): 1353–7.
32. Masopust D, Schenkel JM. The integration of T cell migration, differentiation and function. Nat Rev Immunol. 2013; 13(5): 309–20.
33. Abdool Karim SS, Kashuba AD, Werner L, Abdool Karim Q. Drug concentrations after topical and oral antiretroviral pre-exposure prophylaxis: implications for HIV prevention in women. Lancet. 2011; 378(9787): 279–81.
34. Jaspan HB, Liebenberg L, Hanekom W, Burgers W, Coetzee D, Williamson AL, et al. Immune activation in the female genital tract during HIV infection predicts mucosal CD4 depletion and HIV shedding. Journal of Infectious Diseases. 2011; 204(10): 1550–6.
35. Garcia-Lerma JG, Aung W, Cong ME, Zheng Q, Youngpairoj AS, Mitchell J, et al. Natural substrate concentrations can modulate the prophylactic efficacy of nucleotide HIV reverse transcriptase inhibitors. Journal of Virology. 2011; 85(13): 6610–7.
36. Mureithi MW, Poole D, Naranbhai V, Reddy S, Mkhwanazi NP, Sibeko S, et al. Preservation HIV-1-specific IFNgamma+ CD4+ T-cell responses in breakthrough infections after exposure to tenofovir gel in the CAPRISA 004 microbicide trial. Journal of Acquired Immune Deficiency Syndromes. 2012; 60(2): 124–7.
37. Crotty S. A brief history of T cell help to B cells. Nat Rev Immunol. 2015; 15(3): 185–9.
38. McKinnon LR, Hughes SM, De Rosa SC, Martinson JA, Plants J, Brady KE, et al. Optimizing viable leukocyte sampling from the female genital tract for clinical trials: an international multi-site study. PLoS One. 2014; 9(1): e85675.
39. Liebenberg LJ, Gamieldien H, Mkhize NN, Jaumdally SZ, Gumbi PP, Denny L, et al. Stability and transport of cervical cytobrushes for isolation of mononuclear cells from the female genital tract. J Immunol Methods. 2011; 367(1-2): 47–55.
40. Archary D, Liebenberg LJ, Werner L, Tulsi S, Majola N, Naicker N, et al. Randomized Cross-Sectional Study to Compare HIV-1 Specific Antibody and Cytokine Concentrations in Female Genital Secretions Obtained by Menstrual Cup and Cervicovaginal Lavage. PLoS One. 2015; 10(7): e0131906.
41. Ngcapu S, Masson L, Sibeko S, Werner L, McKinnon LR, Mlisana K, et al. Lower concentrations of chemotactic cytokines and soluble innate factors in the lower female genital tract associated with the use of injectable hormonal contraceptive. J Reprod Immunol. 2015; 110: 14–21.

Part V
Essential Support Activities for the Conduct of Clinical Trials

Chapter 12
Good Practices in the Conduct of Clinical Trials: Good Community, Pharmacy and Laboratory Practices

Tanuja N. Gengiah, Natasha Samsunder, Janet A. Frohlich and Fanelesibonge Ntombela

1 Introduction

The outcomes of clinical trials could lead to new product, drugs or vaccine licensure and be used beyond the countries where the clinical trials were conducted or the populations included in the trial. To ensure that clinical trials are undertaken at a similar standard across the world, the International Committee on Harmonisation of Clinical Trials established a set of essential steps, also referred to as Good Clinical Practice (GCP) that govern the conduct of all clinical trials. In addition, the Human Subjects Protection (HSP) Act ensures that the rights of study participants are respected. Over and above GCP and HSP training that all study staff undertaking clinical trials are required to complete annually, integrity and accountability of study product; appropriate and high quality conduct of laboratory assays and adequate processing and storage systems for specimens collected during study visits as well as community engagement, are key for ensuring scientific integrity and meeting ethical obligations in the conduct of clinical trials. CAPRISA has established the Community, Pharmacy and Laboratory science support cores to ensure that these aspects of clinical trial conduct are addressed. This chapter provides practical guidance to researchers setting up science support cores to enhance the conduct of clinical trials. The field implementation of a clinical trial involves multidisciplinary teams of specialists working together to generate high quality data on the product under investigation, whilst simultaneously ensuring that the safety and rights of study participants are respected. Typically, biological markers are used in measuring key aspects of the trial, including the primary and secondary outcomes.

T.N. Gengiah (✉) · N. Samsunder · J.A. Frohlich · F. Ntombela
Centre for the AIDS Programme of Research in South Africa,
University of KwaZulu-Natal, Durban, South Africa
e-mail: Tanuja.gengiah@caprisa.org

Q. Abdool Karim et al. (eds.), *The CAPRISA Clinical Trials: HIV Treatment and Prevention*, DOI 10.1007/978-3-319-47518-9_12

In multi-centre and multi-country studies some of the laboratory assays are undertaken in a centralised laboratory while others are undertaken in local laboratories. The Good Laboratory Practice Guidelines were established to minimise wide variability between laboratories participating in a clinical trial and ensure similar standards and quality assurance steps are in place across all laboratories including for specimen collection, shipping, processing and storage in biobanks. The communities where clinical trials are conducted vary, with some being more experienced and familiar with rights of trial participants and ethical obligations of the study team to research participants than others. It is critical that trial participants are fully informed about the study and participation is voluntary. Good Pharmacy Practice (GPP) ensures that adequate supplies of products are in place and that the storage, dispensing and accountability systems are in place in addition to ensuring that the conduct of clinical trials of investigational products meet both local and sponsor regulatory requirements.

2 Good Pharmacy Practice in Clinical Trials

2.1 The CAPRISA Research Pharmacy Core

The CAPRISA Research Pharmacy Core was established in July 2003 and has supported over 35 clinical trials in 13 years of its existence. Continuously striving to maintain high standards of excellence in clinical trial conduct, the pharmacy core has established strong, reliable systems for investigational drug accountability, temperature control and monitoring at all required ranges. Further trial related support includes pharmacy driven activities that enhance participant retention and procedures to meaningfully contribute to medication adherence support. The organisational structure of the CAPRISA research pharmacy core is strategically designed to efficiently and simultaneously support multiple clinical trial protocols. This is achieved by a seemingly hierarchal human resources structure, where, despite the lines of accountability and reporting, all pharmacists are trained on every active protocol at their site pharmacy and are ably supported by trained pharmacy technicians and administrative clerks (Fig. 1).

This organisational model ensures rapid implementation and continuous support of new protocols within each research clinic. There are several activities at the CAPRISA pharmacies that are proactively designed for resource savings and efficiency. All site pharmacy personnel are cross-trained on all protocols active at their research site, although only one pharmacist is designated to the pharmacist of record role, whilst the others are listed as back-up pharmacists for that network/protocol. This system allows for efficiency in managing multiple protocols, making effective use of staff and enables rapid deployment of staff to new protocols; effectively reducing personnel costs for new protocols in a pluripotent clinical research site. The research pharmacies also employ pharmacy technicians, who are referred to as post-basic pharmacist assistants in South Africa, and pharmacy clerks to assist the

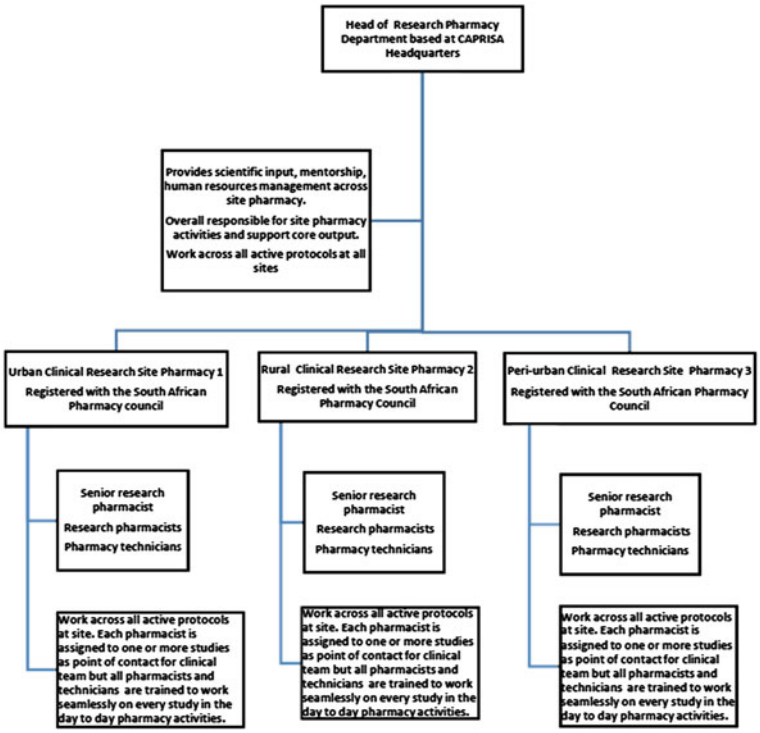

Fig. 1 CAPRISA research pharmacy organisational structure

site pharmacist with dispensing and administrative tasks. These staff categories are proficient to work under the direct supervision of a pharmacist and are a staff category that affords a cost saving for the salary allocation when compared to hiring pharmacists only for all pharmacy tasks.

In addition, each established Research Clinic Site Pharmacy is fully equipped to manage complex protocols and support studies with high accrual targets. Quality management of pharmacy processes is a priority for the pharmacy support core and several effective measures are in place to ensure high quality pharmaceutical services that directly contribute to trial integrity.

2.2 Constructing Clinical Trial Compliant Research Pharmacies

Establishing the infrastructure for a Research Pharmacy is a complex, costly and labour intensive process that may take several years to complete. Several important activities, in addition to procurement of the necessary equipment, needs to be

systematically undertaken whilst exercising due diligence to ensure that all local pharmacy regulatory requirements as well as international sponsor requirements are satisfied (Table 1). South African pharmacies operate in compliance with the Good Pharmacy Practice (GPP) guidelines [1], the Pharmacy Act [2] and the Medicines and Related Substances Act [3].

The prototype model described below emanates from meeting the research focus of CAPRISA, viz., anti-retroviral based and tuberculosis prevention and treatment trials; microbicide and vaccine trials and provision of available clinical care to study participants and ensures a locally and internationally compliant Research Pharmacy infrastructure.

2.3 Clinical Trial Pharmacy Operations at CAPRISA

There are several activities that must occur before, during and after a trial that falls under the scope of responsibility of the research pharmacist working on the clinical trial. These are listed briefly in Table 2 and offer some insight when planning for implementation of a clinical trial from the research pharmacy perspective. All activities for clinical trials fall under the aegis of the South African Good Clinical Practice [5] and ICH guidelines for good clinical practice [4].

2.4 Pharmacy Quality Management

Pharmacy processes, SOPS and systems should be reviewed annually at minimum and on an ad hoc basis if the need arises. The following pharmacy activities should be subjected to regular quality checks.

2.4.1 Quality Assurance (QA) and Quality Control (QC) of Study Product Dispensing

When study product is dispensed, every effort should be made to ensure that the pharmacy staff who initially prepare the study product (may be a pharmacist or a technician) is different from the pharmacy staff (pharmacist only) who checks the final study product and dispenses to the study participant. This real-time double check is documented by the two signature system. In the event of staff shortages the second signature should be obtained as soon as the appropriate staff member is able to review the documentation. Prior to issue of study product to a study participant or study staff member, the study participant's identity must be confirmed, either directly with the study participant, or indirectly with the study staff member collecting the prepared study product.

Table 1 Essential activities in constructing a compliant research pharmacy

Item	Activity	Comment
1.	Employ a full- time registered pharmacist to oversee the construction of the research pharmacy	Pharmacist must be registered with the relevant local authority to practice as a pharmacist and be familiar with SA and ICH GCP [1, 4] and Good Pharmacy Practice guidance [1]
2.	Ensure pharmacy space can be secured and separated from rest of the clinical trial activities	Access control to clinical trial pharmacy is essential
3.	Ensure pharmacy floor plan is designed in compliance with local specifications including creation of counselling hatches and private and semi-private counselling areas	SA GPP furnishes minimum standards for pharmacy premises, facilities and equipment [1]
4.	Ensure continuous temperature control in the pharmacy premises	Air-conditioning with both heating and cooling functionality is required
5.	Ensure installation of both primary and secondary continuous temperature monitoring systems, where the primary device must generate alert notifications when temperatures deviate from acceptable ranges	Some sponsors may also require a manual min/max reading of temperatures. The temperature system deployed must also be capable of monitoring relative humidity and temperature's in all fridges and freezers
6.	Ensure creation of drug storage areas that can be secured and are not directly visible outside the pharmacy by people standing at the pharmacy dispensing hatch or entryway	Pharmacy staff may be unblinded to certain treatment assignments therefore it is essential to ensure study drugs are not externally visible
7.	Obtain necessary prescribed reference books	Several prescribed reference books are required to be housed in an institutional pharmacy
8.	Obtain registration of pharmacy premises	This process involves Department of Health licensing in addition to South African Pharmacy Council GPP compliance and registration and may take between 6 and 18 months until finalisation of the process
9.	Equip the pharmacy with fridges and freezers as well as back up fridges and freezers and a Class IIb biohazardous safety cabinet	For vaccine trials fridges and freezers may need to cover ranges between 2–8 °C, −40 °C, −86 °C and BSC units will need to be externally exhausted
10.	Equip the pharmacy with computers, label printers, photocopiers, electronic dispensing system and fax machines	The research pharmacy should have fully functional administrative capacity so that sensitive experimental drug information does not leave the pharmacy for photocopying or faxing
11.	Set up systems for local ordering of ancillary medication	This may only be possible when the pharmacy is fully licensed. Not all drugs are provided by the protocol and sponsors

(continued)

Table 1 (continued)

Item	Activity	Comment
12.	Ensure security of the pharmacy premises	Including security gates, installation of alarm systems
13.	Ensure occupational health and safety measures are in place for the pharmacy premises	Provision of fire extinguishers, biohazardous waste spill kits, eye wash facilities
14.	Ensure the pharmacy premises has a suitable waiting area that is designed with infection control in mind	Pharmacy waiting areas in a clinical research site should be for exclusive use of participants waiting for pharmacy services and depending on the type of research, arrangement of chairs need to comply with infection control protocol

2.4.2 QA and QC of Pharmacy and Study Records Including CRFs (Case Report Forms)

Pharmacy records in which the pharmacist is required to make written entries, are subject to quality control (QC) activities at the time of the entry by a second pharmacy staff member. However, if that is not feasible, then the second QC check will occur within the week of the entry being made and noted as such. For CRFs without confidential product information, the QC check will be made by site data staff.

2.4.3 QA and QC Pharmacy Regulatory Files

The pharmacy regulatory files for each active study are reviewed and updated each quarter. This, together with effective and accurate real-time double checks, and a two signature system at each research site pharmacy, results in efficiencies in preparing for sponsor study monitoring visits and further allows the team to manage more protocols.

2.4.4 Equipment Maintenance and Calibration

Effective quality management extends to ensuring that equipment used in the study pharmacy, that may potentially impact study product quality, is subject to annual certifications, servicing and calibration.

