Chapter 7
HIV Vaccine and Passive Immunity Trials

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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

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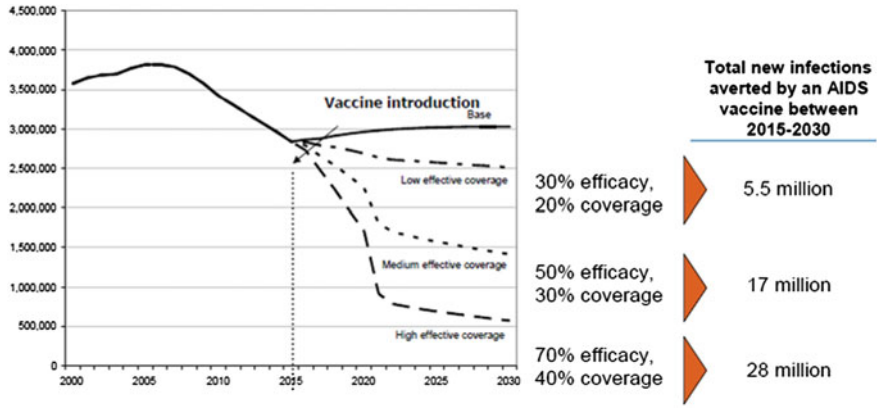

Fig. 1 The potential impact of an AIDS Vaccine

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

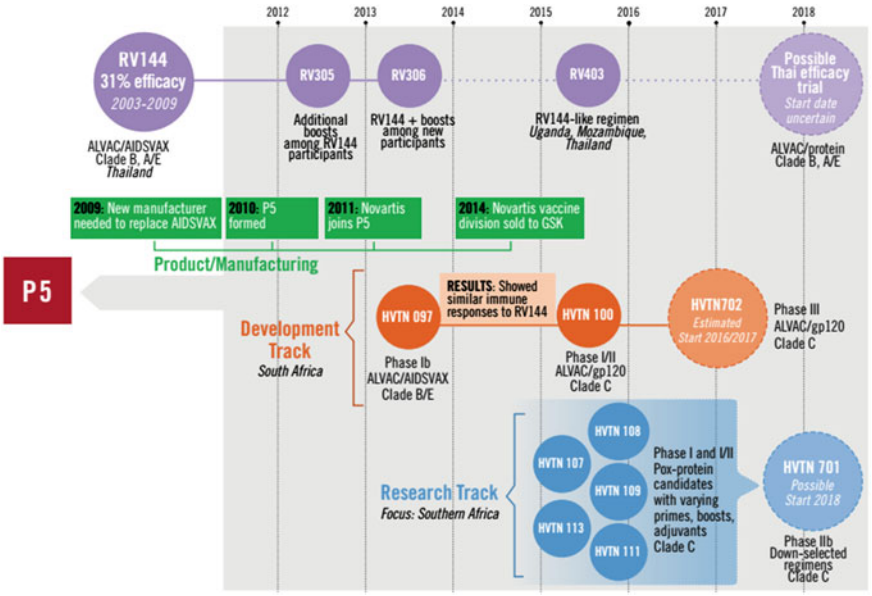

Fig. 2 Pox-Protein Public-Private Partnership (P5) partnership Vaccine Programme. *Source* http://www.avac.org reproduced with permission from AVAC

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).

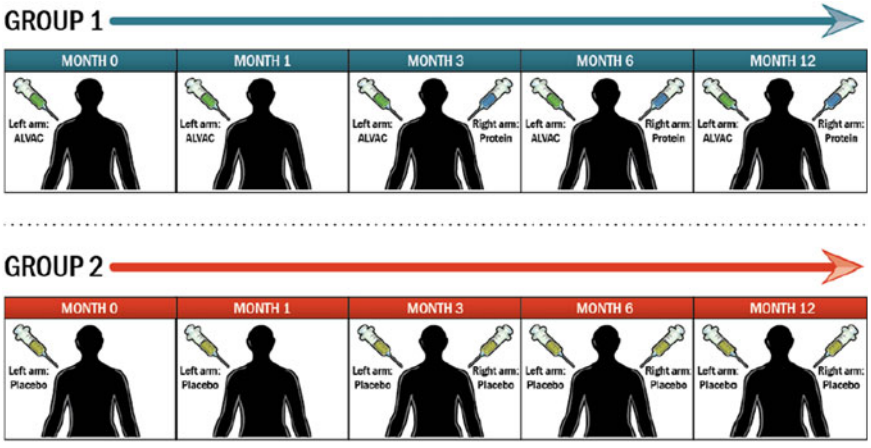

Fig. 3 Vaccination schedule in HVTN 100

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

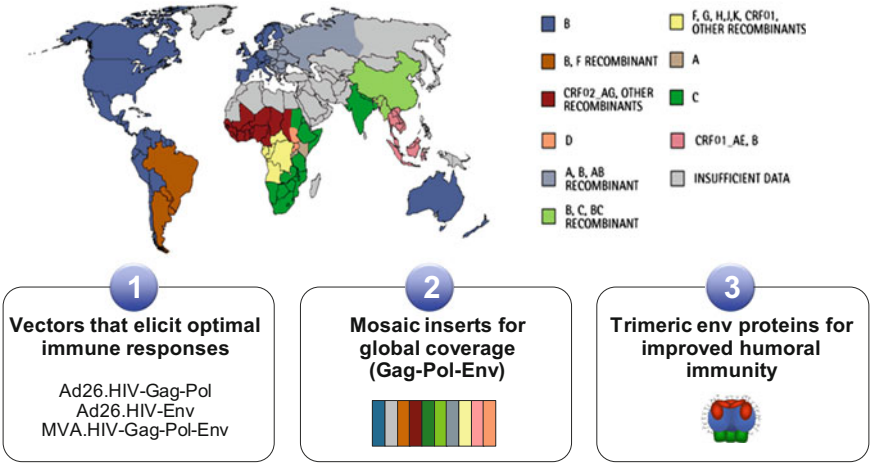

Fig. 4 Mosaic Vaccine components of the HIV-V-A004 trial. *Source* Reproduced with permission from Janssen Pharmaceuticals

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.

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