Challenges in the integration of TB and HIV care: Evidence for improving patient management and health care policy

by

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DOCTOR OF PHILOSOPHY (Medicine)

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26 November 2015

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DECLARATION BY SUPERVISOR

As the candidate’s supervisor I, Prof Salim S Abdool Karim, agree to the submission of this thesis.

Signed: __________________________

Date: 26 November 2015
AUTHORS DECLARATION

DECLARATION

I, Kogieleum Naidoo, declare that
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(iii) This dissertation does not contain other persons’ data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.
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ETHICS DECLARATION

The studies described in this thesis were approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (E107/05 and B248/05).
DEDICATION

For my husband Indresh, and my children Keshaav and Kiarin, for the endless source of inspiration, motivation and support. Without you, nothing would be possible……
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<th>Description</th>
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<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>Anti-TB</td>
<td>Anti-tuberculosis</td>
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<tr>
<td>ACTG</td>
<td>AIDS Clinical Trials Group</td>
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<tr>
<td>ADI</td>
<td>AIDS Defining Illness</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
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<td>ART</td>
<td>Antiretroviral Therapy</td>
</tr>
<tr>
<td>CAPRISA</td>
<td>Centre for the AIDS Programme of Research South Africa</td>
</tr>
<tr>
<td>CAMELIA</td>
<td>Cambodian Early versus Late Introduction of Antiretrovirals</td>
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<tr>
<td>CAT</td>
<td>CAPRISA AIDS Treatment</td>
</tr>
<tr>
<td>CHAI</td>
<td>Clinton Health Association Initiative</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<tr>
<td>DILI</td>
<td>Drug Induced Liver Injury</td>
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<td>EFV</td>
<td>Efavirenz</td>
</tr>
<tr>
<td>GDP</td>
<td>Gross Domestic Product</td>
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<td>HAART</td>
<td>Highly Active Antiretroviral Therapy</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<td>IRR</td>
<td>Incidence Rate Ratios</td>
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<td>Immune Reconstitution Inflammatory Syndrome</td>
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<tr>
<td>MTB</td>
<td>Mycobacterium Tuberculosis</td>
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<td>MDR-TB</td>
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<td>MTB/RIF</td>
<td>Mycobacterium Tuberculosis/Rifampicin</td>
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<tr>
<td>MH</td>
<td>Mantel-Haenszel</td>
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<tr>
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<td>Non-communicable disease</td>
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<tr>
<td>NEJM</td>
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<tr>
<td>NNRTI</td>
<td>Non-nucleoside Reverse Transcriptase Inhibitor</td>
</tr>
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<td>NVP</td>
<td>Nevirapine</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
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<td>PEPFAR</td>
<td>President’s Emergency Plan for AIDS Relief</td>
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<td>RCT</td>
<td>Randomised Controlled Trial</td>
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<td>Treatment</td>
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<td>RR</td>
<td>Relative Risk</td>
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<td>SAS</td>
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<td>Starting ARV Therapy at Three Points in Tuberculosis</td>
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<tr>
<td>SSA</td>
<td>sub-Saharan Africa</td>
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<tr>
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<td>Tuberculosis</td>
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<tr>
<td>TB-HIV</td>
<td>Tuberculosis-Human Immunodeficiency Virus</td>
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<tr>
<td>TB-IRIS</td>
<td>Tuberculosis Immune Reconstitution Inflammatory Syndrome</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>XDR-TB</td>
<td>Extensively Drug Resistant Tuberculosis</td>
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<td>YLS</td>
<td>Year of Life Saved</td>
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ABSTRACT

TB infection remains a leading cause of morbidity and mortality among patients with HIV infection, while HIV is the strongest risk factor for development of active TB. Integration of HIV and TB treatment is key to reducing mortality in co-infected patients; but many obstacles stand in the way of effective scale-up of this approach to HIV-TB treatment. The challenges associated with HIV-TB integration extend from clinical complexities in individual patient management, to impediments in health service organization and prioritization to address this urgent public health priority, especially in sub-Saharan Africa where TB-HIV co-infection rates reach 80%.

The purpose of this study was to assess and identify strategies to overcome the challenges in immune reconstitution and drug safety/tolerability when integrating HIV and TB care in a cost-effective manner to reduce co-infection mortality.

Clinical and operational service data from the Starting Antiretroviral therapy at three Points in Tuberculosis Treatment (SAPiT – CAPRISA 003) study, a 3-arm, randomized control trial in 642 newly diagnosed sputum smear-positive TB-HIV co-infected adult patients with screening CD4+ cell count < 500 cells/mm³, were analysed. In addition, the incidence rate of unmasked clinical TB following ART initiation was assessed through a retrospective chart review conducted in HIV infected patients enrolled at the rural CAPRISA AIDS Treatment Programme.