Table 2 Essential pharmacy activity before activation, during activation and after trial completion

Pre-trial activities	Activities during trial	Post-trial activities
Protocol development, particularly study product considerations	Study product procurement including importation	Completion of close-out checklist
Pharmacy SOP and source document development	Ancillary medication ordering	Final study product reconciliation
Creating the study drug label	Ancillary medication labelling	Study product destruction
SSP development, specifically for non-pharmacy study product considerations	Participant pharmacy file creation	Archiving pharmacy files
Pharmacy regulatory file creation	Dispensing prescriptions and product accountability	Correspondence with sponsor
Completing sponsor required PEP modules	Participant counselling	Study audit
Conference calls with sponsor	Weekly stock take	
Site team meetings	Quality assurance pharmacy records	
Study training activities	Daily temperature checks	
Further study specific equipment procurement	Bi-annual equipment calibration	
Infrastructure assessment and amendment	Weekly study team meetings	
Completion of study activation checklist for pharmacy activities	Monthly pharmacy team meetings	
Site team meetings	Quarterly monitor visits	
	Quarterly study product destruction monitor visits	
	Report generation	
	Medication destruction	
	Conference calls with study sponsor	

SOP standard operating procedures, *SSP* study specific procedures manual, *PEP* pharmacy establishment plan

2.5 The Responsibilities of the Research Pharmacist

One of the major responsibilities that research pharmacists need to fulfil is maintaining the blinding in studies, particularly where the pharmacist is the only unblinded member of the study team. Several processes need to be in place to prevent the inadvertent unblinding of the clinical research team. These include the following:

- Training pharmacy staff on the importance of maintaining the blinding and specifying in pharmacy standard operating procedures (SOPs) how this will be done for each study;
- Training pharmacy staff on how to correspond with sponsors and the clinical team when referring to the treatment assignment;
- Denying access of non-pharmacy staff into the research pharmacy to prevent inadvertent unblinding;
- Ensuring that all manual pharmacy documents are stored securely and never leave the pharmacy until after study close-out;
- Ensuring that any electronic records are password protected and secured on the server; and
- Not be involved in any processes involving assigning relatedness of product to adverse events.

2.6 Challenges and Lessons Learnt

Over the years the pharmacy support core has had to overcome several unanticipated challenges during the conduct of clinical trials. Strong, effective systems for dispensing and accountability as well as creative ways of ensuring existing infrastructure is used effectively has assisted in overcoming these situations. Examples of the systems implemented to overcome some of the challenges are provided below:

Co-enrolments of study participants in similar clinical trials at other sites: Systems for accountability of unused returned study product was instrumental in identifying participants who were co-enrolled in clinical trials in other organisations through participants returning study products from other studies they were simultaneously participating in but had not disclosed to study staff.

Product sharing between participants and others: Again systems for accountability of unused returned study product and participant adherence counselling was instrumental in identifying participants who were sharing product with other participants and non-study participants.

Unblinding of the blinded pharmacist: Due to a sponsor oversight a pharmacist was inadvertently unblinded to all variants of study product on a clinical trial by email. The process implemented thereafter was swift and thorough containing the oversight and preventing any further damage to study integrity.

Back-up electricity supply challenges during nationwide planned and unplanned power outages: During the period of frequent 'load-shedding' in South Africa, which was implemented by the national electricity provider to maintain the electricity grid, back-up generators were under considerable strain to support demand. The pharmacy core split study vaccine between fridges and freezers and split the equipment load between the primary and secondary generators. In this way, the risk of catastrophic vaccine loss in the event of generator failure during power outage was considerably reduced.

These lessons learnt were important for the support core and taught us to always expect the unexpected and that there is no substitute for good planning and having robust systems in place.

3 Good Laboratory Practice in Clinical Trials

3.1 The CAPRISA Research Laboratory Core

CAPRISA undertakes investigator-led clinical trials and also participates in multi-centre studies. The CAPRISA HIV Research Laboratory (CHRL) supports all research underway at CAPRISA, including providing input during protocol design and making recommendations on appropriate assays, development of Laboratory Request Forms (LRF) for documenting laboratory requests and findings, and setting up systems required for ensuring high quality on-site testing, specimen shipment, processing and capturing of all specimens received, and following up on outstanding laboratory results. During study implementation the Laboratory Core ensures ongoing validation and quality assurance checks of all on-site tests, and implements appropriate and efficient specimen shipping by laboratory staff from each of the CAPRISA clinics to the CHRL where they are distributed to the appropriate routine or research laboratory as per study protocol.

The CAPRISA Laboratory was established in 2003 with a small, well-defined portfolio that has since expanded to include routine assays as well as experimental laboratory testing.

The CHRL/Laboratory Core supports all CAPRISA Clinics. Laboratory staff based at the CAPRISA Clinics also complete rotations at the CAPRISA Laboratory and vice versa. A key additional role of the CAPRISA laboratory core relates to managing the CAPRISA Biobank and includes specimen processing, storage and shipping to the relevant collaborator laboratories. The CAPRISA Biobank/specimen repository has ultrafreezers and liquid nitrogen freezers for both long- and short-term storage and currently houses close to a million barcoded vials with an efficient specimen retrieval system.

The laboratory has a staff complement of 25 people, including medical technologists, laboratory technicians, laboratory assistants, medical scientists, and postdoctoral fellows. The Laboratory Core has the capacity to process 400–500 specimens per day and to work across multiple studies.

All the laboratories are equipped with state-of-the-art technology and if required CAPRISA also has access to the equipment in the other specialist laboratories located in the DDMRI and the adjoining KwaZulu-Natal Research Institute for TB and HIV (K-RITH).

3.2 Overall Laboratory Structure

The Laboratory Core is led by a Laboratory Director who manages and oversees all aspects of the laboratory, ensures that the laboratory functions optimally and that quality of testing performed in the laboratory is of the highest level.

The CHRL is comprised of 4 components; (1) an HIV Research Laboratory, Diagnostic Laboratory and Specimen Repository/Biobank, located at the CAPRISA headquarters at the Doris Duke Medical Research Institute (DDMRI); (2) a Mucosal Immunology Laboratory, also located in the DDMRI; (3) on-site laboratories at each Clinical Research Site (CRS); and (4) collaborating laboratories.

Daily sample collection, point-of-care testing, sample distribution and result report dissemination occurs at the CAPRISA Clinic Laboratory level. Diagnostic testing, sample processing and dispatching are done centrally.

The laboratory is staffed with skilled experienced professionals who are registered with the HPCSA in their respective disciplines. Each staff member has an appropriate job description. Laboratory technologists and technicians are trained to be proficient in the techniques and assays performed in the laboratory and work on a rotational basis in different areas of the laboratory. All staff are compliant with Good Clinical Laboratory Practice (GCLP), Good Clinical Practice (GCP) and Human Subjects Protection (HSP).

3.3 Duties and Responsibility of Laboratory Personnel

The on-site laboratory staff are responsible for ensuring that adequate test kits are available, maintaining appropriate and adequate supplies to enable study specific protocol procedures to be undertaken, maintaining a database of all specimens collected and shipped to the CAPRISA laboratory, preparing specimens for shipping, following up on all outstanding laboratory results and liaising with the central laboratory on all study specific laboratory issues.

All samples received are logged into the CAPRISA Laboratories Information Management System (LIMS) viz. LABWARE which facilitates sample labelling, storage and retrieval. There are well defined rules governing working in this laboratory and all procedures are documented according to GCLP Guidelines. All equipment is on generator backup. Temperature and power supply in all areas and to all freezers are monitored continuously by the University of KwaZulu-Natal Risk Management System for power and an electronic temperature monitoring system (Omniflex) for temperature. A separate wash room exists for autoclaving and waste disposal.

All laboratories are linked to the central LABWARE system, which enables patient demographics to be logged onto a central database. LABWARE is validated according to the FDA guidelines and this is linked to a central server so that all work is stored on the live system. Different levels of staff have different levels of

authority for use on LABWARE. LABWARE is pre-programmed prior to a study starting with all the scheduled study visits and what assays and sample preparation processes are required for each visit. This is linked by visit codes as per those stipulated in the study protocol and each study participant is assigned a unique Patient Identification Number (PID) linked to a unique study number.

All equipment is serviced periodically in line with manufacturers' requirements or the requirements stated by the GCLP and FDA guidelines. Records of service, calibrations or repairs are kept in equipment files at the respective laboratories for easy access. Preventative services and calibrations are noted on the monthly maintenance schedule which indicates which equipment requires service or calibration monthly. This is a quick and easy method of monitoring and ensuring services and calibrations occur timeously to prevent unreliable results or down time.

3.4 Mucosal Immunology, Virology and Humoral Immunology Laboratories

The Mucosal Immunology Laboratory is housed in the central CAPRISA Research Laboratory and conducts basic science and translational research. The fundamental aim of the Mucosal Immunology Laboratory is to build local capacity in basic science and technical infrastructure to investigate important concepts in genital mucosal immunology and to inform on future initiatives leading to the design of effective interventions to prevent HIV infection. This laboratory focuses on basic science research in the areas of T-cell immunology, humoral immunity, innate immunity and female genital tract anatomy. Several established and renowned national and international laboratories are already supporting the Mucosal Immunology Laboratory by affording members the opportunity to receive relevant training in research techniques. Each collaboration was strategically developed to supplement the research capacity of CAPRISA with the individual basic science strengths of the respective associated laboratories in the form of research and intellectual expertise and technical skills. Scientific leadership for the Mucosal Immunology Laboratory is provided by a mucosal immunologist.

The experimental virology laboratory is housed at the University of Cape Town and undertakes all the experimental virological research including the viral diversity research.

The experimental humoral immunology laboratory is housed at the National Institute of Communicable Diseases in Johannesburg.

Specimens for the experimental laboratories outside of Durban are shipped on request or in batches.

3.5 *Chain of Custody and Work Flow*

The CAPRISA Laboratory Core has a courier network to ensure that samples are collected and delivered on time to the correct laboratory. The courier system is outsourced to Global Clinical Virology Laboratories. This outsourcing of the courier services is cost-effective as the network of couriers are all managed directly by Global Clinical and Virology Laboratory who ensure that;

- The courier International Air Transportation Association (IATA) certification is current and complies with the transport of medical specimens;
- The vehicles are serviced and in good road worthy condition;
- Specimens are transported on time in a temperature controlled environment;
- Samples are transported to the central laboratory by couriers who are stationed at each CAPRISA clinic. Courier shipments from urban and peri-urban research sites are at least hourly;
- Two courier shipments are done per day from the rural site to ensure that samples, especially PBMC samples, are not delayed at site.

Samples leaving the site laboratories are always accompanied by the laboratory request form detailing the specific participants PID number, visit code, date and time of sample collection, and who took the specimens. A shipping manifest is also completed, which lists all the samples shipped in that batch as well as defines the sample type and how many samples were collected.

4 Approaches for Optimising Efficiencies to Support the CAPRISA Clinics

The CAPRISA Laboratory utilises the same policies and procedures in all components of the Laboratory Core. This ensures standardisation across all components and minimises duplication of resources at the CAPRISA Clinics. This strategy has proven to be cost-effective and ensures that fewer staff are required to perform multiple and varying tasks in the time allocated.

Multiple laboratory staff members are trained on each protocol being conducted at CAPRISA and hence they are able to work across protocols. During the setup of a new study protocol the Laboratory Core Leader will work closely with the study team to ensure that all assays and procedures are being performed efficiently and optimally. In some instances certain tests are undertaken at an outsourced laboratory to standardise methodology and ensure cost-effectiveness. This may occur if the assay or procedure is highly specialised or as an interim measure if the team is in the process of establishing a new procedure.

The laboratory purchases stock in bulk for all laboratory activities to obtain the most competitive pricing and to ensure sufficient stock is available at all times. This ensures that testing is undertaken at a low cost without compromising on quality.

5 Laboratory Quality Management

All SOPs are written according to a standard format in line with GCLP. Laboratory SOPs are written detailing every process in the laboratory and how that procedure must be performed. It covers basic aspects such as how to decontaminate the bench tops to very detailed step-by-step methodology on how to process samples for an assay. The SOPs include, but are not limited to, quality assurance, chain of custody, sample collection, sample processing, safety, how to perform every assay, reporting and sample storage. All SOPs are given a unique number and a clear title. SOPs are reviewed at least annually. New SOPs are written prior to new policies, procedures or methodology coming into effect. All policies and procedures are documented in a systematic manner, and under strict version control. A master file of all laboratory SOPs is maintained in the Laboratory Core Leader's office and controlled copies are provided to users of the SOPs which include laboratory staff as well as site study staff. A record of the copies distributed is kept in the master file so that if a new version of the SOP is put into effect, the old copies can be recalled and destroyed and new copies distributed. This ensures that no incorrect version of the SOP is used.

Prior to the implementation of a new procedure/test/study, laboratory staffs are trained to ensure understanding of the SOP. Staff competency is conferred once they have written and passed (with at least an 80 % grade) a written competency test and have been observed performing the procedure or test successfully. Staff are retested annually or when they return to that area of work after more than a year. Records of competency testing and retesting are kept centrally for easy access by auditors.

5.1 Importing and Exporting

Given that CAPRISA is a consortium of five institutions located in four cities, each undertaking different investigations ranging from viral diversity to humoral and cell mediated immunity, shipping of specimens from the central CAPRISA laboratory in Durban is key. With CAPRISA's research agenda covering HIV and TB patients, we have had the opportunity to store multiple types of samples from participants, in some instance pre-infection as well as post-infection. These samples are stored in the CAPRISA Biobank. These samples are available to researchers from throughout the world to use to move the scientific agenda forward. Each potential collaborator or requesting researcher is required to submit a concept sheet of the proposed project that they plan to undertake with a motivation as to how this is in line with CAPRISA's and the field's current research agenda. This concept sheet is reviewed by a committee at CAPRISA and a decision made to provide the samples or not to provide them. Once this is approved CAPRISA's regulatory team works with the investigator and their institution to draw up a Materials Transfer Agreement

(MTA) which is an agreement between CAPRISA and the institute indicating amongst other things the use of the samples, the return of the leftovers, payment, and publication rules. An application is made to all affected bioethics committees requesting ethics approval to undertake the project. Once this is granted an application for an export and import permit is made to the South African Department of Health. This application includes a motivation of why the samples are required to be shipped, the volumes, types of samples and numbers of samples being shipped. Each application is reviewed and once all queries and questions are resolved, then the export permit is granted. On receipt of a shipping request that has been approved by the Principal Investigator of the specific study, an IATA certified staff member prepares the shipments. Samples are retrieved from multiple freezers under strict conditions so as to never compromise the integrity of the samples. Shipments are prepared with all the necessary documents filed with the courier company as well as the receiving institute. The standard timeline maintained by the CAPRISA Laboratory is that from receipt of a request to shipping is not more than 2 weeks. The IATA trained staff are experienced at sending ambient shipments, dry ice shipments and liquid nitrogen shipments. Biospecimens are shipped to other collaborating laboratories within and outside South Africa.

5.1.1 Laboratory Certification and Quality Assurance

CAPRISA's Research Laboratory is a registered laboratory with the Health Professions Council of South Africa (HPCSA) under the CAPRISA Registration number: 2002/024027/08; UKZN Registration Number 1949/0322.

The CAPRISA laboratory has since its inception in 2003 been establishing and setting up policies, procedures and systems according to the ISO 15189:2012 Medical Laboratories standard and in accordance with the Code of Federal Regulations Title 42: Public Health, Part 493 Laboratory Requirements, Title 21: Food and Drugs, Part 58 Good Laboratory Practices for Non-Clinical Laboratory Studies. By early 2007 all of these policies, procedures and systems were sufficiently established and sufficient documentation of the quality assurance system was in place to invite a formal audit to be conducted by the South African National Accreditation System (SANAS). Since this audit the CAPRISA Laboratory been SANAS accredited and has been able to retain its SANAS accreditation status by routinely performing well in the external quality assurance programs for the assays undertaken at the laboratory.

All instruments and assays are validated in accordance with the DAIDS guidelines and FDA CRF Part 21 stipulations.

The CAPRISA laboratory has been audited by Pharmaceutical Product Development (PPD) on instruction from the DAIDS according to the FDA and GCLP guidelines, and Westat and FHI360's Regulatory Assurance and Quality Assurance department in preparation for a FDA audit. The laboratory has received favourable audit reports for all studies being conducted at CAPRISA.

The CAPRISA Laboratory subscribes to an extensive Internal and External Quality Assurance program. The External Quality assurance programs include multiple panels from UKNEQAS, CAP, OWA and VQA.

If problems are encountered there are standard procedures to troubleshoot and establish the source of the errors. Records of all internal controls are kept in the respective assay file and a non-conformance record and corrective action form are completed and filed. The number of non-conformances and corrective actions recorded monthly is monitored and proactive action taken. The team also holds management review sessions to measure the laboratories' performance against previously established key performance indicators.

Laboratory staff are experienced in using LABWARE and LDMS for sample storage, shipping and assay result transmission. The staff members are also well versed in each funder's requirements and timelines and function optimally across multiple projects at any given time.

