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

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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.

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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.

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