Overall, mortality was 56% lower (RR=0.44; 95% CI: 0.25 to 0.79; P = 0.003) in patients initiated on ART during TB treatment compared to ART deferral to after TB treatment completion. However, the risk of immune reconstitution inflammatory syndrome (IRIS) was higher (incidence rate ratio (IRR), 2.6 (95% CI, 1.5 to 4.8); P < 0.001, in patients initiating ART within the first 2 months compared to later ART initiation during TB treatment. In the most severely immuno-compromised patients (CD4 counts <50 cells/mm³) early ART integration was associated with an almost five-fold increased risk of IRIS (IRR 4.7 (95% CI, 1.5 to 19.6); P = 0.004. Patients initiating ART in the first 2 months of TB therapy had higher hospitalization rates (42% vs. 14%; P = 0.007) and longer time to resolution (70.5 vs. 29.0 days; P = 0.001) than patients in the other two groups. When assessing available evidence, these results indicate that ART initiation in patients with CD4 cell counts ≥50 cells/mm³ would be most appropriate after completion of intensive phase of TB therapy, a strategy that was found to cost $1840 per patient treated. Among HIV infected patients initially screening negative for TB there was a four-fold higher incidence rate of unmasking TB in the first 3 months after ART initiation, compared to the subsequent 21 months post-ART initiation.
The new information generated by this study provides important evidence for policy and clinical management of patients with HIV and TB co-infection. Firstly, careful clinical vigilance for ‘unmasked’ TB is required in patients initiating ART. Secondly, the survival benefit of AIDS therapy in TB patients can be maximized by initiating ART as soon as possible after TB therapy has been started in patients with advanced immunosuppression, i.e., those with CD4+ counts <50 cells/mm³. However, patients with higher CD4+ cell counts should delay ART initiation to at least 8 weeks after the start of TB therapy to minimize the incidence and duration of immune reconstitution disease and consequent hospitalization. Thirdly, this approach, which is at variance with current World Health Organization policy and guidelines, is cost-effective and readily implementable within the clinical setting. Finally, addressing the operational challenges to HIV-TB treatment integration can improve patient outcomes with substantial public health by reducing mortality by the most important causes of death in South Africa.
CHAPTER 1
INTRODUCTION

1.1 Summary of the HIV-TB treatment context

Tuberculosis (TB) infection contributes extensively to morbidity and remains a leading infectious cause of death among patients with HIV, while HIV remains the strongest risk factor for development of active TB. In sub-Saharan Africa (SSA) TB-HIV co-infection rates are as high as 80%, with South Africa holding a disproportionate burden of these two diseases with approximately 12.2% of the population infected with HIV in 2012 and 450000 new TB cases notified in 2013 alone. In 2004, the WHO proposed an interim policy for collaborative TB/HIV activities. Yet, in 2010, only 34% of TB patients underwent HIV testing, and only 46% of HIV-positive TB patients received antiretroviral therapy (ART). Finding the optimal time to initiate ART in TB HIV co-infected patients remained an urgent public health priority. The timing of ART initiation in TB patients presents a clinical challenge of competing risks and benefits. On one hand, deferred ART to after the start of TB therapy is associated with increase mortality and AIDS disease progression, while early initiation of ART during TB therapy raises concerns over increase risk of immune reconstitution inflammatory syndrome, non-adherence from the high pill burden, and overlapping side effects from co-administration of three antiretroviral drugs with the standard four drug anti-tuberculosis therapy. In addition, the translation from research to implementation of TB HIV co-treatment as part of national health guidelines, has uncertain cost implication. Observational and cohort studies prior to 2010 offered guidance but the lack of randomized control clinical trials investigating optimal timing of ART initiation in TB patients left many important yet unanswered questions.

1.2 Aims and Objectives

The overarching aim of the study was to assess the impact of ART initiation in TB-HIV co-infected patients with respect to mortality; unmasking TB; TB associated immune reconstitution inflammatory syndrome, drug tolerability and additive toxicity, and costs and cost effectiveness of co-treatment.

Specific Objectives

1. To quantify the burden of HIV associated TB among patients initiating antiretroviral therapy in rural KwaZulu-Natal

2. To assess IRIS incidence, severity, and outcomes in patients with HIV-related tuberculosis receiving integrated compared to sequential TB and HIV treatment.

3. To assess the costs and cost effectiveness of starting ART at various time points during TB treatment in patients with CD4 cell counts ≥50cells/mm³
Additional Objectives:
1. To compare morbidity and mortality in patients receiving integrated compared to sequential TB and HIV care.
2. Review and critically appraise the literature to determine the optimal timing of ART initiation in TB HIV co-infected patients.
3. To assess drug tolerability and toxicity when combining ART with anti-TB drugs in patients with HIV related tuberculosis receiving integrated compared to sequential TB and HIV care.

1.3 Literature Review

1.3.1 The Epidemiologic burden of TB-HIV co-infection
Tuberculosis (TB) infection contributes extensively to morbidity and remains a leading infectious cause of death among patients with HIV (1-5). In 2013, global estimates of individuals with HIV infection was 35.2 million (6), and TB infection 2.2 billion, with 9.4 million new cases of TB disease (7). HIV remains the strongest risk factor for TB among those with new or latent Mycobacterium tuberculosis (MTB) infection (8-11), and has also been strongly associated with an increased risk of TB associated death. The risk of TB disease is highest soon after HIV sero-convertion, doubles within the first year of HIV acquisition (5, 12, 13), and becomes more pronounced with advancing immunosuppression (14, 15). The risk of TB in individuals with HIV infection is 20-37 (16) times higher than in those without HIV infection, and in some settings in sub-Saharan Africa (SSA), the prevalence of HIV co-infection in TB patients is as high as 907 per 100000 population (Table 1). Approximately 75% of all HIV-associated TB occurs in Africa with countries in sub-Saharan Africa reporting HIV co-infection rates of more than 50% of all TB cases notified (Figure 1) (7).

Table 1: HIV Prevalence in new TB cases: sub-Saharan Africa region, 2013 (7)

<table>
<thead>
<tr>
<th>Rank</th>
<th>Country</th>
<th>Rate per 100,000</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Swaziland</td>
<td>907</td>
</tr>
<tr>
<td>2</td>
<td>Zimbabwe</td>
<td>433</td>
</tr>
<tr>
<td>3</td>
<td>Lesotho</td>
<td>424</td>
</tr>
<tr>
<td>4</td>
<td>South Africa</td>
<td>857</td>
</tr>
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</table>

The global burden of TB- HIV-co-infection peaked at 1.4 million cases in 2005, with approximately 480 000 TB deaths among co-infected patients accounting for about 25% of all deaths in HIV infected
patients (Figure 1) (7, 11, 17, 18). In addition, data showing 1.1 million HIV-TB co-infected cases reported in 2014, indicates that the burden of HIV-associated TB remains ongoing (7).