6 The CAPRISA Community Core

CAPRISA research has been informed and shaped by ongoing community and key stakeholder engagement and partnerships since inception. It is premised on a long-term commitment by CAPRISA in undertaking research in the rural, urban and peri-urban communities where the research clinics are based, to enhance responses to the HIV and TB epidemics. Participation in clinical trials of investigational new drugs in research naïve populations with low literacy levels, who have been subjected to years of discrimination and are bearing the brunt of HIV that carries its own set of challenges in terms of stigma and discrimination, requires special attention by researchers to ensure that participation is fully informed and voluntary. The community engagement process represents ethics in action and ensures mutual respect, accountability and a shared responsibility in undertaking research that includes the trial volunteers as well as the communities they live in. The trust that exists between CAPRISA and its key stakeholders (government, local non-governmental organisations, faith based and other civic structures) has evolved through regular, open and frank dialogue. Each community is different in its composition and dynamics within and between groups and individuals and there are also some common characteristics. Dialogue with the community needs to be cognisant of this diversity. Community members in CAPRISA studies comprise political and civic leaders, relevant service providers, traditional leaders, faith-based organisations (FBOs), members of civil society and previous study participants. Co-ownership of the research by community leadership and other community representatives including participants and the study team is critical to the successful conduct of research and adoption of the findings emanating from the research endeavour. At CAPRISA this is formalised through Community Research Support Groups (CSRGs) at each Research Clinic that is encompassed in an overarching umbrella body referred to as the Community Advisory Board (CAB).

Representatives at each CSRG are identified through community nominations and members hold a fixed term of office. Secretariat support for the CABs and CSRGs is provided by CAPRISA Community Programme staff (CPs). CPs provide ongoing training and support and technical updates to the members of the CSRG and CAB. The Community engagement process is initiated prior to study initiation, and continues during the study and on completion of the study.

The Community Research Support Group (CSRG) serves as a nexus between the communities in which the research is being conducted and the research team. The CAB provides a formal mechanism for interacting with the CAPRISA research teams and represents the consolidated membership of the CSRG at community level. The role of CAB members is to represent the diverse communities, demographics, and constituted CRSG at the site and to advise, consult and collaborate with the CP and research teams (Table 3). CRSGs at each site represent a protocol or a network (non-network studies or network studies) within the CAB. CAB/CSRG members serve a 2-year term of office. The CAB meets at least quarterly to discuss emerging information and issues at the site and provides and receives feedback through the CSRG representative for each scientific priority. The site CSRGs play an active role as an interface between the researchers and community members, serving as advocates for the community's best interests and ensuring that the researchers are aware of any concerns within the community about the research being conducted.

The key responsibilities of the CSRG are to:

- provide input into the importance and relevance to the community of the research question;
- provide input on protocol, the informed consent process, information, educational and promotional materials;
- provide culturally appropriate terms for complex scientific language;

Table 3 Increased level of CAB involvement in the community programme

	Inform	Consult	Collaborate
CAB	Provide research staff with information to inform protocol development and implementation Keep CSRG members informed of decisions at site level	Obtain community feedback, challenges, and community research priorities to inform the site Liaise with key constituents and stakeholders	Partner with the site leadership in sharing community best practices Shared dissemination of study progress and findings
CP Leadership	Support the CAB in their work in CSRG Attend CAB meetings	Keep CAB informed of how their input influenced decisions Ensure CAB/CSRG activities are defined in budget	Participate in evaluating CAB and CSRG community involvement activities Support cross CSRG activities at the Research Clinics

- provide perspectives on issues likely to arise during the study;
- voice concerns from stakeholders and study participants;
- support and promote outreach and educational activities;
- support and advise in the development and implementation of recruitment and retention strategies;
- promote and advise on referral arrangements for study participants when appropriate;
- disseminate project information to key role-players/stakeholders
- serve as a resource to the CAPRISA CP and liaison staff; and
- provide feedback to researchers about community concerns and their perceived research priorities.

6.1 Pre-trial Planning

6.1.1 Knowledgeable and Prepared Community and Study Participants

An aware, knowledgeable and prepared community at each stage of the study is essential. An established CP is in place at the CAPRISA rural, peri-urban and urban sites. Although the sites differ, through the technical support of the CP, long-term relationships have been built in the communities in which the sites are located with a strong research literacy foundation built through community education programs that have been implemented according to the specific needs of the community and participants at each site.

6.2 Structure of the CAPRISA Community Core

The CAPRISA Community Core is led by the Head of the CP and a Deputy Head. They provide oversight to each of the Community Core Site Coordinators and community outreach workers. The Community Core Site co-ordinators in turn manage a team of community outreach staff at each Research Clinic. The Community Outreach staff at each Research Clinic are usually from the community and have a good understanding of the community, the study population and the community stakeholders at their site. The key responsibilities of the CP Coordinator at each site is to coordinate information dissemination, recruitment and participant tracking strategies to enhance retention rates. The CP Coordinators with the outreach workers also facilitate community participation in all aspects of the community programme ensure effective collaborations with relevant service providers, non-governmental organizations (NGOs), community-based organizations (CBOs) and key role-players; support local community education and training programs that build awareness and

knowledge; and ensure that the community and study participant interests are represented. Community outreach workers/educators, recruiters, participant trackers and community outreach/peer educators are employed at each site and they work across CAPRISA studies. The Head and Deputy Head of the CP provide similar support to the CAB. Table 4 provides a more detailed description of the roles and responsibilities of various staff within the CAPRISA Community Programme.

6.3 Addressing Stigma and Discrimination

In the pre-planning phase and throughout the conduct of the study, understanding and addressing barriers to participation in the community, real or perceived stigma and discrimination is important. Regardless of the stage of the trial, knowledge of HIV status at individual and community level is a key to changing the course of the epidemic as this is the gateway to treatment and prevention services. A community that is open to knowledge about HIV provides a supportive environment for HIV treatment and prevention research and services [6–9].

Table 4 Community programme staff role and responsibilities

Head and deputy head of the community programme	Site community program coordinator	Community outreach staff
• Provide technical support to core staff to facilitate the planning, organising, implementing and evaluation of their community involvement strategies • Conduct community needs assessments • Provide technical support to the Community Advisory Board (CAB) • Advise investigators and project staff on issues related to community preparedness and involvement activities • Ensure synergies and collaboration between all Community Program staff • Monitor the maintenance of effective partnerships with key stakeholders • Ongoing assessment of CAB and Community Research Support Groups training needs • Coordinate training workshops	• Facilitate community preparedness activities • Establish and provide technical support to the CSRG • Coordinate recruitment, education and participant tracking strategies • Facilitate community participation in all aspects of the research • Ensure effective collaborations with relevant service providers, NGOs, CBOs and key role-players • Support relevant community education and training programs that build awareness and knowledge, facilitate participant recruitment and address retention and adherence • Ensure that the community and study participant interests are represented	• Provide HIV/AIDS education • Assist with the implementation of the CAPRISA Community Outreach Program • Assist with the co-ordination of community meetings • Provide information on new research findings; and proposed research to potential research participants and community • Assist with community mapping and obtaining locator data • Assist with general research administration • Assist with translation for study participants

6.4 Ongoing Dialogue and Engagement During the Clinical Trial

- ***During protocol development***
  Proposed studies are discussed with the CAB and CSRG during concept stage to establish acceptability of the proposed research. A good example here is in relation to the dosing strategy used for CAPRISA 004. Most PrEP studies of oral tenofovir were using a daily dosing strategy. The potential research participants in CAPRISA 004 were consulted about the trial under development and specifically asked about how they would use the product. They were quite categorical that their risk related to when they had sex with their partner and given that their partner was a migrant labourer who they saw infrequently they wanted a product that they could use when they were having sex and not every day.
- ***Pre-enrolment and General information sessions***
  A lexicon is developed with the community and the CAB/CSRG to develop sensitive and linguistically correct wording for participant information documents and informed consent process. The CAB/CSRG assists with translation of the documents
- ***Recruitment, accrual and follow-up***
  The CAB/CSRG provides input into the recruitment plan for the most appropriate recruitment strategies and is consulted for further guidance when accrual figures are not being met. The CAB and community stakeholders included in this process play a vital role in addressing community myths about the study and trial related stigma and minimises miscommunications [10]. The CAB and community are informed about the potential for co-enrolment and what systems are in place to avoid this. The CAB, however, retains their autonomy throughout the trial as a support structure for the community and the participants.
- ***Preparation for DSMB outcomes***
  Different scenarios are developed to disseminate key outcomes of DSMB reviews to the CAB and community stakeholders to minimise miscommunications.
- ***On completion of a clinical trial***
  - Study exit plan
    The study exit plan is developed with the CAB and key stakeholders early in the trial preparedness process and includes unexpected trial closure. Given the longer term commitment of CAPRISA to the communities it works in, this is less of an issue. The community is usually informed of new and planned studies when a specific trial is ending.
  - Dissemination of results
    Through the signing of a confidentiality agreement the study results are disseminated to the CAB and study participants before being publicly announced. A transparent process is essential for recognising the community as partners in the research and building trust for future research.

- Post-trial product access
  Early in the trial, development plans should be in place to make the product or procedure tested in the trial available to trial participants and the local community, should the new product or procedure be scientifically proven to be effective and have no safety concerns [10].
- Ongoing health care
  Partnerships need to be in place with health care services for referral of participants' post-trial for ongoing HIV care and support and other health services.
- Destruction of stored specimens
  To further build trust and demonstrate transparency throughout the study, CAB/CSRG members are invited to witness the destruction of stored specimens where no consent was obtained.

6.5 Preparing for Communicating Progress of Trials

In the context of ongoing communication with community, participants and key stakeholders, communication and dissemination of new information of a trial in the field or a trial coming to an end should not be complex. What is essential is a clear communication plan for consultation with community and key stakeholders and should include:

- An explanation of complex scientific issues;
- A listing and details of key issues;
- The trigger for the specific meeting, e.g. outcome of a DSMB meeting or if a study is ending the implications of the study findings for licensure or its impact on the field; and
- Co-ordination with other planned Communication strategies.

This type of communication plan ensures that unanticipated delays or premature termination of trials, new findings from other studies and its impact on the current study are adequately considered and addressed proactively [11].

7 Conclusion

While we have shared in this chapter our experiences from three science support cores in CAPRISA they are by no means the last word on the subject. Ultimately, these science support cores' inputs into the conduct of clinical trials need to be adapted to the research question and trial design. Importantly, a continuous improvement approach ensures that these science support cores remain at the cutting edge of their field to bring maximum value-add to the clinical trial being conducted.

References

1. The South African Pharmacy Council. Good Pharmacy Practice Manual. Fourth ed; 2010.
2. Pharmacy Act (Act 53 of 1974), Regulations and Rules (Ethical Rule 4).
3. Republic of South Africa. Medicines and Related Substances Control Act (Act 101 of 1965) and General Regulations (section 22A, Regulation 34, 35). Available at http://www.mccza.com/Publications/DownloadDoc/44 (accessed 30 January 2016).
4. International conference on harmonisation, Guidileine for Good Clinical Practice. Retrieved 12 January 2016 from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html.
5. South African Department of Health. Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa. 2006.
6. Frohlich J, Kirkendale SS, Wilson WL, Abdool Karima Q, Morin SF, Wakefield S. Establishing community involvement in an international HIV prevention research network: Issues and challenges. July 7–12; 14: abstract no. MoPeG4170. 1. Int Conf AIDS; 2002; 2002.
7. Swartz L, Kagee A. Community participation in AIDS vaccine trials: empowerment or science? Soc Sci Med 2006; 63(5): 1143–6.
8. Campbell C, Nair Y, Maimane S. Building contexts that support effective community responses to HIV/AIDS: a South African case study. Am J Community Psychol 2007; 39 (3-4): 347–63.
9. Tindana PO, Singh JA, Tracy CS, Upshur REG, Daar AS, Singer PA, et al. Grand challenges in global health: community engagement in research in developing countries. PLoS Med 2007; 4(9): e273.
10. UNAIDS. Good Participatory Practice. Guidelines for biomedical HIV prevention trials. 2011.
11. Robinson ET, Baron D, Heise LL, Moffett J, Harlan SV. Communications Handbook for Clinical Trials. Family Health International.; 2010.

Chapter 13
Ethical and Legal Considerations for Realising Post-trial Access of Novel Experimental Interventions: Lessons from the CAPRISA 004 Trial

Jerome Amir Singh

1 Normative Ethics and Post-trial Obligations

Normative ethics is a branch of philosophy that explores how one ought to act, morally speaking. From a normative ethics perspective, ensuring that research participants enjoy post-trial access to an intervention that they were instrumental in proving the efficacy and/or effectiveness of, is a realisation of the principles of *Justice* (giving people what they deserve, and apportioning benefits in an equitable way), *Reciprocity* (a benefit received by society and science is returned with a benefit to those who made a sacrifice; i.e. study participants) and *Beneficence* (the duty to do or produce good). These principles have profoundly influenced international research ethics guidance documents in relation to post-trial accessibility of study interventions.

1.1 International Research Guidance Instruments and Post-trial Obligations

When the CAPRISA 004 trial results were published, clinical trial guidance documents offered no guidance on post-trial access. Neither the International Council on Harmonisation's (ICH) 1996 *Harmonised Tripartite Guideline for Good Clinical Practice,* nor the ICH's 1997 *General Considerations for Clinical Trials*,

J.A. Singh (✉)
Centre for the AIDS Programme of Research in South Africa,
University of KwaZulu-Natal, Durban, South Africa
e-mail: Singhj9@ukzn.ac.za

J.A. Singh
Dalla Lana School of Public Health and Joint Centre for Bioethics,
University of Toronto, Toronto, Canada

Q. Abdool Karim et al. (eds.), *The CAPRISA Clinical Trials: HIV Treatment and Prevention*, DOI 10.1007/978-3-319-47518-9_13

nor the World Health Organisation's 2002 *Handbook for good clinical research practice* (*GCP*): *Guidance for implementation,* provided any guidance on the issue of post-trial access to efficacious study interventions. On the other hand, the world's two most prominent international research ethics guidance documents—the Declaration of Helsinki and the CIOMS Guidelines—did provide guidance on this issue.

Paragraph 30 of the 2000 version of the Declaration of Helsinki [3] states:

> At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

In 2004, the World Medical Association (WMA) published a note of clarification on paragraph 30. It states:

> The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

Post-trial access to study interventions is also highlighted in guideline 10 of the 2002 revision of the CIOMS Guidelines [4]. It states:

> Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that:
>
> • any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.

The accompanying commentary on guideline 10 states:

> *…[I]f an investigational drug has been shown to be beneficial, the sponsor should continue to provide it to the subjects after the conclusion of the study*, and pending its approval by a drug regulatory authority. The sponsor is unlikely to be in a position to make a beneficial investigational intervention generally available to the community or population until sometime after the conclusion of the study, as it may be in short supply and in any case cannot be made generally available before a drug regulatory authority has approved it.

Interestingly, the 2008 revision of the Declaration of Helsinki [5] contains arguably watered-down language in relation to post-trial obligations. Paragraph 33 states:

> At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

In 2007, UNAIDS and WHO jointly published a guidance document entitled *Ethical considerations in biomedical HIV prevention trials.* Guidance Point 19 (Availability of Outcomes) of this guidance document states:

> During the initial stages of development of a biomedical HIV prevention trial, trial sponsors and countries should agree on responsibilities and plans to make available as soon as possible any biomedical HIV preventive intervention demonstrated to be safe and effective, along with other knowledge and benefits helping to strengthen HIV prevention, to all participants in the trials in which it was tested, as well as to other populations at higher risk of HIV exposure in the country, potentially by transfer of technology.

None of the above ethics guidance documents stipulate a timeframe in respect to post-trial access to study interventions, nor whether such guidance is restricted to any particular phase of clinical trials. It is thus not clear whether post-trial obligations apply to phase 2 trials, or only phase 3 trials.