A total of 1.5 million people died from TB disease in 2013 (7). Of concern, 360 000 of these TB patients who died were HIV-positive (Figure 2) (7). South Africa holds a disproportionate burden of these two diseases with approximately 12.2% of the population (6.4 million persons) infected with HIV in 2012 (19), and 450 (410–520) thousand new TB cases notified in 2013 alone (7). The province of KwaZulu-Natal, South Africa, one of the global epicentres of TB HIV co-infection, has a population of approximately 1.2 million HIV-infected individuals, a TB co-infection rate of 70% (20) and a background TB notification rate of 1094 cases per 100,000 population (7, 21, 22).

Identifying effective mechanisms of reducing the nearly 0.5 million HIV associated TB deaths that result each year has therefore been identified as a priority globally (1).
1.3.2 The epidemiologic Interaction between TB and HIV

Tuberculosis, first introduced to South Africa in the 17th century by European immigrants, became established among miners and their families in rural communities in the 19th century (23). Although TB incidence rates increased to approximately 350/100,000 population in the 1960s, reports show a decline during the 1970s (24). The central tenet of tuberculosis control, the WHO DOTS strategy, was based on the principles of prompt detection and effective treatment of infectious patients with the goal of interruption of TB transmission and reduction in TB prevalence (25, 26). The rising HIV prevalence in sub-Saharan Africa (Figure 3) (27), contributes to increased TB susceptibility at a population level. The increasing burden of TB fostered by the HIV epidemic has generated several challenges in DOTS as the mainstay of the TB control strategy. HIV mediates increased susceptibility to active tuberculosis through reactivation of latent TB infection or progression of newly acquired TB infection to disease (28, 29). The escalating numbers of TB cases resulting from the maturing HIV epidemic plunged South Africa into having one of the worst TB crisis in the world. TB notification rate showed an almost 4-fold increase from 163/100,000 in 1986, to 628/100,000 in 2006 (30).

Figure 2: Global and South African TB and HIV epidemics in 2012 (6, 7)
The striking difference in TB susceptibility and TB outcomes among HIV infected and uninfected patients was demonstrated in South African gold miners, where TB notification rates among HIV-negative miners remained stable between 1990 and 1999, compared to the 4-fold increase in TB notification rates among HIV-positive miners (31). Furthermore, TB mortality rates in the general population increased 2.8-fold from 78/100,000 in 1990 to 218/100,000 in 2006 (20).

The impact of HIV on the increasing burden of tuberculosis at a population level was described in rural KZN using census derived estimates that showed an increase in TB incidence from 154/100 000 in 1991 to 413/100 000 in 1995 (32). This increase occurred while the prevalence of HIV infection in women attending antenatal clinics in KwaZulu-Natal increased from 1.61% in 1990 to 18.23% in 1995. Furthermore, the proportion of tuberculosis cases attributable to HIV infection was estimated to be at least 44% in 1995 (32).

1.3.3 Rationale for TB and HIV treatment integration
The epidemiology of the TB and HIV epidemics overlap substantially and significant benefits exist to both programs, to patients and their communities if both TB and HIV are simultaneously addressed via an integrated approach. The development of simple and sustainable strategies for HIV care delivery to large numbers of patients in resource poor settings remains a key priority especially as increasing
evidence became available on the substantial morbidity and mortality benefit through use of ART therapy (33). Various models of HIV care provision were suggested, and among these was a proposed strategy to integrate HIV care into existing TB programs (34-36).

As TB remains the commonest presentation of AIDS in most resource limited settings, HIV screening in TB programs provides a cost-effective method of identifying patients likely to benefit from antiretroviral therapy and an efficient mechanism for rapidly scaling up ART initiation given the large co-infection disease burden (11, 37). In 2010, despite evidence in support of this approach, only 34% of TB patients underwent HIV testing, and only 46% of HIV-positive TB patients received antiretroviral therapy (18).

Existing TB services in many developing countries offer the opportunity of utilising existing established infrastructure for expansion to include HIV services: including laboratory and radiological support services, systems for drug procurement, and systems to monitor treatment adherence and toxicity. The multitude of potential benefits to integration include an increase in HIV and TB case detection through efficient targeted screening in HIV and TB populations, the use of an established TB infrastructure to deliver AIDS care, and an opportunity to reduce the TB case fatality rate in HIV infected patients (38). While it was proposed that this strategy would enable initiation of ART for newly identified HIV infected patients during TB treatment and facilitate management of those who develop TB during treatment for HIV, evidence to support improved outcomes and guidance for successful implementation of this strategy was lacking. Furthermore, the timing of ART in TB patients presents a clinical challenge of competing clinical risks and benefits (Figure 4) (39). On one hand, deferred ART to after the start of TB therapy is associated with increase mortality and AIDS disease progression, while early initiation of ART during TB therapy raises concerns over increase risk of non-adherence to TB therapy and ART from the high pill burden associated with dual therapy, immune reconstitution inflammatory syndrome, and overlapping side effects from co-administration of three antiretroviral drugs with the standard four drug anti-tuberculosis therapy (39).
1.4 Impact of TB HIV treatment integration on mortality

1.4.1 Early evidence describing the impact of ART on mortality in TB-HIV co-infected patients

Early published data showed higher case fatality rates in HIV associated TB patients despite effective TB treatment (40), and extremely high TB associated mortality in HIV infected patients enrolling into care programmes (41). Subsequently, evidence emerged showing that ART provision could significantly impact TB case fatality in co-infected patients through demonstration that ART use among TB patients contributed to substantial decreases in morbidity and mortality (3, 42).

Data published in 2001 from African cohorts demonstrated TB case fatality rates of 16% to 35% among HIV infected patients not receiving ART compared to 4% to 9% among HIV uninfected patients. Subsequent to publication of these findings, data from several cohort and observational studies (n=11) provided information on the impact of ART on survival of patients with HIV-associated TB (Table 2), by demonstrating that concurrent ART reduced mortality risk by 64% to 95% in patients receiving treatment for HIV-associated TB (41-49).
<table>
<thead>
<tr>
<th>Main Author</th>
<th>Journal and Year of Publication</th>
<th>Title of paper</th>
<th>Primary Objectives</th>
<th>Study Design</th>
<th>Country</th>
<th>Sample Size</th>
<th>Impact of ART on Mortality</th>
</tr>
</thead>
</table>
| Varma, J.K  | BMC Infectious Dis. (2009)      | HIV care and Treatment factors associated with improved survival during TB Treatment in Thailand | • Identify and quantify the relative benefit of biomed interventions assoc. with survival during TB TREATMENT  
• to evaluate the optimum time to initiate ART,  
• evaluate the AEs and survival associated with different regimens | Prospective, multi-centre, Observational Study | Thailand | 667 | Patients who took ART had 1/5 the risk of dying than those who did not take ART, risk of dying was further reduced with early ART initiation and concomitant use of fluconazole. |
| Velasco, M  | J AIDS (2009)                   | Effect of simultaneous use of HAART on survival of HIV-TB patients | • Assess the effect of HAART on the survival of patients with TB | COMESEM Cohort Study | Spain | 6934 | Simultaneous HAART And TB Treatment in HIV-TB patients is associated with improved survival. |
• To compare clinical outcomes relative to initiation of anti-TB therapy between patients randomised to early vs. delayed ART | Randomised pilot study | Tanzania | 70 | Early ART can be well tolerated by HIV/TB co-infected subjects with low risk IRIS, there may be more AE’s with early ART which warrants regimen switches. Early ART lead to virologic suppression and increased CD4. |
<p>| Akksilp, S  | Emerging Infectious Diseases (2007) | ART during TB treatment &amp; marked reduction in death rate | Estimate the benefit of ART in reducing mortality during TB treatment in HIV-TB infected patients in rural Thailand. | Prospective study: population-based surveillance system | Thailand | 329 | Deaths of patients with TB-HIV remain high despite increased access to ART, few HIV-TB patients receive ART |</p>
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<th>Main Author</th>
<th>Journal and Year of Publication</th>
<th>Title of paper</th>
<th>Primary Objectives</th>
<th>Study Design</th>
<th>Country</th>
<th>Sample Size</th>
<th>Impact of ART on Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zachariah, R</td>
<td>INT J TUBERC LING DIS (2007)</td>
<td>Does ART reduce case fatality among HIV + patients with TB in Malawi</td>
<td>• To report on case fatality among HIV-TB infected patients while on TB Treatment • Identify whether ART initiated in continuation phase reduces case fatality</td>
<td>Retrospective cohort analysis</td>
<td>Malawi</td>
<td>983</td>
<td>ART provided in the continuation phase does not have significant impact on reducing case fatality</td>
</tr>
<tr>
<td>Nahid, P</td>
<td>AM J Resp Crit Care Med (2007)</td>
<td>Treatment outcomes of HIV-TB patients</td>
<td>To evaluate treatment outcomes for HIV infected patients stratified by duration of rifamycin-based-TB therapy</td>
<td>Retrospective Case review</td>
<td>San Francisco</td>
<td>700</td>
<td>HIV infected patients receiving 6-month rifamycin based course/intermittent therapy had higher relapse rate than HIV+ patients who received longer therapy or daily therapy.</td>
</tr>
<tr>
<td>Dheda, K</td>
<td>JID (2004)</td>
<td>Outcome of HIV associated TB in the era of HAART</td>
<td>Compare characteristics and outcome of patients infected with TB-HIV treated before HAART era vs. during HAART era</td>
<td>Chart review</td>
<td>London</td>
<td>96</td>
<td>HAART substantially reduces new AIDS events and death in co-infected patients.</td>
</tr>
<tr>
<td>Hung, C</td>
<td>AIDS (2003)</td>
<td>Improved outcomes of HIV-1 infected adults with TB in the era of HAART</td>
<td>Compare the survival and treatment responses to ART between HIV-1 and active TB and without</td>
<td>8 year prospective observational study</td>
<td>Taiwan</td>
<td>125</td>
<td>No significant difference between groups</td>
</tr>
</tbody>
</table>
These data collectively contribute analysis on 23,507 patients, of these, half of whom were from resource-limited settings. Among these eleven studies, eight studies found significant reductions in mortality associated with ART use in tuberculosis treatment, whereas three found no impact of ART on mortality (Table 2) (43-45, 47, 49-55). A longitudinal cohort study conducted in South Africa, (42) demonstrated extremely high rates of AIDS or death among ART naïve patients in the first 6 months after enrolling into HIV treatment programmes. The high death rate was seen among WHO stage 3 patients, before the development of AIDS defining illnesses (ADI), and a high risk of ADI’s was seen in those with CD4 cell counts between 200 and 350 cells/mm³ (42), highlighting the need for timely ART initiation. The key unanswered question in the clinical management of patients with HIV-associated TB was the optimal time to start ART during TB treatment. The 2005 WHO Expert consultation (56) into research priorities in collaborative TB-HIV activities therefore recommended that finding the optimal time to initiate ART in TB-HIV co-infected patients was an urgent public health priority. On one hand, mortality rates and AIDS disease progression are extremely high among patients waiting to start ART in resource-limited settings, however, early initiation of ART in TB HIV increases the risk of immune reconstitution inflammatory disease, morbidity from co-administering TB drugs with ART, thereby increasing costs of caring for co-infected patients. In addition, issues of tolerability, pill burden, and drug interactions between ART and TB therapy had the potential to undermine both ART therapy as well as TB outcomes.