1.2 Domestic Research Ethics Guidance Instruments and Post-trial Obligations

South Africa's then applicable national research ethics guidance document, *Ethics in Health Research: Principles, Structures, Processes*, published in 2004 [6], is silent on the issue of post-trial obligations. In regard to access to study medication following completion of clinical trials, paragraph 3.4 of South Africa's 2000 national ethics guidelines on clinical and epidemiological research, entitled *Ethical Considerations for HIV and AIDS Clinical and Epidemiological Research*, states:

> Many patients who participate in HIV and AIDS treatment trials, have no alternative access to drug therapy. Where a patient has a therapeutic response to a study drug, that patient should be offered ongoing treatment. In designing studies, consideration should be given to the costs of long term provision of study drugs and of clinical monitoring, including the costs of medical staff. The duration of drug therapy in a study should be clearly stated in the patient information section of the informed consent document [7].

This guideline is silent on post-trial obligations in relation to prophylactic (preventive) interventions. Similarly, South Africa's 2006 *Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa* [8] (GCP Guidelines) does not mention post-trial access to prophylactic interventions, although paragraph 2.3.12.1.4 of the South African 2006 GCP Guidelines does explicitly refer to access to study medications following the completion of a HIV clinical trial. It states:

> On completion of a trial, trial participants should be referred to existing health care services, with the understanding that there is progressive implementation of state supported Anti-Retroviral Therapy (ART).

Notwithstanding CAPRISA not making any explicit promises to CAPRISA 004 study participants in relation to their post-trial access to tenofovir gel, CAPRISA's leadership considered it important to consider the ethical and legal implications of several post-trial options available to the organisation in relation to CAPRISA 004 trial participants.

2 Options for Realising Post-trial Access of Tenofovir Gel to Relevant Participants of the Caprisa 004 Trial

CAPRISA explored at least three options in relation to its post-trial obligations to relevant participants of the CAPRISA 004 trial:

(a) CAPRISA not providing post-trial access of tenofovir gel to relevant CAPRISA 004 trial participants but referring all CAPRISA 004 study participants to existing health services for prevailing standard of care/prevention;
(b) CAPRISA providing relevant CAPRISA 004 trial participants with tenofovir gel through a 'compassionate use' regulatory mechanism; and
(c) CAPRISA providing tenofovir gel to relevant CAPRISA 004 trial participants through the conduct of an open label implementation trial.

Each of these options carried ethical and legal implications.

(a) **CAPRISA not providing post-trial access of tenofovir gel to relevant CAPRISA 004 trial participants but referring all CAPRISA 004 study participants to existing health services for prevailing standard of care/prevention**

As noted earlier, research ethics guidance documents offer some guidance on providing study participants with post-trial standard of care/prevention. Paragraph 33 of the 2008 version of the Declaration of Helsinki states (relevant words italicised for emphasis):

> At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, *access… to other appropriate care or benefits*.

Paragraph 2.3.12.1.4 of South Africa's 2006 GCP Guidelines states: 'On completion of a trial, trial participants *should be referred to existing health care services…*'

At the conclusion of the CAPRISA 004 trial, the then prevailing standard of HIV prevention in South Africa for females was universal access to condoms and risk reduction counselling at designated state facilities. While it would have been legally permissible for CAPRISA to refer HIV-negative CAPRISA 004 trial participants to existing healthcare services, in CAPRISA'S view, doing so would have violated the ethical principles of Reciprocity, Justice and Beneficence, outlined above. Moreover, such conduct would arguably have violated guideline 10 of the 2002 CIOMS Guidelines, paragraph 33 of the Helsinki Declaration, paragraph 3.4 of South Africa's 2000 Department of Health guidelines on Ethical Considerations for HIV and AIDS Clinical and Epidemiological Research, and paragraph 2.3.12.1.4 of South Africa's 2006 GCP Guidelines. While none of the above ethics principles and guidelines are binding, CAPRISA's leadership believed they imposed a moral duty on the organisation and its investigators to take affirmative measures to realise tenofovir gel access to CAPRISA 004 trial participants.

(b) CAPRISA providing relevant CAPRISA 004 trial participants with tenofovir gel through a 'compassionate use' regulatory mechanism

'Compassionate use' regulatory mechanisms are intended to give patients with a life-threatening, long-lasting or seriously disabling disease, who have no available treatment options, access to treatments that are still under development and that have not yet been authorised. For example, in the context of the European Union (EU), patients suffering from a disease for which no satisfactory authorised alternative therapy exists or who cannot enter a clinical trial, may make use of an unauthorised medicinal product in a compassionate use programme [9]. Section 21 of South Africa's Medicines and Related Substances Control Act, 101 of 1965, may be described as a 'compassionate use' mechanism as it allows for the MCC to authorise the sale of unregistered medicines for certain purposes. It states:

(1) The council may in writing authorise any person to sell, during a specified period to any specified person or institution, a specified quantity of any particular medicine which is not registered;
(2) Any medicine sold in pursuance of any authority granted under sub-section (1) may be used for such purposes and in such manner and during such period as the council may in writing determine;
(3) The council may at any time by notice in writing withdraw any authority granted in terms of sub-section (1) if effect is not given to any determination made in terms of sub-section (2).

Like the EU compassionate use mechanism, section 21 has traditionally been reserved for patients with a seriously debilitating disease, or a life-threatening disease, and who cannot be treated satisfactorily by an authorised medicinal product (put differently, those with dire and otherwise untreatable conditions). In the aftermath of the CAPRISA 004 trial result, it was (and still is) doubtable whether the MCC would/will allow section 21 to be used as an access mechanism for a prophylactic intervention, such as tenofovir gel. Even if the MCC were to approve the provision of tenofovir gel under a section 21 application, CAPRISA was mindful of the legal implications of doing so.

Legal implications of utilising a compassionate use regulatory mechanism to facilitate the provision of an unregistered intervention to trial participants

South Africa's Medicines and Related Substances Act does not indemnify manufacturers of 'compassionate use' drugs or products, nor the clinicians who prescribe them. Notwithstanding tenofovir's excellent safety profile, in terms of South African tort (delict) law, the sponsor, principal investigator/host institution, treating clinician and possibly even the MCC itself, could be held jointly and severally liable in a malpractice action if the investigational agent was wrongly prescribed or its use/application resulted in harm to its recipients. South Africa's Consumer Protection Act (CPA), 68 of 2008, parts of which became operational in October 2010, and the remainder, by April 2011, was also relevant to consider. In terms of the CPA, the producer, importer, distributor (which could conceivably include CAPRISA) or retailer of any goods (such as a microbicide product) is liable

for any harm caused wholly or partly as a consequence of supply and any unsafe goods, product failure or defect or hazard in the goods, or inadequate instructions or warnings provided to an individual pertaining to any hazard arising from or associated with the use of any goods. All the individual would need to do is prove that the harm was caused by the defective product in question. Because the CPA is based on 'no-fault' liability, it would not be necessary for an affected individual to prove negligence on the part of the clinician or any of the other role players relevant to the product, unlike traditional malpractice claims. Exclusion of liability clauses is thus relevant to consider.

Exclusion of liability clauses have been deemed legal by South Africa's Supreme Court of Appeals in the 2002 case of *Afrox Healthcare BPK v Strydom* [10]. However, judgment in this case was handed down before the enactment of the CPA. The CPA prescribes only limited grounds of liability exclusion, which are outlined in section 48 of the Act. The CPA's 'no-fault' and exclusion of liability provisions were thus carefully considered in the context of post-trial access of tenofovir gel.

Section 48 of the CPA (which became operational on 1 April 2011) contains a general prohibition on unfair, unreasonable and unjust contract terms and also prohibits any agreement that requires a consumer to waive any rights, assume any obligations or waive any liability of a supplier on terms that are unfair, unreasonable or unjust or if such terms are imposed as a condition of entering into an agreement. The section also lists criteria in order to determine whether a condition of a contract is unfair, unreasonable or unjust terms, which include the following:

1. Terms that are 'excessively one-sided in favour of any person other than the consumer or other person to whom goods or services are to be supplied';
2. Terms which are 'so adverse to the consumer as to be inequitable'; and
3. If the consumer relied upon a false, misleading or deceptive representation or statement of opinion provided by or on behalf of the supplier, to the detriment of the consumer.

Section 51 of the CPA prohibits an exemption of a supplier of goods or services from liability for any loss directly or indirectly attributable to gross negligence (for example, lost income on the part of a research participant) of the supplier or any person acting for or controlled by the supplier. By implication, a clause exempting liability for ordinary negligence is not prohibited. Given these provisions, it is possible to mitigate the chances of a product liability lawsuit in relation to compassionate use of an unlicensed product by including an indemnity/exclusion of liability clause in the informed consent form. This could be phrased as follows [11]:

I herewith confirm,

1. That I was comprehensively informed about the use of the unlicensed product xxx in the framework of "compassionate use";
2. That I understood the content of this patient information and of the xxx patient information sheet;
3. That I have been informed about risks and side effects of this product;

4. That all my questions were answered comprehensively and in an understandable fashion; and
5. That I consent to the use of the unlicensed product xxx within the framework of "compassionate use" and that I will waive liability claims on the treating physician and dispensing pharmacy.

Such wording is arguably just, fair, and reasonable, and not contrary to public policy.

It was contemplated that if CAPRISA were to obtain MCC approval to register tenofovir gel in terms of section 21 of the Medicines and Related Substances Control Act, the organisation had to consider taking out product liability insurance in the event of a product-related injury arising, especially as the follow-up phase 3 confirmatory trial results were still outstanding. In the 2002 South African case of *Ceiba-Geigy (Pty) Ltd v Lushof Farms (Pty) Ltd en 'n Ander* [12], the Supreme Court of Appeals confirmed that when a manufacturer produces and markets a product without conclusive prior tests, and when the utilisation thereof in the recommended manner is potentially hazardous to the consumer, such negligence on the part of the manufacturer may expose it to delictual liability to the consumer. The court also held that a contractual nexus between the manufacturer and the consumer is not required (this would apply to the CAPRISA context where there is no direct link between the product manufacturer (Gilead) and the product recipients (study participants).

Compelling the MCC to register tenofovir gel on the basis of participant right to health

CAPRISA leadership contemplated the possibility of the MCC refusing to register tenofovir gel in terms of section 21 of the Medicines and Related Substances Act, and whether such registration could be compelled by a court order on the basis of the research participants' constitutional right to health. There was, and, to date, still is no precedent in South African law for the constitutional right of patients to access unapproved, experimental, but potentially life-saving drugs or products. Section 39 of South Africa's Constitution obliges the country's courts to consider international law and grants discretion to the courts to consider foreign law, where applicable. It is thus relevant to consider how other countries have handled such legal claims.

The issue of post-trial access to unapproved, experimental, but potentially life-saving drugs or products has come before US courts. In the 2007 US case of *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach* [13], the court ruled against any constitutional right of a patient to access unapproved, experimental, but potentially life-saving drugs. It is very likely that South African courts could adopt a similar stance. On the other hand, the 2008 US case of *Gunvalson v PTC Therapeutics* [14], was not based on the patient's constitutional right to health, but on the drug manufacturer's pledge to a dying boy. In this case, the defendant had promised the boy participation in its later trials. The court held this amounted to a promise to provide him with its experimental drug no matter what, even if he no longer qualified for any research protocol that would provide any data that would be useful to the defendant's ongoing research. Accordingly, the court

ordered the US drug manufacturer to provide a life-saving experimental drug to the boy outside the context of a clinical trial. Given that tenofovir gel is prophylactic in nature, not therapeutic, it is unlikely that South African courts will adopt a similar stance, particularly since CAPRISA did not promise or guarantee CAPRISA 004 study participants that they would enjoy post-trial access to tenofovir gel.

Given all the above factors, CAPRISA opted not to pursue a compassionate use mechanism to facilitate CAPRISA 004 study participants accessing tenofovir gel.

(c) **Providing tenofovir gel to relevant CAPRISA 004 study participants through the conduct of an open label implementation trial**

CAPRISA considered the implications of conducting an open label implementation trial to ensure that CAPRISA 004 study participants enjoyed relatively prompt access to tenofovir gel. It was believed that such an option satisfied the ethical principles of Reciprocity, Justice and Beneficence. Moreover, this option would realise the post-trial duties of investigators and sponsors outlined in international and domestic research ethics guidance documents, highlighted above.

In considering this option, CAPRISA leadership had to contemplate how to manage post-trial access of tenofovir gel to participants if the product was ultimately not registered. In addressing this issue, an important question arose: If a follow-up trial(s) yielded negative efficacy results, would CAPRISA still have an obligation to continue providing tenofovir gel indefinitely to CAPRISA 004 trial participants? US case law is instructive here.

In the 2006 US case of *Abney v. Amgen* [15] the plaintiffs were research participants in a clinical drug trial sponsored by Amgen Inc. When the study was terminated early on safety grounds, the plaintiffs, who claimed to have been benefiting from the drug, sued Amgen claiming that the company was legally required to continue providing them with the drug. The plaintiffs claimed, amongst others, that the drug was effective and that the principal investigators promised that the plaintiffs would continue to receive the medication, and that Amgen was accordingly bound by those promises. The court found that there was no evidence of a promise by Amgen to continue providing the plaintiffs with the drug following the termination of the study as neither the University of Kentucky (the host institution for the trial) nor the principal investigators were agents of Amgen (the latter were deemed to be independent contractors to Amgen). The court held that there was also no evidence that the University or the principal investigators had the authority to bind Amgen via their promises to the plaintiffs. In ruling against the plaintiffs, the court stated that the plaintiffs 'might have considered suit against the University of Kentucky's Institutional Review Board and the physician investigators involved in the clinical trial. It was the University that was legally bound by the Informed Consent Document and thus arguably legally obligated to continue to administer the treatment to the plaintiffs'. The Abney case illustrates that sponsors and investigators need to be careful about the representations they make to research participants. Moreover, even a study that has been stopped on safety grounds may be actionable by study participants who claim they had been deriving benefit therefrom.

Although the Abney case is not binding on South African courts, it offers valuable lessons for South African investigators of a proof-of-concept trial, and any follow-up confirmatory trials. If trial participants are prospectively informed that there is no guarantee that they will continue receiving the experimental intervention after the follow-up confirmatory trial ends, particularly if the confirmatory trial yields negative results, there would be no reasonable grounds for trial participants to develop legitimate expectations in relation to their post-trial access to the experimental intervention.

After weighing its options, CAPRISA opted to provide CAPRISA 004 trial participants access to tenofovir gel through the conduct of an open label implementation trial, which eventually was titled the CAPRISA 008 trial (for more on the design and regulatory approval process of the CAPRISA 008 trial, see Chap. 5). During the conduct of the CAPRISA 008 trial, the FACTS 001 trial yielded negative efficacy results. As a result, tenofovir gel did not ultimately obtain licensure as a HIV prevention intervention. Consequently, Gilead, the drug sponsor, ceased its production of tenofovir gel. In line with the rationale outlined earlier, post-trial access of tenofovir gel for relevant CAPRISA 004 and CAPRISA 008 trial participants ceased upon the conclusion of the CAPRISA 008 trial. Such an outcome is disappointing, but ethically and legally defensible.

3 Conclusion

Sponsors and investigators have an ethical obligation to provide trial participants with post-trial access to a proven efficacious intervention when it is feasible to do so. In determining how to ensure such access, various post-trial access options should be considered. CAPRISA's experience in realising its post-trial obligations to CAPRISA 004 trial participants may be instructive to others contemplating post-trial access of novel experimental interventions.

References

1. Abdool-Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE et al. Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women. *Science* 2010; 329(5996): 1168–74.
2. Rees H, Delany-Moretlwe SA, Baron D, Lombard C, Gray G, Myer L et al. FACTS 001 Phase III Trial of Pericoital Tenofovir 1% Gel for HIV Prevention in Women [Abstract 26LB]. Conference on Retroviruses and Opportunistic Infections (CROI); 2015 23-26 February 2015; Seattle, Washington; 2015.
3. World Medical Association. Declaration of Helsinki: *Ethical Principles for Medical Research Involving Human Subjects.* 52nd WMA General Assembly, Edinburgh, Scotland, October 2000.