1.4.2 Recent evidence describing the impact of ART on mortality in TB-HIV co-infected patients

Published data from several large trials including cohort and observational studies and randomised control trials (RCTs), became available since 2009 and have informed guidelines (Table 3 and Table 4) (46, 52, 57-69) on optimal timing of ART in TB patients. The vast majority of these strategy trials show that ART co-administered with TB therapy provides an improved survival benefit, hence the recommendation by the WHO that ART be provided to all patients together with their TB treatment, regardless of CD4 cell count. There was concurrence in the findings of all these studies regarding patients with advanced immunosuppression (CD4 cell counts <50 cells/mm³); mortality was reduced when ART was started within the first 2 weeks of TB treatment. For patients with less advanced immunosuppression (CD4 cell counts ≥50 cells/mm³), these studies suggested that ART might be deferred until completion of the intensive phase of TB treatment without negatively impacting survival.
Table 3: Data from Cohort and observational studies evaluating the Impact of ART on mortality in HIV infected TB patients: 2009-2015

<table>
<thead>
<tr>
<th>Main Author</th>
<th>Journal and Year of Publication</th>
<th>Title of paper</th>
<th>Primary Objectives</th>
<th>Study Design</th>
<th>Country</th>
<th>Sample Size</th>
<th>Impact of ART on Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saraceni, V</td>
<td>Braz J Infect Dis (2014)</td>
<td>Survival of HIV patients with TB started on simultaneous or deferred HAART in the THRio cohort, Rio de Janeiro, Brazil</td>
<td>To compared survival among patients who initiated HAART within 60 days of TB Treatment to those who started HAART &gt;60 days of TB treatment or never started</td>
<td>Observational cohort analysis</td>
<td>Rio de Janeiro</td>
<td>947</td>
<td>HAART initiated early after TB Treatment in co-infected patients was associated with 89% reduction in the risk of death compared to delayed HAART initiation</td>
</tr>
<tr>
<td>Yang, C</td>
<td>BMC Infectious Diseases (2014)</td>
<td>The impact of HAART initiation timing on HIV-TB Co-infected patients, a retrospective cohort study</td>
<td>To understand the TB outcome of HIV-infected adults under routine programmatic conditions in Taiwan</td>
<td>Population-based, retrospective cohort study</td>
<td>Taiwan</td>
<td>229</td>
<td>Initiating HAART during TB Treatment is associate with better one-year survival, although the earlier initiation within 60 days of TB Treatment did not show statistical differences in survival than later initiation.</td>
</tr>
<tr>
<td>Han, S</td>
<td>HIV Med (2014)</td>
<td>Prognostic significance of the intervals between the initiation of ART and anti-TB Treatment in HIV-TB co-infected patients: Results from the TREAT Asia HIV Observational Database</td>
<td>This study evaluated the effect of time intervals between the initiation of ART and TB Treatment on clinical outcomes in HIV-TB co-infected patients in an Asian regional court</td>
<td>Prospective, observational cohort study</td>
<td>Asia-Pacific Region</td>
<td>768</td>
<td>Treatment outcomes and overall mortality of HIV-TB co-infected patients who started ART within 90 days of TB Treatment did not differ from those who started ART started later. Overall mortality was higher among patients diagnosed</td>
</tr>
<tr>
<td>Main Author</td>
<td>Journal and Year of Publication</td>
<td>Title of paper</td>
<td>Primary Objectives</td>
<td>Study Design</td>
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<td>Sample Size</td>
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<tr>
<td>Lettow, M</td>
<td>Public Health Action (2011)</td>
<td>Timing and uptake of ART during Treatment for active TB, in HIV co-infected adults in Malawi</td>
<td>To determine at programme level if earlier initiation of ART in co-infected patients receiving TB Treatment will increase the uptake and continuation of ART.</td>
<td>Prospective observational pilot programme</td>
<td>Malawi</td>
<td>2155</td>
<td>Earlier initiation of ART in co-infected patients receiving TB Treatment improved the uptake and continuation of ART. ART guidelines changed from initiating ART after 2 months to as soon as possible</td>
</tr>
<tr>
<td>Franke, MF</td>
<td>PLoS Medicine (2011)</td>
<td>Effectiveness of Early ART initiation to improve survival among HIV infected Adults with TB: A retrospective cohort study</td>
<td>To confirm results from randomized trials among a cohort of HIV-infected adults who were diagnosed with TB under routine programmatic conditions, rather than by sputum smear or culture</td>
<td>Retrospective Chart Review</td>
<td>Rwanda</td>
<td>308</td>
<td>Early cART reduced mortality among individuals with low CD4 cell counts and improved retention in care, regardless of CD4 cell count.</td>
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</table>

Treatment: Treatment  
Py: person years  
CD4 cell count: cluster of differentiation 4  
HIV-TB: Patients co-infected with HIV and TB
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<th>Main Author</th>
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<th>Sample Size</th>
<th>Impact of ART on Mortality</th>
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</thead>
<tbody>
<tr>
<td>Amogne, W</td>
<td>PLOS One (2015)</td>
<td>Efficacy and Safety of ART initiated 1 week after TB Treatment in Patients with CD4 cell count &lt;200 cells/mm³: TB-HAART Study, a Randomized Clinical Trial</td>
<td>To determine risk of mortality if ART initiated 1, 4 and 8 weeks after TB treatment start.</td>
<td>Randomized Clinical Trial</td>
<td>Addis Ababa, Ethiopia</td>
<td>478</td>
<td>ART 1 week after TB did not improve survival. 2/3 mortality occurred within first 2 weeks.</td>
</tr>
<tr>
<td>Mfinanga, S.G</td>
<td>Lancet (2014)</td>
<td>Early vs. delayed initiation of HAART for HIV positive adults with newly diagnosed pulmonary TB (TB-HAART): a prospective, international, randomized, placebo-controlled trial</td>
<td>This study assessed the effect of early vs. delayed initiation of ART on TB Treatment outcomes for HIV+ people with CD4 cell count of at least 220 cells/mm³ with newly diagnosed, smear positive, culture-confirmed TB</td>
<td>Prospective, international, randomized, placebo-controlled Trial</td>
<td>South Africa, Tanzania, Uganda, Zambia</td>
<td>1675</td>
<td>ART can be delayed until after 6 months of TB Treatment for HIV+ patients who have CD4 cell count &gt;220 cells/mm³. No significant difference between groups.</td>
</tr>
<tr>
<td>Manosuthi, W</td>
<td>J AIDS (2012)</td>
<td>Time to ART between 4 weeks and 12 weeks of TB Treatment in HIV-infected patients: Results from the TIME Study</td>
<td>The determine the optimal timing for ART initiation aimed at reducing the mortality among HIV infected patients with active TB in a middle-income country</td>
<td>Open-label, randomized controlled trial</td>
<td>Thailand</td>
<td>156</td>
<td>Immediate ART initiation in TB-HIV co-infected patients did not confer a survival advantage when compared to initiation of ART at 12 week. Predictors of poorer survival included low baseline CD4 cell counts.</td>
</tr>
<tr>
<td>Sinha, S</td>
<td>BMC Infectious Disease (2012)</td>
<td>Early vs. delayed initiation of ART for Indian HIV infected individuals with TB on anti-TB Treatment</td>
<td>To compare early (2-4 weeks) and delayed (8-12 weeks) initiation of ART after commencement of anti-TB Treatment</td>
<td>Randomized open, label trial</td>
<td>India</td>
<td>150</td>
<td>No significant difference in mortality among HIV-TB co-infected patients initiating ART 2-4 weeks after commencing ATT (early ART group), and those receiving it 8-12 weeks after starting ATT (delayed ART group).</td>
</tr>
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<td>Main Author</td>
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<tr>
<td>Torok, M.E</td>
<td>CID (2011)</td>
<td>Timing of Initiation of ART in HIV associated TB-meningitis.</td>
<td>To determine whether immediate ART reduced the risk of death</td>
<td>Randomized, double blind, placebo-controlled trial</td>
<td>Vietnam</td>
<td>253</td>
<td>Immediate ART does not improve mortality in patients presenting with HIV-associated TB meningitis. The overall, mortality among patients with TB meningitis who were treated with ART was similar to patients who did receive Treatment during TB Treatment.</td>
</tr>
<tr>
<td>Abdool Karim, S</td>
<td>NEJM (2011)</td>
<td>Integration of ART with TB Treatment</td>
<td>Determine the impact of ART timing on clinical outcomes in patients with HIV-TB</td>
<td>Three-group, open label, randomized controlled trial</td>
<td>South Africa</td>
<td>642</td>
<td>The incidence rate of AIDS or death in the earlier ART group compared to the late-ART group was 6.9 cases per 100 py versus 7.8 per 100 py, respectively.</td>
</tr>
<tr>
<td>Blanc, F</td>
<td>NEMJ (2011)</td>
<td>Earlier vs. Later start of ART in HIV infected Adults with TB</td>
<td>To determine whether the earlier initiation of ART (2 weeks after the onset of TB Treatment) as compared with later initiation (8 weeks after), could reduce mortality among patients with advanced immunodeficiency</td>
<td>Prospective, randomized multi centre, open label superiority trial (CAMELIA)</td>
<td>Cambodia</td>
<td>661</td>
<td>Initiating ART 2 weeks after the start of TB Treatment significantly improved survival among HIV-infected adults with CD4+ T-cell counts of 200 cells/mm³ or lower.</td>
</tr>
<tr>
<td>Havlir, D.V</td>
<td>NEJM (2011)</td>
<td>Timing of ART for HIV-1 Infection and TB</td>
<td>To determine the proportion of patients who survived without an AIDS-defining illness at 48 weeks</td>
<td>Open label randomized study</td>
<td>Brazil</td>
<td>809</td>
<td>Overall, immediate ART did not reduce AIDS-defining illness and death compared to early ART. For persons with CD4 lymphocytes &lt; 50 cells/mm³, immediate ART had 42% less AIDS defining illness and death compared to early ART.</td>
</tr>
<tr>
<td>Main Author</td>
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<tr>
<td>Abdool Karim, S</td>
<td>NEJM (2010)</td>
<td>Timing of Initiation of ART during TB Therapy</td>
<td>To determine the optimal time to initiate ART in HIV-TB co-infected patients receiving TB treatment</td>
<td>Open-label, randomized, controlled trial</td>
<td>South Africa</td>
<td>642</td>
<td>Initiation of ART during TB therapy in patients with confirmed HIV-TB co-infection reduced mortality by 56%.</td>
</tr>
<tr>
<td>Shao, H.J</td>
<td>AIDS Research &amp; Human Retroviruses (2009)</td>
<td>Early versus Delayed fixed dose combination Abacavir/lamivudine/zidovudine in patients with HIV-TB in Tanzania</td>
<td>Assessment of safety and efficacy of ABC/3TC/ZDV in TB-HIV co-infected patients and to compare outcomes, including TB-IRIS, between patients in the early vs. delayed ART, relative to anti-TB therapy start.</td>
<td>Randomized pilot study</td>
<td>Tanzania</td>
<td>70</td>
<td>Early ART can be well tolerated by HIV/TB co-infected subjects with low risk IRIS, although more regimens switches from treatment related AE occurs. Early ART lead to benefits in virological suppression and increased CD4 cell count.</td>
</tr>
</tbody>
</table>

Treatment: Treatment  
Py: person years  
CD4 cell count: cluster of differentiation 4  
HIV-TB: Patients co-infected with HIV and TB
These findings have been incorporated into WHO guidelines which has since recommended 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/mm³), 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 randomized 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 CNS associated TB-IRIS (67).