4. Council for International Organizations of Medical Sciences (CIOMS) and World Health Organization (WHO). (2002). *International Ethical Guidelines for Biomedical Research Involving Human Subjects.*
5. World Medical Association (WMA). Declaration of Helsinki. 59th WMA General Assembly, Seoul, October 2008.
6. Department of Health, South Africa (2004). *Ethics in Health Research: Principles, Structures Processes*. Accessible: http://www.doh.gov.za/docs/factsheets/guidelines/ethnics/index.html.
7. Department of Health, South Africa (2000). Ethical Considerations for HIV and AIDS Clinical and Epidemiological Research. Accessible: http://www.doh.gov.za/aids/docs/ethical.html#testing.
8. Department of Health (2006). *Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa.*
9. European Medicines Agency Committee for Medicinal Products for Human Use (CHMP). Guideline on Compassionate Use of Medicinal Products Pursuant to Article 83 of Regulation (EC) No 726/2004. Accessible: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004075.pdf.
10. *Afrox Healthcare BPK v Strydom* 2002 (6) SA 21 (SCA).
11. Tsianakas A, Schiller M, Luger, TA, Sunderkötter C. The option of compassionate use in metastatic. melanoma – way out of a therapeutic dilemma? J Dtsch Dermatol Ges. 2009; 7: 671–678.
12. *Ceiba-Geigy (Pty) Ltd v Lushof Farms (Pty) Ltd en 'n Ander,* 2002 (2) SA 447 (SCA).
13. *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, 495 F.3d 695 (D.C. Cir. 2007).
14. *Gunvalson v PTC Therapeutics, Inc* Civ. No. 08-3559 (WJM). http://druganddevicelaw.net/Opinions%20in%20blog/Gunvalson%20opinion.pdf.
15. Abney v. Amgen, Inc., 443 F.3d 540 (6th Cir. 2006).

Chapter 14
Grants Management

Marian Swart, Devenie Latchmanan, Nasrin Amla and Carl Montague

1 Introduction

Undertaking research that involves the conduct of randomised controlled trials requires substantial funding. Each pivotal study undertaken at CAPRISA requires funding and other resources for a period of 5–7 years. Writing and submitting grants is an essential part of securing funds for the research underway at CAPRISA. Indeed, CAPRISA was established in 2001 through a competitive grant application process in response to a call for applications for programme grant awards made by the US National Institutes of Health (NIH) to enhance the response to the HIV epidemic in resource constrained settings. The funding base of CAPRISA has since diversified. This chapter provides an overview of systems in place at CAPRISA for grants management, but is more broadly applicable for institutional or individual project grants management. Grants Management is an essential and supportive component of the conduct of research and ensures accountability to the research sponsor.

There are a wide spectrum of sponsors who support research and applying for research funds is generally a competitive process. Once the funding has been awarded there is an obligation on the recipient of the award to ensure that all sponsors' requirements are met. It is crucial that the grantee is fully aware of what these requirements are and to ensure that systems are in place to manage these grant funds and all the accompanying contractual requirements. The process whereby grant activity is managed and coordinated to ensure compliance with each sponsors' requirements within a specific time frame is called grants management [1].

Project awards are generally made to institutions rather than individuals and institutions are responsible for ensuring that all the systems are in place to manage the awards. Poor management of awards can lead to sponsors withholding funds or

M. Swart · D. Latchmanan (✉) · N. Amla · C. Montague
Centre for the AIDS Programme of Research in South Africa,
University of KwaZulu-Natal, Durban, South Africa
e-mail: Devenie.latchmanan@caprisa.org

Q. Abdool Karim et al. (eds.), *The CAPRISA Clinical Trials: HIV Treatment and Prevention*, DOI 10.1007/978-3-319-47518-9_14

no longer awarding grants to these specific institutions. Various systems need to be put in place to ensure compliance with sponsors' requirements. These systems can be categorised under compliance, financial management, human resource management and general administration.

1.1 Compliance

Most sponsors have some form of grants policy that applies to all grantees and it is the responsibility of the grantee to ensure that they familiarise themselves with the requirements and also stay informed of any updates or changes to these requirements. The individual or department responsible for compliance should have systems in place that ensure compliance to these requirements. Examples could be the setting up of an electronic alert system for annual compliance requirements, e.g. annual Conflict of Interest declarations and Human Subjects Protection and Good Clinical Practice training and refresher training. Many sponsors also have various ways of ensuring that institutions and PIs are kept up to date regarding changes through e mail updates, RSS (Rich Site Summary) feeds and social media.

Ensuring compliance with all sponsors' requirements starts from the point where a decision is made by the research team to apply for a specific grant in response to a funding opportunity announcement (FOA) by a sponsor. The FOA needs to be very carefully reviewed by the potential Principal Investigator (PI) as well as the individual or department responsible for ensuring compliance. All requirements set out in the FOA need to be met when submitting an application and this could be anything from specifications about font size and paper size to legal requirements related to human subjects and animal protection. Each institution will have a designated Authorized Organisation Representative (AOR) or Authorized Signing Official whose signature on all grant-related documents certifies organisational compliance or intention to comply with sponsors' policies, certifications and assurances.

Grant application submission would generally be done by the designated compliance individual or department on behalf of the institution and PI. Prior to submission, this individual or department must ensure that the application is fully compliant with sponsors' requirements as outlined in the FOA. Failure to do this could lead to the application being rejected for non-compliance and not being reviewed at all. It is advisable for the PI to ensure that compliance is monitored by the individual or team within the institution responsible for compliance as well. Ultimately the continuation of funding and/or new grant funding by a specific sponsor is dependent on ensuring that compliance requirements are met. Ignorance is not accepted as an excuse for non-compliance.

The compliance individual or team is responsible for registering the institution and ensuring the information is regularly updated to ensure ongoing validity of registration for electronic grant application systems, which may be required prior to the application being submitted, e.g. eRA Commons and SAM (System for Award

Management). The PI should confirm the active status of the institution's registration and obtain the institution's registration numbers required on the grant application, e.g. Data Universal Numbering System (DUNS) number and Employer Identification Number (EIN) number, from the compliance individual or department.

If an institution is receiving an award from a specific sponsor for the first time, the sponsor might send in a team to review the various systems of the institution to assure themselves that the institution is capable of managing the award within acceptable grant management principles and guidelines. This review could cover everything from the management structure of the institution to ensuring that there are written policies and procedures for financial management, human resource management, information systems management and any other relevant requirements. Examples of some such essential policies relate to procurement, asset management and travel.

The award letter or grant agreement is a legal document which is usually issued annually. The initial award letter will provide an approved budget for the first year with a commitment for funding of the additional years, depending on the availability of funds. The award letter is issued to the institution, not to an individual. Once the award letter has been received it must be read thoroughly by both the PI and the compliance individual or department and all the salient requirements should be noted. It could be useful for the compliance individual or department to provide a summary of the requirements to the PI, key personnel, AOR and Financial Manager. Requirements could be anything from financial and narrative reporting deadlines, including the frequency of these reports, as well as terms and conditions relating to the use of the funds, situations where prior approval from the sponsor is obligatory and requirements related to changes in key personnel. Other terms and conditions could relate to acknowledgement of sponsor in publications and presentations, human subject protection, animal welfare, confidentiality and data and safety monitoring.

The compliance individual or department is responsible for the monitoring of compliance with sponsors' requirements and should set up an electronic alert system for all reporting and other deadlines, which would alert both him/herself and the PI. In addition, the compliance individual or department should send out e-mail alerts to the PI and/or the Financial Department well ahead of reporting deadlines as an additional measure to ensure that the deadlines are met. For some sponsors, the AOR is responsible for submission of the reports electronically and the PI should work with the compliance individual and department to ensure the reports are completed and submitted before the deadline. The quality of the research being done might be outstanding but if the award is not managed well and all deadlines are not met, this could jeopardize future funding.

Changes to awards normally need prior approval from the sponsor and the compliance individual or department is responsible for ensuring that a request is sent to the sponsor with the signature of the AOR and the PI. Examples of such changes could be a carryover of unspent funds, change of grantee organisation, a change of PI, a change in scope of project or a no-cost extension request.

The compliance individual or department is responsible for ensuring that a comprehensive system for filing of all documentation pertaining to grants from application through to final close out reports is maintained. This could also be set up as an electronic system.

1.2 Financial Management

Prudent financial management of grant funds within the requirements as set by the sponsor is of prime importance. The process starts with the preparation and submission of the budget. Most budgets consist of personnel costs, equipment costs, supplies, travel costs, consortium costs (if there is a partner doing a small part of the work in the project), other costs (e.g. participant reimbursements, clinical trial insurance, participant retention costs, communication costs, rental) and indirect costs. Once the award is made, the funds must be managed within accepted financial management practices and in accordance with sponsor's requirements.

The budget is crafted during the application stage in response to a FOA. The budget is put together from information gleaned from the research proposal and in close consultation with the PI. Further guidance is provided in the FOA and cognisance needs to be taken of the Grants Policy of the sponsor, specifically in relation to direct and indirect costs as well as allowable and unallowable costs.

Direct costs are those costs that are directly related to the project being undertaken. Some cost principles that are generally applied by sponsors include the reasonableness of costs, whether costs can be directly assigned to the grant, whether there is consistency in the assignment of costs and whether the sponsor's terms and conditions are met.

The indirect cost is a percentage of the direct costs (usually excluding equipment costs) that is allowed by the sponsor to cover compliance obligations, e.g. ethics approval and approval of drug use by a national approval body.

Some costs are not covered by sponsors and could range from local sales taxes to construction costs depending on the sponsor and the type of grant. It should also be noted that sponsors will not usually compensate for exchange rate losses, but on the other hand will not expect the grantee to refund exchange rate gains. Generally, the sponsor would expect the grantee to spend exchange rate gains on the project.

When the award letter is received, the financial team must compare the budget submitted to the budget awarded and adjust the budget, in consultation with the PI, accordingly. Sponsors have various systems for providing funding to grantees. These range from providing funding up front in advance, either quarterly, six-monthly or annually, to a cost reimbursement system of some sort. More and more sponsors now use a cost reimbursement system which allows them to monitor expenditure more closely. Cost reimbursement systems could consist of monthly invoicing to a sponsor, often with supporting documentation, or an electronic draw-down system with specific parameters guiding draw-downs.

The financial team must set up a monthly financial monitoring system to monitor expenditure against budget. The accounting system should allow for each award to be managed in a separate ledger account. For reporting and auditing purposes, the income and expenditure of various grants should not be mixed. There are various electronic financial management systems available such as Pastel and SAP, which ensure that funds are managed in line with sponsors' requirements.

Monthly management reports must be prepared and reconciled to the ledger accounts. These reports should also include a projection of anticipated costs until the end of the budget period. These reports should be discussed with the PI every month as it allows the PI to check expenditure against budget to ensure that neither over- nor under-expenditure occurs. Over-expenditure could be an indication of poor financial management while under-expenditure could indicate that the activities as outlined in the research proposal are not being undertaken. There could be valid reasons for this, e.g. delays in protocol approvals, which therefore delay the start-up of a project. It is important to communicate with the sponsor if there are valid delays so that there are no unexpected surprises for the sponsor at the end of a budget period.

The financial team is responsible for asset management within an organisation. They will manage the procurement process in-line with the procurement policies and the available budget, ensure that the asset register reflects the assets against the appropriate grant for which they were purchased and oversee the annual asset count. Sponsors might from time to time require that assets purchased with grant funds be returned to the sponsor at the end of a project or alternatively, be donated to a charitable organisation. There may also be branding or marking requirements for equipment purchased with funds from certain sponsors.

Some sponsors routinely request an annual audit of their specific awards if the total awards to the institution exceed a threshold value. These audits are costly but can usually be included as a direct cost in the budget for the specific project. Other sponsors may require that the institution submit their annual audit report each year. If sponsors have any concerns they might request an audit of the specific award.

1.3 Human Resources

Human resources are managed in accordance with the labour laws applicable to the country in which the employee is employed. Sponsors' requirements cannot override in-country legislation that governs labour relations in a particular country. In addition, there are local health and safety requirements that need to be met.

The Human Resources (or Personnel) departments of institutions administer all aspects related to employees in these institutions, including staff appointments for specific projects funded through external sources. Recruitment and selection policies and procedures of the institution must be followed and the principles of fairness and equity should be applied.

Staff, regardless of source of funding, should be managed within the human resource policies and procedures of the institution concerned and this would include remuneration policies, disciplinary and grievance procedures and performance evaluation procedures, amongst others. All staff should have job descriptions which need to be reviewed and updated at least every two years. It may also be appropriate for the Human Resources department to manage confidentiality agreements and annual conflict of interest declarations.

Sponsors require confirmation that personnel that are funded through awards made by them actually work on their projects. The sponsor's policies usually provide guidance on methods that are acceptable for documenting personnel effort on a project. Various electronic time and attendance systems are available to assist with monitoring employee activity and include reporting functions. In addition, time sheets are also an important tool which allows sponsors to assess staff activities in projects funded by them.

1.4 General Administration

The duties of general administrative staff include responsibility for implementation of the travel policy, asset management, overseeing alterations and renovations, fleet management, setting up of meetings, drafting of minutes and maintenance of records including archiving.

Administrators are usually responsible for making travel arrangements for researchers. They must be trained in the requirements of the travel policy and ensure that they adhere to these requirements. This would include ensuring use of the correct class of air travel and car hire as well as booking hotel rooms within allowable rates. Generally, funders will not fund business class travel except in exceptional circumstances, nor will they fund five-star hotel accommodation or luxury car hire. Some sponsors also have restrictions on the airlines to be used for travel funded through their grants.

Administrators are responsible for managing the assets of an organisation. While the financial team should maintain the asset registers the administrators are responsible for doing an annual asset count and reporting the results to the financial team. The administrators are also responsible for ensuring that assets are well maintained. In addition, the administrative team are responsible for ensuring that all assets are insured.

Administrators are responsible for ensuring that alterations and/or renovations are carried out within the institutions procurement policy guidelines for service providers and if funded through a grant, within the sponsors' policies and procedures. Generally, sponsors will not fund building projects that change the foot print of a building, but alterations or renovations to make a space suitable for project activities might be an allowable cost.

Institutions will usually have an individual responsible for managing the fleet of vehicles. There should be a policy about the type of vehicle to be purchased, the

procedures related to the running and maintenance of the vehicle as well as a timeframe for replacement of a vehicle. Log books have to be kept to record all trips and all drivers must have valid unendorsed drivers licences which are reviewed annually to ensure that they remain valid and unendorsed. In addition, all local laws regulating road traffic in the country in which the vehicle is being used have to be adhered to. For instance, special licences may be required for drivers of vehicles transporting more than a certain number of people.

Administrators will ensure that all vehicles are insured and have procedures in place to process insurance claims when necessary. Sponsors will consider funding the purchase of vehicles if required for the project but might require that a specific make/brand of vehicles be purchased, e.g. if US funding, US-manufactured vehicles should be purchased.

Administrators may be responsible for setting up meetings for project staff. This would include identifying a venue, setting a date and time, ensuring that an agenda is available for the meeting as well as any pre-reading material that might be required. They ensure that an attendance register is signed by all participants in the meeting. Further, they attend the meeting to record the proceedings and then capture these in draft minutes which, once approved and finalised, are circulated to all who attended the meeting. Minutes of these meetings are filed and form an essential part of project documentation.

Sponsors require that all project documents be maintained for a specified period of time before being destroyed. Each institution should have a policy and procedure in place to ensure the maintenance of these records. Administrators would also be responsible for ensuring the archiving of records at the close of a project either on-site or off-site. Off-site archiving needs to be assessed for efficiency of retrieval of archived files and for level of security in terms of theft and fire before a service provider is secured.

2 Conclusion

The grants management team form an essential part of the project team, ensuring that all sponsors' requirements are met. Poor grants management can lead to forensic audits, the withholding of funds or ultimately the exclusion of an institution from future grant funding.