1.5 The clinical challenges associated with TB-HIV treatment integration

The timing of ART in TB patients presents a clinical challenge of competing risks and benefits. On one hand, deferred ART to after the start of TB therapy is associated with increased in mortality and AIDS disease progression, while early initiation of ART during TB therapy is associated with a concern about the increase risk of paradoxical immune reconstitution inflammatory syndrome (IRIS), overlapping side effects from co-administration of three antiretroviral drugs and the standard four drug anti-tuberculosis therapy, and a high pill burden (70-74). The occurrence of these clinical challenges can complicate that management of TB HIV co-infected patients as it is often difficult to differentiate these from adverse events due to ART or TB drugs, failure of TB treatment or occurrence of another HIV-related complications.

1.5.1 Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS will remain an important medical problem as the global scale up of ART initiation continues toward a test and treat approach, expanding rapidly in settings where TB is endemic and patients still present for ART at very low CD4 cell counts – all known risk factors for IRIS occurrence. ART enables immune recovery through suppression of HIV replication, resulting in an increase in circulating CD4 cell counts, restoration of immune responses to specific pathogens over time, and ensuing clinical benefits. Immune restoration may result in paradoxical clinical deterioration from immune-pathological reactions in patients on effective treatment and arises from the body’s renewed ability to produce an immunologic response that is inflammatory in nature following initiation of ART or tuberculosis treatment. This clinical scenario is termed “IRIS,” or “immune restoration disease.” Consensus case definitions of paradoxical TB IRIS have been published (72), and as there are currently no laboratory test to confirm the presence of IRIS, paradoxical IRIS remains a clinical diagnosis only. While IRIS occurrence has been associated with a wide range of infectious agents, and autoimmune phenomena, the commonest association has been with mycobacterial infections, especially Mycobacterium tuberculosis infection (75). Published evidence from observational and retrospective studies show that TB-associated IRIS occurs in approximately 11% to 71.4% of TB HIV co-infected patients that initiate
ART (Table 5) (76-81). Reports of high rates of IRIS irrespective of background rates of TB, has been a key reason for clinicians deferring ART initiation patients currently receiving TB treatment.
Table 5: Impact of ART initiation in TB-HIV co-infected patients on Incidence of paradoxical TB-IRIS: Summary of published studies from cohorts of > 100 patients (n = 27 studies)