References

1. Deborah L Ward. Effective Grants Management. Jones and Bartlett Publishers, LLC, 2010. ISBN 976-0-7637-4984-2.
2. NIH Grants Policy. http://grants.nih.gov/policy/nihgps/index.htm

Chapter 15
Taking Science to the People: CAPRISA Communication and Media Strategies for Announcing Outcomes of Pivotal Study Findings

Smita Maharaj

1 Introduction: The Media as 'Amazingly Powerful Allies'

> I did my first microbicide clinical trial in 1994. Fifteen years later I'm still learning. One thing I have gained in my experience is that the media – particularly print media and the radio – are amazingly powerful allies—**Professor Salim Abdool Karim, MBChB, Ph.D., Director of CAPRISA** [1]

During the early years of the HIV epidemic, the national media in South Africa, and indeed the media globally, played an important role in educating the public and creating an awareness of the devistation and potential impact of the disease. Despite some inevitable cases of sensationalism or misreporting of scientific facts, in general, the call for urgent action and greater support for HIV research by scientists and AIDS activists was successfully heightened through the media.

The South African response to the HIV epidemic since the first reported cases in the early 1980s during the apartheid era and subsequently in democratic South Africa has had many ups and downs. The most pivotal, and the lowest moment though is undoubtedly in the late 1990s, when South Africa's president and health minister at the time publicly revealed their AIDS denialist stance. The timing could not have been worse given the large numbers of South Africans who were ill and dying when antiretroviral drugs were available for treatment of AIDS patients and preventing transmission of HIV from infected mothers to infants. The hosting of the XIIIth International AIDS Conference in Durban in 2000 served as a watershed moment in the national response to HIV, giving local and international AIDS researchers and activists an opportunity to speak truth to power. Prominent scientists including Professors Malegapuru Makgoba, Hoosen Coovadia and Salim

S. Maharaj (✉)
Centre for the AIDS Programme of Research in South Africa,
University of KwaZulu-Natal, Durban, South Africa
e-mail: Smita.maharaj@caprisa.org

Q. Abdool Karim et al. (eds.), *The CAPRISA Clinical Trials: HIV Treatment and Prevention*, DOI 10.1007/978-3-319-47518-9_15

Abdool Karim were among those who took up the mantle, challenging the government's stance on AIDS and antiretroviral therapy (ART). The deleterious impact of AIDS denialism on South African national treatment policies and programmes, were extensively covered by media around the world, as well as in South Africa. While it is difficult to quantify their contribution, these stories undoubtedly made a major contribution to ending the period of AIDS denialism in South Africa. Importantly, for many the reality of the HIV epidemic and the face of AIDS in sub-Saharan Africa was brought to the fore. The Treatment Action Campaign led marches preceding and during the International AIDS Conference in 2000, which together with global solidarity, resulted in, amongst other initiatives, the establishment of the Global Fund for AIDS, TB and Malaria and the US Presidents Emergency Programme for AIDS Relief (PEPFAR) and the transformation of AIDS from an inevitably fatal condition to one that is chronic and manageable. Today, South Africa has one of the largest AIDS treatment programmes and globally about 50 % of those in need of care are successfully accessing services, but much more needs to be done to prevent new infections and reduce the numbers of people dying from AIDS.

Shortly after the 2000 International AIDS Conference, CAPRISA was established by Professor Salim Abdool Karim together with long standing collaborators and colleagues through a consortium of five partner institutions in South Africa and the United States. CAPRISA rapidly achieved a reputation—at home and abroad—as a reliable source of information on the state of the HIV epidemic in an environment in which such information was an essential bulwark against denialism. The establishment of this reputation was based on years of nurturing relationships and partnerships with advocates, community leadership, key stakeholders including journalists to communicate research findings emanating from research on the evolving HIV epidemic to inform an evidence-based response to the epidemic. The availability of scientists working on HIV and AIDS to speak to media and take time to explain and demystify science has enhanced the quality of reporting and has facilitated wider diffusion of new knowledge being generated. Given the immediacy of AIDS, the need for access to information and solutions as they emerge has led to precedents in communication of new knowledge.

Given the core purpose of CAPRISA viz to undertake research to advance understanding of HIV prevention, pathogenesis and treatment of AIDS that is locally important and globally relevant, communication of findings of the research in the traditional peer-reviewed literature is as important as is communication to the general public and to key decision-makers. The latter is particularly important as often the research findings are but the first step to informing policy and practice that have the potential to improve the lives of individuals and communities.

The spread of the epidemic around the world coincided with another global phenomenon: the rapid development of electronic media and communication channels, which transformed, and are still transforming, the way we communicate new scientific findings, bringing greater immediacy and access to news across continents. Thus, information featured in a particular medium in South Africa (print) can serve as a lead for a global news article, often in a different medium

(online), in the United States; another in China and yet another (broadcast) in the United Kingdom. The reach is vast. The power of communication is intense and robust and science communication strategies adopted by CAPRISA have had to keep abreast with these developments.

HIV is a global health issue. New knowledge about the epidemic deserves and requires consistent, frequent and rigorous communication. As the international scientific community grapples with novel ideas to end AIDS the development of a vaccine or cure still has some way to go. Maintaining public awareness of, and support for, the progress towards this goal is critical, particularly in light of the extensive funding attached to the research.

The outcomes from pivotal clinical trials represent some of the most tangible products or outcomes of the medical research process. However, when published in scientific journals, this scientific information has a limited audience. Communicating the outcome of a HIV clinical trial in an effective way that can be understood, is critically important for three reasons: to inform the broader public—which includes affected communities—about new drugs for prevention and treatment; to inform opinion makers of new research findings; and to generate interest among scientists and researchers, which may lead to meaningful collaborations.

In addition to facilitating the transmission of scientific knowledge, a carefully structured communications strategy also has the effect of bringing transparency and greater credibility to the research process, which may not be fully understood or appreciated by the broader public.

In outlining the key elements of such a communications strategy, this chapter will draw on the communication strategies employed from three major CAPRISA research findings: the SAPIT trial announced in Durban, South Africa on 17 September 2008; the CAPRISA 004 trial announced in Vienna, Austria on 20 July 2010; and the Broadly Neutralising Antibody study announced in Johannesburg, South Africa on 22 October 2012. The chapter makes some general comments about media relations before moving on to more practical suggestions for developing a communications plan.

2 Building Relationships with the Media

> They really have such an important role to play in informing and in educating people about HIV/AIDS. We shouldn't let the occasional blip sully … that relationship. They do a superb job—**Professor Salim Abdool Karim, MBChB, Ph.D., Director of CAPRISA** [1]

Relationships with media representatives are of fundamental importance to the success of any media strategy. It is prudent for communications staff to invest in long-term professional relationships with reliable journalists who have a reputation for fair, balanced and intelligent reporting. Ideally, such journalists would also be

supported in such an approach by the media houses or publications that employ them. This latter point is relevant because, with the advent of online and social media, the traditional media landscape has undergone phenomenal change and newsrooms operate on severely limited resources. This means fewer specialist journalists and less time for all journalists—specialist or otherwise—to compile accurate, considered, in-depth articles.

Identifying and liaising on a regular basis with individual media contacts who have some understanding of science will help to ensure that reporting of research findings is balanced and accurate. But even so, the technical complexity of some scientific breakthroughs may necessitate a pre-briefing of journalists—even specialist journalists—prior to the official announcement. This approach allows all writers to research and prepare articles that are accurate, consult other scientists, have greater depth, and is extremely helpful for media workers in terms of meeting increasingly tight deadlines.

Where possible, a media/communications officer should be accessible to journalists outside of formal briefings, even if responses to controversial issues are being sought. This could be an in-house person or the services of an external communications company could be utilized, depending on resources available. Timeous responses to media queries and requests for comment and clarifications go a long way towards establishing relationships with media personnel that are based on mutual trust and respect. Where questions cannot be answered immediately, prompt follow-up is necessary. Importantly, the risk of inaccuracies in stories is significantly reduced through this approach.

2.1 What Is News?

> Our task as researchers is just to ensure that we provide them [media journalists] with the kinds of information that contribute to improving the public's understanding of what we are trying to do and where we are trying to go. As a scientist, I know we have breakthroughs all the time, but they are often miniscule. They are barely a single step of one of the four legs of a tortoise. You can't be going around all the time to the newspapers and saying, 'This is really newsworthy'. Rather, you have to wait for there to be big news and something worthwhile…—**Professor Salim Abdool Karim, MBChB, Ph.D., Director of CAPRISA** [1]

In planning publicity to share results from a clinical trial it is essential to understand what constitutes news. Commercial newspapers will prioritise stories that sell their product. All media outlets will be looking for stories that will attract readers and provide fresh, interesting and significant content. In this respect it is useful to ask the following questions (Box 1) when preparing a communication plan for a clinical trial result:

Box 1: Questions to answer when preparing to communication results from a clinical trial
Is it of public interest? Why?
Is it if scientific interest? How?
Is the study distinctive and original?
Is the technology/drugs innovative?
Is it measurable in relation to the impact on lives?
What is the scale of the impact economically?
What is the social scale of the impact?
Is it exceptional in shaping future health policies?
Will it contribute to and shape future research?
Who will benefit from this study?
How will populations benefit?

Understanding what is of interest to the media requires some knowledge of the full range of media forms. These forms encompass broadcast, print and digital media. Understanding the various target audiences of such media will guide the content of a press release, which can then be tailored to meet the requirements of specific media.

Arguably, a business or financially-oriented newspaper will have little interest in the outcome of a clinical trial. However, highlighting a statistical analysis or potential economic impact arising out of the trial results would be of interest.

A community newspaper is more likely to focus on the impact of the findings on communities, the views of participants from that community and the views of community leaders. Broadcast media will interview the Principal Investigators of the study, government representatives and regulatory bodies to unpack the relevance of the results. Broadcast television networks may produce a documentary that traces the origins of the research idea and the outcome of the study.

The geographical reach—local, national or international—of the publication being targeted is also important and will inform the way specific content about the trial is tailored.

3 Key Elements of a Communications Plan for Clinical Trials

3.1 Key Messages

Identifying the key messages to be transmitted to media in relation to the outcome of a clinical trial is of critical importance. Usually, two scenarios are planned: a plan for a positive outcome (results are what the study set out to achieve); and an

alternative plan if the results are negative. Best practice in media relations prescribes that three to five powerful key messages that will influence the reader and shape opinions are central in the final media statement.

For example, in the CAPRISA 004 media statement the key messages were as follows:

1. Researchers have achieved an important scientific breakthrough in the fight against HIV and genital herpes with a vaginal gel that significantly reduces a woman's risk of being infected with these viruses.
2. The microbicide containing 1 % tenofovir—an antiretroviral drug widely used in the treatment of HIV—was found to be 39 % effective in reducing a woman's risk of becoming infected with HIV during sex and 51 % effective in preventing genital herpes infections in the women participating in the trial.
3. Tenofovir gel could fill an important HIV prevention gap by empowering women who are unable to successfully negotiate mutual faithfulness or condom use with their male partners.

All key messages were picked up and reflected in front-page stories of prominent United States newspapers: *The New York Times*, *The Washington Post* and *Wall Street Journal* (Fig. 1).

Fig. 1 Front-page reports of the CAPRISA 004 study published in leading newspapers in the US

In a front-page story headlined "*2 African studies give women hope in fighting HIV*", *The New York Times* emphasises that the results were an African scientific breakthrough as well as its positive benefits for women (Key message 1). Subsequent sub-headings and straplines went on to emphasise the trial's impact on HIV prevention intervention ("*Focus on prevention*") rather than a vaccine (Key message 2), and the likely delay in public access to the vaginal gel ("*Payments promising—vaginal gel may be years from public*"). The story was accompanied by an engaging photograph of some of the women attending the results announcement. Together with the photograph, the story presents an effective communication package, reflecting the significance of the science, the potential impact of the findings and, importantly, through its photograph, emphasises the accountability of the research process in respect of participants.

Likewise, *The Washington Post* of the same day carried the story on its front page under the headline: "*Gel found to reduce AIDS risk in women*". The scientific significance of the findings is quickly reiterated through the secondary strap: "This really is a game-changer"—a quote supplied from Harvard researcher Dr. Bruce Walker. Early in its story, *The Wall Street Journal* acknowledges the gel's potential to empower women (Key message 3), a third of whom, the article notes, said their partners were "unaware" they were using the gel.

The key messages in the SAPIT trial media statement were as follows:

- A South African treatment study has shown that mortality among TB-HIV co-infected patients can be reduced by a remarkable 55 %.
- The study shows that integrating TB and HIV treatment and care saves lives.
- The SAPIT trial results provide compelling evidence to support the World Health Organisation's call for the greater collaboration between TB and HIV treatment services.
- The findings of the SAPIT study call for the accelerated implementation of routine HIV testing in TB treatment services.

The key messages in the Broadly Neutralising Antibodies media statement were:

- A unique change in the outer covering of the virus found in two HIV-infected South African women enabled them to make potent antibodies which are able to kill up to 88 % of HIV types from around the world.
- This ground-breaking discovery provides an important new approach that could be essential in making an AIDS vaccine.
- Broadly neutralising antibodies are considered key to making an AIDS vaccine.

The focus was on the study outcomes and their impact on stakeholders. Major daily South African newspapers such as *Business Day*, *Cape Argus* and *Cape Times* covered the story, emphasising the fact that the findings brought scientists closer to

a vaccine. In all stories, there was extensive use of quotations from the key investigators, other scientists in the field and key stakeholders.

3.2 Quotations

Quotations included in media statements save the journalist the time and effort involved in having to personally identify and contact the relevant person—although they still have the prerogative to do so. The best person to be approached for a quotation should be identified in advance. These usually include the PI/PIs of the study, a senior health government official and the Managing Director of the drug company.

Examples of quotations in the media statement of the CAPRISA 004 study:

- Tenofovir gel could fill an important HIV prevention gap by empowering women who are unable to successfully negotiate mutual faithfulness or condom use with their male partners—***Quarraisha Abdool Karim, co-principal investigator***
- Tenofovir gel has a potential dual effect in preventing HIV. Since women with genital herpes are much more likely to become infected with HIV, the additional protection of tenofovir gel against herpes creates a second mechanism whereby the gel may have a bigger impact in preventing HIV—***Salim Abdool Karim, co-principal investigator***
- We are proud to have partnered with CAPRISA and CONRAD on this important study. We see it as a major victory in the field of HIV prevention research. This is the first evidence that an antiretroviral drug in a gel form—a microbicide —can reduce HIV and genital herpes infection in women—***Ward Cates, President of FHI***
- CONRAD has given the rights to manufacture this gel to the government of South Africa to get this much needed product to women in South Africa as rapidly as possible—***Henry Gabelnick, Executive Director CONRAD***.

3.3 Background Information

Background information to the trial is needed in order to ensure well-rounded story outcomes that fully capture the significance of the trial. Key messages are also relevant when producing background information, as the following example illustrates (Box 2):

Box 2: Example of key messages on the general background of the CAPRISA 004 trial

- **What kind of study?**
  - First clinical trial to provide results on ARVs for HIV prevention
  - Study of a drug effective in treating AIDS—Tenofovir, but formulated as a gel for vaginal use
- **Study design**
  - Double-blinded, randomised, placebo-controlled trial
  - Study included rural women (18–40 years), who have low frequency but very high risk sex; a group well suited to coitally-related gel use
  - Dosing strategy: one dose up to 12 h before and one dose up to 12 h after sex and not more than two doses in a day
- **High-risk participants**
  - study involved 889 urban and rural South African women at high risk of HIV infection
  - HIV incidence rate in the study population was 9/100 person-years
- **Study quality and standards**
  - high retention rate: 95 %
  - low pregnancy rate: 4 per 100 women-years
- **Funders and researchers**
  - Jointly funded by the United States and South African governments
  - Study undertaken by consortium of the South African and the US organisations
  - Led by South African researchers
  - Included a public–private partnership—Gilead contributed free active ingredient to make the gel

Safety

- Tenofovir gel is safe
  - No serious adverse events related to product use
  - No genital safety concerns
  - No evidence of systemic toxicity—due to low levels of drug in blood when applied in the vagina
- **No Tenofovir resistance identified**
  - Tenofovir gel users who became HIV-infected did not acquire or develop drug-resistant strains of the virus

4 Communication with Key Stakeholders

Identifying key stakeholders will guide the formulation of concise, relevant messages in a communications plan. Stakeholders for a clinical trial may include a wide range of entities, ranging from participants and community leaders to government officials, pharmaceutical companies and scientists in similar fields. Importantly, the list of stakeholders will also include partners, who must be informed of significant

outcomes. Partners include founding bodies, collaborative partnerships, funding agencies and advocacy groups. Through a network of partnerships, a greater understanding of the challenges and success of your clinical trial can be communicated. Again, understanding the interests of the individual stakeholder will guide what is communicated and how.

4.1 Communication with Participants

Communication with participants and the community from which they are drawn is an essential component of any clinical trial communications plan. Community members at trial sites must be thoroughly briefed. Tailor communication in the preferred language of the community to ensure that there is clarity and understanding. Jargon should be avoided and concepts should be clearly explained to avoid ambiguity and misunderstanding. Understandably, communities show a keen interest in knowing the results of the trial and what it means for people who would benefit from the finding. Another issue consistently raised by community members is public or post-trial access or when the relevant product will be available at public health clinics and how study participants and communities where the research was undertaken will receive access to the innovation.

5 Social Media

Platforms such as Facebook, Twitter, Instagram and blogs have revolutionised communication, rendering all communication instantaneous. The immediacy of social media and the extensive communication range requires careful management and execution to maximise impact and discussions. During the release of the earlier CAPRISA trials, the use of social media was minimal. However, today a social media plan forms an integral component of the broader communication strategy and dialogue on the outcome of a clinical trial requires immediate responses.

6 Websites

An organisation's website is the lens through which the world has access to the core activities, mission and values of organisations. Access to a website makes a first and lasting impression. Content management is therefore of critical importance. As a powerful visual and content tool, the website can and should be used to great effect

to inform the public and stakeholders of the outcome of a clinical trial. The web has an added benefit of space which allows for the posting of images, graphics and additional content that can be easily accessed by journalists.

7 Planning Process

7.1 Planning the Announcement of a Clinical Trial

A well-crafted communications plan can serve as a springboard for ongoing interviews for months after the initial announcement. Planning for the announcement of results should commence 6 months before the close of a trial. Begin by putting together a dedicated communications team comprising representatives of collaborating partners including study sponsors. Particular attention should be given to communication with the organisation's key governance structures such as Scientific Advisory Board, Board of Control and executive committees. Importantly, the date of the announcement will consider set embargoes and whether there will be a joint or solo announcement as well as where the announcement will be made—the CAPRISA 004 trial was announced simultaneously in Vienna at the XVIII International AIDS Conference and in Durban, South Africa where the trial was conducted and with the release of the peer-reviewed publication. Create a database of reputable media contacts including science, medical specialist writers and key stakeholders. Identify primary and secondary spokespersons, usually the PIs or a senior scientist on the study. Delegate roles and responsibilities and arrange media training for investigators. Identify possible newsworthy angles for broadcast interviews, feature articles and opinion pieces.

Other issues to be addressed in the plan include the following:

- Compile a results dissemination calendar for the pre-embargo period, the day of the announcement and post-release.
- Media statement, including messaging, quotations, community perspectives, date of media release and embargo date, fact sheet and background information on the institution, the study and principal investigators.
- Frequently asked Questions and Answers.
- Press briefings, including date, invitations and coordination.
- Plan to publish a statement on the website and social media and monitor results.
- Monitoring and documenting of media queries, responses and coverage.
- Identify appropriate individuals like community representatives for personal interviews, pre- and post release.

An example of a communications plan is provided in Box 3.

Box 3: Example of communications plan for the CAPRISA 004 trial

Communications objectives
• Raise internal and external awareness of CAPRISA 004 • Build understanding, enthusiasm and support for 004 • Help avoid or mitigate potential controversies • Share lessons learned • Ensure the success and utilisation of the study results
Internal communication This will be handled by CAPRISA 004 staff through protocol team/leadership/site meetings and emails
Flow of information to external partners • Which venues? (Meetings, interpersonal communication, etc.) • Newsletter(s)? Covering what? For which audiences? • Mix of updates and efforts that promote a positive image • Media outreach
Proactive plan for unexpected events or negative news • Outline what will happen, who will communicate what to whom, if crisis emerges • Develop messages for positive, neutral or negative outcomes of other studies • Brainstorm possible "curveballs" and have plans for how to handle: e.g. disgruntled staff member who goes to the media; groups that believe that the trial should not go forward without additional studies to ensure participant safety; accusation by civil society group of exploitative research, genetically modified vaccines, etc. • Identify individuals known to initiate negative communications, whether activists, competitors or groups seeking to advance their own agendas at the expense of the trial. Have basic plans for steps to take when these individuals "go negative". Determine ahead of time who to inform or enlist, and identify options for handling

7.2 Compiling a Media Statement

There will be several drafts of the media statement before agreement is reached on the final copy. The PI of the study plays an integral role in compiling the first draft, together with members of the communications team. The statement must be precise and provide the media with pertinent information like the name and results of the trial, importance of the trial in relation to the epidemic, scientific questions that the trial answered, the population in which the trial was undertaken and the region/s where the study was taken. Equally, information on the development of the drug and regulatory processes followed prior to the trial, is of public interest. What was the impact of the trial on study participants and measures to deal with any adverse outcomes of the drug? Quotations add value to press releases and the views of

opinion makers must be included. Include quotations from, for example, the PI/s of the study, study sponsors, a senior government official, usually the Minister of Health or Science and Technology, the key collaborators, and key advocacy groups and other key stakeholders. Favourable efficacy results will require timeframes for confirmatory trials or regulatory approvals if relevant or indicated. If the results are negative, include information about other research underway or alternative strategies in development.

Headlines make a first and lasting impression. The headline of the media statement should carry the results of the trial and generate curiosity and excitement: **Example: CAPRISA 004**: "Study of Microbicide Gel Shows reduced risk of HIV and Herpes Infections in Women".

Profiles on the organisation and partner institutions should follow at the end of the statement.

Media statements should include separate background documents on the study that includes information on why the study was necessary, the purpose of the study and trial, the significance of the findings, the population profile, as well as details of the safety monitoring committee and its recommendations. If a trial or an arm of the trial was stopped it is necessary to explain why this was so and the implications of any decision to halt an arm of a trial. The background information should also include the trial's funders and information about next steps in relation to the study participants.

The background document is informative and saves the journalist time researching information. A fact sheet on statistics and analysis is always useful for a journalist. Anticipate questions/comments from key stakeholders and prepare a Q&A sheet. Remember, journalists appreciate organisations that are candid.

7.3 Press Conferences

Determining whether a press conference is necessary is a frequent dilemma for the study team. The rule of thumb is that a conference should be called in a situation where complex scientific announcements have the potential to send an ambiguous message, or where scientific jargon is likely to be better explained face-to-face, or the results of a trial are overwhelmingly positive and have a public health impact.

When it comes to the location of a conference, it should be held at a central point close to the primary study site/s and within close proximity to television networks and media houses. Inform stakeholders that you are planning a press conference. Generate interest and an element of curiosity in anticipation of the results. The timing of the press conference should allow for breaking news globally as well as make the prime news spot in the country in which the press conference is being held.

Upon inviting the media, it is useful to send a "Save the Date" or media advisory first. The media advisory alerts the media to the planned press conference and should encourage journalists to attend. The copy should be concise with details of

the date, time and venue. Also include the purpose of the press conference and a clear informative headline that will generate interest. This is followed by the official invitation. Invite key stakeholders who can comment with authority on the subject matter. Decide on the format and who will participate in the briefing. Prepare a Q&A and consider all possible angles. All information, including backgrounders, should be contained in a press pack. In addition to information about new evidence and latest scientific developments, this information will, for example, include a profile of study participants, the number of participants infected during the trial, the course of action to be taken and support offered to infected study participants, and how the trial will inform health policy.

Breach of an embargo is rare as it can mean a loss of credibility for a particular media outlet. There is the potential that future interactions with the media may be strained. In the event of a breach, it is best to immediately advise your media contacts that the embargo has been broken by calling each journalist personally and advise them of any changes in plans. At the press conference thank the journalists for upholding the ethics of journalism. If there are serious repercussions from the breach of the embargo you may lodge a complaint with the relevant local media ethics oversight body such as the Press Ombud.

8 Media Training

Media training is essential for scientists dealing with the media for the first time. It is wise to invest in media training if PIs have not been through a comprehensive media training programme. Training should be scheduled at least 2 months prior to the announcement of the results and should cover print and broadcast media. Training will ensure that messages and responses are delivered with clarity and ease.

9 Media Monitoring

Monitoring of online, print and broadcast media is an essential facet of any media strategy. Comments and opinions on the trial must be monitored and tracked. This is important as inaccurate or misrepresentation of the facts can be corrected. Independent media monitoring services should be appointed to analyse media coverage with daily alerts and reports. Advertising value equivalent (AVE) analyses, undertaken by independent media monitoring houses, provide comprehensive reports of coverage in geographic areas and the equivalent costs thereof.

10 Results Dissemination Calendar

The results dissemination calendar provides a framework of timelines, activities and roles and responsibilities during the pre-embargo period, the day of the announcement and post announcement. The calendar is a living document and should be updated continuously to ensure that there is clarity on the execution of tasks. The following headings could be used:

Results dissemination calendar			
Timeframe	Stakeholder	Activity	Responsibility
7 days prior to the release	Mr Joe Smith Senior government official	Telephone call	PI
3–5 days prior to the release			
1 day prior to the release			
A few hours before the release			
At the release			
Following the release			

At all times it is important to respond to any concerns and challenges that may arise, either externally or internally. During the trial, regular discussions with the PI and study coordinators will help communications officials to get a clear understanding of the progress and unforeseen changes that may arise during the trial and at the results stage. It is important to develop a database for information recording. The information documented will guide the final communications plan and content and help to ensure a smooth overall process.

11 Conclusion

Given the immediacy and relevance of outcomes from biomedical research at an individual and population level there is growing interest and demand for rapid communication of key research findings, not only through traditional mechanisms such as conferences, peer-reviewed literature and traditional print and electronic media, but also through more novel social media platforms and face-to-face communication with key stakeholders. There is no single approach to successful communication, but what is critical and essential is thorough and complete planning that starts months before results become available; good training of the messengers within the team; having a key message or story to communicate; nurturing relationships with key stakeholders very early in the research process and adapting the key messages to the diverse recipients. In this chapter we have drawn on our experiences of communicating key findings from clinical trials that have immediate

impact for policy and practice; or that have changed or advanced thinking in the field or have catalysed a new approach to our response to HIV and AIDS. Samples of a media statement and a background document are provided at the end of the chapter. This chapter is not meant to be the last word on science or RCT communication because, as with the scientific endeavour, it needs constant innovation so that the purpose of communicating is accomplished.

Appendix 1: Sample Press Release/Media Statement and Q&A Background Document

Important New Research Findings on Treatment of TB-HIV Co-infection

A South African treatment study has shown that mortality among TB-HIV co-infected patients can be reduced remarkably by 55 %, if antiretroviral therapy (ART) is provided with TB treatment. The study is an open-label randomised trial known as the SAPIT (Starting Antiretrovirals at three Points in Tuberculosis) trial. TB-HIV co-infected patients assigned randomly to receive ART together with their TB treatment (integrated treatment arm) were compared with patients assigned to receive ART upon completion of TB treatment (sequential treatment arm).

Professor Salim S. Abdool Karim, Director of the Centre for the AIDS Program of Research in South Africa (CAPRISA) at the University of KwaZulu-Natal, led the SAPIT trial. "The study shows that integrating TB and HIV treatment and care saves lives", he said. The trial was conducted at the CAPRISA eThekwini TB-HIV Clinic which is attached to the Prince Cyril Zulu TB clinic, the largest TB clinic in Durban, South Africa. The study started in June 2005 and completed enrollment in July 2008.

The trial enrolled 645 patients with TB and HIV co-infection; 431 patients in the integrated treatment arm and the 214 patients in the sequential treatment arm. Twenty six patients in the sequential treatment arm died (mortality rate of 11.6 per 100 person years) compared to the 24 patients who died in the integrated treatment arm (mortality rate of 5.1 per 100 person-years). As a result, the study's independent Safety Monitoring Committee recommended, in their review of the trial in September 2008, that the sequential arm of the trial be stopped and that ART be initiated in this group as soon as possible. The committee further recommended that the two sub-groups within the integrated treatment arm (early TB-HIV treatment and post-intensive phase TB-HIV treatment) should continue as per protocol.

Dr Peter Piot, Executive Director of UNAIDS, commented: "These important results show that a 'two diseases, one patient, one response' integrated approach to TB/HIV treatment avoids unnecessary deaths from TB, the leading cause of death in people living with HIV in Africa." TB is the most common disease occurring in the late stages of HIV infection in southern Africa. As a result, many people

throughout southern Africa are first identified as HIV infected when they develop TB. The findings of the SAPIT study call for the accelerated implementation of routine HIV testing in TB treatment services.

The SAPIT trial results provide compelling evidence to support the World Health Organization's call for greater collaboration between TB and HIV treatment services and provides empiric evidence of the benefits from the initiation of antiretroviral therapy in TB-HIV co-infected patients. Dr Paul Nunn of the Stop TB Department at the World Health Organization commented, "The results to date clearly show the urgent necessity to make ART available to HIV infected patients with TB worldwide."

Ambassador Mark Dybul, Coordinator of the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) said: "Scaling up collaborative TB/HIV activities is a priority for PEPFAR. We remain committed to increasing screening for both HIV and TB, which will allow greater numbers of patients to benefit from these study results."

In South Africa it is estimated that about 70 % of all TB patients are infected with HIV. Hence, HIV testing is a critical first step to the integration of antiretroviral therapy into TB services. It is estimated that about 250,000 of the 353,879 TB patients diagnosed in South Africa in 2007 were HIV positive. If the study's findings as an evidenced based approach for the medical care of TB-HIV co-infected patients are implemented, just in South Africa alone, it would result in an additional 100,000 to 150,000 TB patients being initiated on ART, resulting in about 10,000 deaths being averted each year.

The key implication of the study is its potential to impact on clinical practice for implementation of ART provision in TB services in order to save lives. UNAIDS and WHO have been calling for the integration of TB and AIDS care over the last few years. These findings provide further impetus to encourage implementation of this combined approach to TB–HIV co-infection. In addition, monitoring the proportion of TB–HIV co-infected patients receiving combined TB and HIV treatment should become a standard indicator in AIDS treatment programmes.

The study was made possible through funding from the PEPFAR, the Global Fund to fight AIDS, TB and Malaria (GFATM), the US National Institutes of Health (NIH), the University of KwaZulu-Natal and CAPRISA.

Questions and Answers on the outcome of the SAPIT trial

1. What does the acronym 'SAPIT' stand for?
Starting Antiretroviral therapy (ART) in three Points In Tuberculosis therapy.

2. What is the SAPIT trial?
The SAPIT trial is a **randomized** (all patients in the trial had an equal chance of being placed in any of the three study groups), **open-label** (this means that both the study staff and the patient were aware of the study group to which the patient had

been randomized) clinical trial, comparing three treatment strategies of ART initiation in HIV-TB co-infected patients. The same ART combination of once-a-day ddI, 3TC and efavirenz was used in all three trial arms. A once-a-day regimen was selected in order to integrate the ART into the TB directly observed therapy method of providing TB treatment.

The difference between the three study groups is not which antiretroviral drugs they received, since this was standardized, but when the antiretroviral drugs were initiated in relation to initiation of TB treatment. The three study groups are:

Group 1: ***Early integrated treatment arm:***	Patients start ART as soon as possible within the first two months of starting TB treatment
Group 2: ***Late integrated treatment arm:***	Patients start ART as soon as possible after completing the 2-month intensive phase of TB treatment (i.e. generally, this means initiation of ART in third or fourth months after TB treatment initiation)
Group 3: ***Sequential treatment arm:***	Patients start ART as soon as possible after completing their TB treatment (i.e. generally, this means initiation of ART 6–8 months after TB treatment initiation).

3. What is the main purpose of the SAPIT trial?

The primary objective of the trial was to determine the optimal time to start ART in patients on TB treatment. Specifically, the trial assesses whether integrated TB and HIV treatment differs from sequential HIV treatment following TB treatment. Further, whether integrating HIV treatment early in TB treatment differs from integrating HIV treatment late in TB treatment.

The primary outcome in the trial is a comparison of mortality (clinical status) at 18 months after TB treatment initiation in HIV-TB co-infected patients who initiated ART with TB treatment, at the end of the intensive phase of TB treatment and upon completion of TB treatment.

4. How many patients were enrolled in the SAPIT trial?

The SAPIT trial has completed enrollment with 645 patients enrolled. These patients were men and women 18 years or older with smear-positive pulmonary TB and HIV infection.

5. When did the trial start?

The first patient was enrolled on 28 June 2005. The last patient was enrolled on 11 July 2008.

6. Who conducted the SAPIT trial?

The trial was conducted by the Centre for the AIDS Program of Research in South Africa (CAPRISA). The trial was conducted by the CAPRISA TB-HIV treatment research team at the CAPRISA eThekwini TB-HIV research unit, located in the Warwick avenue triangle adjacent to the Prince Cyril Zulu Communicable Diseases Centre (the old Durban Chest Clinic). The study team comprised Prof. Salim S Abdool Karim (Principal Investigator), Dr. Kogie Naidoo (Project Director), several doctors, nurses, pharmacists, statisticians, research co-ordinators and assistants, data mangers, laboratory technicians, counselors, community liaison officers and field workers.

7. What is a Trial Safety Monitoring Committee?

A clinical trial entails a relationship between participants and investigators in which there is an element of mutual respect and responsibility. The investigators are obliged to minimize harm and maximize benefit for the study participants, which is a key requirement for the health and safety of participants. To this end, safety monitoring is essential in clinical trials. Safety Monitoring Committees meet at specified times, usually annually, unless there is a reason to call an extraordinary meeting, where they review the study protocol, impact of new findings from related studies on the trial, the progress of the trial, data quality, participant recruitment and retention, and most importantly participant risk versus benefit based on trial data.

To avoid conflicts of interest, an independent safety monitoring committee (SMC), external to the study team, is usually established to assess safety within the trial and to recommend alteration or termination of the trial when significant benefits or risks have developed or the trial is unlikely to be concluded successfully. This committee usually consists of experts in the field of study (e.g., clinical trial experts, statisticians, ethicists) who are able to interpret the data to assess patient safety and study outcomes. Study staff does not participate in or attend such meetings, except for key individuals of the study team such as the principal investigator and statistician who attend to respond to queries from the committee.

8. What did the Safety Monitoring Committee overseeing the SAPIT trial recommend?

The Safety Monitoring Committee met on Monday, 1 September 2008, and recommended the following after its review of the trial data:

i. In light of the finding that the integrated arms have a significantly lower mortality rate, the Committee recommended that the sequential treatment arm be stopped immediately. It further recommended that the patients in the sequential treatment arm be initiated on ART as soon as possible and that all the patients in this arm be followed up in the trial as per protocol.
ii. The Committee recommended that the two integrated arms should continue as per protocol with no changes.
iii. The Safety Monitoring Committee commended the study team for the quality of study conduct.

9. Why did the Trial Safety Monitoring Committee stop the sequential treatment arm of the SAPIT trial?

The mortality rate was 55 % lower in the integrated treatment arms when compared to the sequential treatment arm. This means that deaths can be more than halved by combining ART with TB treatment. There is only a very small probability that the finding of a benefit of integrated TB and AIDS care is due to chance (p-value = 0.0049); this enhances confidence in the results of the trial.

The Committee found that the 431 patients in the combined (late & early) integrated treatment arm and the 214 patients in the sequential treatment arm were similar for age, gender, WHO stage, CD4 count, viral load and the multi-drug resistant TB rate on entry into the trial. This data analysis comprises about 60 % of the follow-up time that would be expected to be accrued at the end of the trial. It showed that 26 patients in the sequential arm died (mortality rate of 11.6 per 100 person years) compared to 24 patients in the combined integrated arm (mortality rate of 5.1 per 100 person-years). This reduction in mortality in the integrated treatment arms was statistically significant both in patients with CD4 counts below 200 and patients with CD4 counts from 200 to 500.

The Safety Monitoring Committee decided that it would not be in the patients' best interests to continue the sequential arm of the trial and hence recommended the initiation of ART in this group as soon as possible. The Committee requested the two integrated care arms continue as per protocol, as it is premature to make any findings at this stage of the trial regarding the timing of when ART should be initiated during the course of TB treatment. Hence, the trial is continuing at this time and further results should be available in 2010.

10. What are the implications for the SAPIT trial of this decision to stop the sequential care arm?

All sequential arm participants have been contacted, and given a scheduled appointments to return to the clinic. Several have already been to the clinic and some have already started ART.

The procedure we had outlined was as follows:

Participants will be seen by a SAPIT counselor who will inform them about the results of the Trial Safety Monitoring Committee review. Participants will be counseled on the benefits of commencing ART as soon as possible, as well as on the risks of deferring treatment in light of the new information. If the participant readily agrees to commencing ART, then specific counseling sessions on adherence education and support will be conducted on the same day, followed by other routine clinical procedures prior to ART initiation (CD4/VL/ Blood safety assessment/ clinical evaluation etc). Participants will be initiated onto ART on review of these parameters, within approximately 1 week. The visit schedule, investigations, treatment, and follow-up will be conducted as is standard for all patients in the trial. If the participant does not agree to immediate ART initiation, then education and counseling with close patient follow-up will continue, until the patient is ready to initiate ART. All patients in all three study arms will be maintained in ongoing care and follow-up until trial completion, which is scheduled for 2010.

11. Why are the Trial's findings significant?

Integrating TB and AIDS treatment saves lives: The SAPIT trial findings provide strong evidence for the integration of TB and AIDS care and treatment. To achieve this, all newly diagnosed TB patients in South Africa need to be offered an HIV test; those who are HIV positive need to be offered a CD4 count and those with CD4 count below 500 offered ART in conjunction to their TB treatment. This public health and clinical care approach to the joint TB and HIV epidemics has the potential to save lives. A rough estimate is that implementation of integrated TB and HIV treatment in South Africa could lead to an additional 100,000 to 150,000 patients (with TB and CD4 < 500) being initiated with ART and thereby prevent about 10,000 deaths each year by the earlier initiation of ART.

Changing clinical practice: Many patients and health care practitioners prefer to wait until TB therapy is complete before initiating ART. The treatment of HIV infection in those co-infected with TB is often deferred due to concerns about drug interactions, drug toxicity and immune reconstitution disease. It has been known for some time that there is a high case fatality among TB-HIV co-infected patients despite appropriate TB chemotherapy, which have led to previous calls for early initiation of ART in TB patients. The SAPIT trial has now provided clinical trial evidence that combining ART with TB care saves lives. It now remains to translate this finding into clinical practice. Government AIDS Programmes and organizations like PEPfAR and the Global Fund may consider including a new metric on integrated TB-HIV treatment when monitoring their ART scale-up programs eg. what proportion of TB patients are on ART? Such a metric on the number of TB patients initiated on ART could serve as an impetus for TB-HIV integration and serve as a key indicator of the success of HIV and TB programs.

Reassessment of international TB-HIV treatment guidelines: The findings of the SAPIT trial will be shared with UNAIDS and WHO; where they can be considered by the committee that recommends guidelines for the treatment of TB-HIV co-infected patients. It is premature to predict if and how the guidelines may change, especially since the study still has another 2 years to go before its full results are revealed.

12. What happens to the trial and its study participants now?

The trial will continue as per the original visit plan and the original schedule of evaluations with the exception of early ART initiation for those participants in the sequential arm. Study participants will continue in follow-up until the trial is completed in late 2010.

13. Who is funding the trial?

The study was funded from five sources:

- the US President's Emergency Plan for AIDS Relief (PEPfAR) funded the care of all the patients in the trial
- the Global Fund to fight AIDS, Tuberculosis and Malaria funded the cost of the drugs used in the trial

- the US National Institutes of Health funded the development of the research infrastructure, including the data management, laboratory and pharmacy cores established through the CIPRA (Comprehensive International Program for Research on AIDS)
- CAPRISA and the University of KwaZulu-Natal funds covered the research costs

14. What is CAPRISA?

CAPRISA is the Centre for the AIDS Programme of Research in South Africa.

CAPRISA was founded by the Universities of Natal, Cape Town, and the Western Cape, Columbia University in New York, and the National Institute for Communicable Diseases in Johannesburg in 2002 as part of the NIAID CIPRA (Comprehensive International Program of Research on AIDS) program. CAPRISA is a designated "UNAIDS Collaborating Centre for HIV Prevention Research". The CAPRISA headquarters is located in the Doris Duke Medical Research Institute at the Nelson R Mandela School of Medicine of the University of KwaZulu-Natal.

More information: www.caprisa.org

Reference

1. Robinson ET BD, Heise LL, Moffett LL, Harlan SV. Communications Handbook for Clinical Trials: Strategies, Tips, and Tools to Manage Controversy, Convey Your Message, and Disseminate Results. Available from: http://www.fhi360.org/sites/default/files/media/documents/Communications%20Handbook%20for%20Clinical%20Trials.pdf (accessed: 22 April 2016). North Carolina: FHI360; 2014.

Chapter 16
What Does the Future Hold for CAPRISA?

Salim S. Abdool Karim, Cheryl Baxter and Quarraisha Abdool Karim

The key CAPRISA priorities when it was established was informed by studies understanding the evolving epidemic and included: i. Preventing HIV infection in young women; ii. Reducing AIDS related mortality due to HIV–TB interactions and iii. Enhancing knowledge of HIV-1 Clade pathogenesis.

As can be gleaned from the previous chapters, CAPRISA has contributed to the substantial global progress on all three fronts, by undertaking pivotal, proof-of-concept studies that have changed World Health Organisation's international and South. African national guidelines on HIV prevention as well as TB–HIV treatment.However, South Africa continues to rank number one in terms of having the most number of new HIV infections and people living with HIV despite vigorous treatment and prevention expansion. Within South Africa, a large number of the people living with HIV, or who have recently acquired HIV are in the province of KwaZulu-Natal. The continued high incidence rates of HIV infection in adolescent girls and young women and high AIDS related deaths despite South Africa having one of the largest anti-retroviral treatment programmes, underscore that these continue to be challenges to ensuring that HIV ceases to be a public health threat.

Importantly, proof-of-concept studies are only the first step in an evidence-based response to the HIV epidemic. CAPRISA continues to undertake laboratory, clinic and field-based studies to better understand the findings from CAPRISA's completed clinical trials; there is a need to invest in addressing the gaps in programmatic scale-up of evidence-based interventions. The current portfolio of studies at

S.S. Abdool Karim (✉) · C. Baxter · Q. Abdool Karim
Centre for the AIDS Programme of Research in South Africa,
University of KwaZulu-Natal, Durban, South Africa
e-mail: Salim.abdoolkarim@caprisa.org

S.S. Abdool Karim · Q. Abdool Karim
Department of Epidemiology, Mailman School of Public Health,
Columbia University, New York, USA

Q. Abdool Karim et al. (eds.), *The CAPRISA Clinical Trials: HIV Treatment and Prevention*, DOI 10.1007/978-3-319-47518-9_16

CAPRISA includes implementation science studies of available evidence on Pre-Exposure Prophylaxis (PrEP) and TB–HIV treatment in order to generate practical information to guide policy and practice and realise the population based impact of scientific advances that CAPRISA and others have contributed to generating. Simultaneously, CAPRISA is conducting a combination of laboratory-based investigations that are informing the next set of pivotal clinical trials on broadly neutralising antibodies and long-acting PrEP, as novel approaches to HIV prevention in women.

In terms of preventing HIV infection in young women, CAPRISA is undertaking epidemiological studies, laboratory-based mucosal immunology and prevention trials evaluating novel strategies as well as assessing the feasibility of integrating HIV prevention services into sexual and reproductive health services. The 39 and 51 % overall protective benefit of tenofovir gel in preventing HIV and HSV-2 infection, respectively, observed in the CAPRISA 004 trial in 2010 led us to: i. evaluate the feasibility and acceptability of integrating tenofovir gel provision into existing family planning services in a primary health care setting (CAPRISA 008); ii. Enhance understanding of the role of genital inflammation in HIV acquisition (CAPRISA 006); and iii. Explore novel approaches to preventing HIV infection in young women (CAPRISA 012 and CAPRISA 018).

CAPRISA has developed a systematic and structured approach to understand who is exposing young women to HIV, why the incidence rates in adolescent girls and young women are so high despite peno-vaginal sex being the least efficient mode of transmission and identifying novel strategies for HIV prevention. The common thread in each of these three areas of research is the way in which CAPRISA uses highly advanced technologies to answer priority public health questions. For example, the use of phylogenetics has advanced the understanding of the cycle of HIV transmission in South Africa and the central role of young men 25–40 years infecting young women <25 years. Another example is the collaborative studies on the vaginal microbiome to identify the causes of genital inflammation. One of these studies, undertaken with the Center for Immunity and Infections at Columbia University, has generated new insights on vaginal dysbiosis (bacterial vaginosis) and specifically the role of *Prevotella bivia* in enhancing HIV acquisition. While this finding needs to be further validated, it opens up new avenues for reducing HIV risk in women. Another of these studies, using proteomics, undertaken jointly with the Public Health Association of Canada, has generated a new hypothesis on the impact of vaginal dysbiosis on the efficacy of tenofovir gel and the importance of a 'healthy' vaginal microbiome for HIV prevention.

The CAPRISA 008, the post-trial access study of tenofovir gel, has demonstrated that it is feasible and acceptable to integrate HIV prevention into family planning services. CAPRISA is drawing on these findings to undertake an implementation study of daily, oral Truvada for HIV prevention. The data from this PrEP implementation study will inform both local policies on PrEP provision and future HIV

prevention trial design in the era of PrEP scale-up. Further, the PrEP implementation studies have created the opportunity to investigate the impact of improving vaginal health on PrEP efficacy in the trial involving regular diagnosis and treatment of bacterial vaginosis.

For new HIV prevention technologies, preparations are underway to undertake a trial to evaluate the safety and protective benefit of CAP256-VRC26.25 (CAPRISA 012) alone and in combination with two other broadly neutralising antibodies. This passive immunity study has been designed to inform future preventative HIV vaccine research. As an attempt to advance the PrEP research agenda, CAPRISA has established a consortium including the Oak Crest Institute of Science in the US, Gilead Sciences in Ireland and St Etienne University in France to develop and test a 6-month tenofovir alafenamide-containing implant. In parallel, CAPRISA continues to support international multi-center studies on the cabotegravir injectable (2-monthly), the VRC01 broadly neutralising antibody (2-monthly infusion) and the dapivirine vaginal ring (monthly) as new longer-acting forms of PrEP.

In terms of reducing morbidity and mortality rates, CAPRISA continues to build on the SAPIT trial findings on integrating HIV and TB services as delays in ARV treatment initiation in patients coinfected with HIV and TB results in a substantial number of preventable deaths. The SUTHI trial is a cluster randomised controlled trial that will use a quality improvement approach to integrate HIV and TB services. Tuberculosis remains the most common opportunistic infection associated with advancing HIV disease and the years of neglect of adequately addressing the TB challenges has resulted in multi- and extremely drug resistant TB that are associated with higher death rates than drug-sensitive TB. The CAPRISA Index trial will assess the added benefit of personalised TB treatment based on whole genome sequencing on TB treatment outcomes.

This chapter and book highlights the iterative nature of knowledge generation, how incremental advances in knowledge enable CAPRISA's researchers to understand emerging phenomena, and informs the next set of research questions; that there is no room for complacency and the joys and beauty of science that is best captured in the words of Nelson Mandela "I have discovered the secret that after climbing a great hill, one only finds there are many more to climb…".

Index

Note: Page numbers followed by f and t indicate figures and tables respectively

Q. Abdool Karim et al. (eds.), *The CAPRISA Clinical Trials: HIV Treatment and Prevention*, DOI 10.1007/978-3-319-47518-9