<table>
<thead>
<tr>
<th>Main Author (Year of Publication)</th>
<th>Journal</th>
<th>Title of paper</th>
<th>Primary Objectives</th>
<th>Study Design</th>
<th>Country</th>
<th>Sample Size</th>
<th>No at risk of Paradoxical TB-IRIS (n)</th>
<th>Paradoxi cal TB-IRIS cases (n)</th>
<th>Paradoxical TB-IRIS incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narita et al (1998)</td>
<td>AM J Respir Crit Care Med</td>
<td>Paradoxical Worsening of Tuberculosis Following Antiretroviral Therapy in Patients with AIDS</td>
<td>To determine the incidence of paradoxical responses in TB-HIV co-infected patients treated with anti-tuberculous therapy and subsequently with combination antiretroviral therapy (ARV),</td>
<td>Prospective cohort Study</td>
<td>USA</td>
<td>116</td>
<td>33</td>
<td>12</td>
<td>36.4</td>
</tr>
<tr>
<td>Breen et al (2004)</td>
<td>Thorax</td>
<td>Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection</td>
<td>To estimate the frequency and nature of paradoxical reactions in a heterogeneous clinic and inpatient population</td>
<td>Retrospective observational cohort study</td>
<td>United Kingdom</td>
<td>100</td>
<td>28</td>
<td>8</td>
<td>28.6</td>
</tr>
<tr>
<td>Shelburne et al (2005)</td>
<td>AIDS</td>
<td>Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy</td>
<td>To determine incidence, risk factors, and IRIS outcomes in HIV-infected patients, co-infected with one of three common opportunistic pathogens, and receiving antiretroviral therapy</td>
<td>Retrospective cohort study</td>
<td>USA</td>
<td>259</td>
<td>86</td>
<td>26</td>
<td>30.2</td>
</tr>
<tr>
<td>Manosuthi et al (2006)</td>
<td>J Acquir Immune Defic Syndr</td>
<td>Survival Rate and Risk Factors of Mortality Among HIV/Tuberculosis-Coinfected Patients with and without antiretroviral therapy</td>
<td>• To determine possible risk factors that related to death among patients • To determine the appropriate timing for initiating ART after TB diagnosis</td>
<td>Retrospective cohort study</td>
<td>Thailand</td>
<td>167</td>
<td>167</td>
<td>21</td>
<td>12.6</td>
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<tr>
<td>Main Author (Year of Publication)</td>
<td>Journal</td>
<td>Title of paper</td>
<td>Primary Objectives</td>
<td>Study Design</td>
<td>Country</td>
<td>Sample Size</td>
<td>No at risk of Paradoxical TB-IRIS (n)</td>
<td>Paradoxic TB-IRIS cases (n)</td>
<td>Paradoxical TB-IRIS incidence (%)</td>
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</tbody>
</table>
| Tansuphasawadikul et al (2007)  | Southeast Asia J Trop Med Public Health | Outcomes of HIV-Infected patients on ART with TB | • To determine the clinical outcomes of TB in HIV-infected patients on ART.  
• To investigate the incidence and manifestations of adverse events and IRIS in association with ART initiation. | Retrospective chart review | Thailand | 101 | 101 | 15 | 14.9 |
| Manosuthi et al (2009)           | AIDS    | Clinical case definition and manifestations of paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome | • To assess performance of the INSHI-2008 definition in a clinical trial  
• To study the clinical manifestations and predictive factors for paradoxical TB-IRIS among patients co-infected with HIV and TB | Prospective cohort study | Thailand | 126 | 126 | 23 | 17.5 |
| Van Tieu et al (2009)            | Aids Research and Human Retroviruses | Immunologic Markers as Predictors of Tuberculosis-associated Immune Reconstitution Inflammatory Syndrome in HIV and TB co-infected persons in Thailand | • To determine specific T helper 1 cytokine markers to predict and diagnose TB-IRIS in HIV and TB co-infected adults after Initiating ART in Thailand  
• To describe the incidence and clinical manifestations of TB-IRIS. | Prospective Randomised Trial | Thailand | 126 | 126 | 22 | 17.5 |
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<tr>
<th>Main Author (Year of Publication)</th>
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<th>Title of paper</th>
<th>Primary Objectives</th>
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<th>Paradoxical TB-IRIS incidence (%)</th>
</tr>
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<tbody>
<tr>
<td>Eshun-Wilson et al (2010)</td>
<td>JIAPAC</td>
<td>Evaluation of Paradoxical TB-Associated IRIS With the Use of Standardized Case Definitions For Resource-Limited Settings</td>
<td>To evaluate paradoxical tuberculosis (TB)-associated IRIS in a large cohort from a TB endemic setting with the use of these case definitions</td>
<td>Retrospective chat review</td>
<td>South Africa</td>
<td>313</td>
<td>313</td>
<td>35</td>
<td>11.2</td>
</tr>
<tr>
<td>Karmakar et al (2011)</td>
<td>Clinical and Developmental Immunology</td>
<td>Clinical Characteristics of Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome in North Indian Population of HIV/AIDS Patients Receiving HAART</td>
<td>•To determine the incidence of IRIS in patients with HIV-associated TB •To identify the risk factors for TB-IRIS</td>
<td>Prospective, observational study</td>
<td>India</td>
<td>224</td>
<td>123</td>
<td>5</td>
<td>4.1</td>
</tr>
<tr>
<td>Letang et al (2011)</td>
<td>PLOS One</td>
<td>Incidence and Predictors of Immune Reconstitution Inflammatory Syndrome in a Rural Area of Mozambique</td>
<td>The incidence, clinical characteristics, outcome and predictors of IRIS in rural Mozambique.</td>
<td>Prospective observational cohort study</td>
<td>Mozambique</td>
<td>136</td>
<td>40</td>
<td>8</td>
<td>20</td>
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<tr>
<td>Lorrent et al (2011)</td>
<td>PLOS One</td>
<td>Incidence and Risk Factors of Serious Adverse Events during Anti-tuberculous</td>
<td>To determine incidence, causes and risk factors for serious adverse events among patients on first-line antituberculous</td>
<td>Prospective observational cohort study</td>
<td>Rwanda</td>
<td>253</td>
<td>167</td>
<td>21</td>
<td>12.6</td>
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<td>Main Author (Year of Publication)</td>
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<td>Limmahakhun et al (2012)</td>
<td>International Journal of STD &amp; AIDS</td>
<td>Treatment outcomes of patients co-infected with tuberculosis and HIV at Chiang Mai University Hospital, Thailand</td>
<td>•To determine treatment outcomes among TB/HIV co-infected patients. •to determine the risk factors related to death and immune reconstitution inflammatory syndrome (IRIS)</td>
<td>Retrospective cohort study</td>
<td>Thailand</td>
<td>171</td>
<td>132</td>
<td>8</td>
<td>6.1</td>
</tr>
<tr>
<td>Agarwal et al (2012)</td>
<td>AIDS Research and Therapy</td>
<td>Tuberculosis associated immune reconstitution inflammatory syndrome in patients infected with HIV: meningitis a potentially life threatening Manifestation</td>
<td>To study the frequency, clinical presentation and outcome of paradoxical tuberculosis associated immune reconstitution inflammatory syndrome (TB-IRIS) in HIV infected patients in a TB hospital in North India</td>
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<td>Annals of Internal Medicine</td>
<td>The Immune Reconstitution Inflammatory Syndrome After Antiretroviral Therapy Initiation in Patients With Tuberculosis: Findings From the SAPiT Trial</td>
<td>To assess IRIS incidence, severity, and outcomes relative to the timing of ART initiation in patients with HIV related tuberculosis.</td>
<td>Randomized, open-label clinical trial</td>
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<td>Primary Objectives</td>
<td>Study Design</td>
<td>Country</td>
<td>Sample Size</td>
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<td>Paradoxical TB-IRIS cases (n)</td>
<td>Paradoxical TB-IRIS incidence (%)</td>
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<td>Time to Initiate Antiretroviral Therapy Between 4 Weeks and 12 Weeks of Tuberculosis Treatment in HIV-Infected Patients: Results From the TIME Study</td>
<td>To determine the optimal timing of ART initiation to minimize the mortality among HIV-infected patients with active TB in the setting of a middle-income country</td>
<td>Open-label, randomized, controlled trial</td>
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<td>Journal of the International Association of Providers of AIDS Care</td>
<td>Clinical Outcomes among HIV/Tuberculosis-co-infected Patients Developing Immune Reconstitution Inflammatory Syndrome after HAART Initiation in South India</td>
<td>To determine the frequency and clinical response of developing IRIS among HIV/TB-co-infected South Indian patients receiving HAART</td>
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<td>To analyze cases of paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) in randomised trial</td>
<td>Randomized clinical trial</td>
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<td>PLOS One</td>
<td>Complications of Antiretroviral Therapy Initiation in Hospitalised Patients with HIV-Associated Tuberculosis</td>
<td>To document causes of clinical deterioration of hospitalised patients with HIV-associated tuberculosis starting antiretroviral therapy in order to inform healthcare practice in low- to middle-income countries</td>
<td>Prospective observational cohort study</td>
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<td>Title of paper</td>
<td>Primary Objectives</td>
<td>Study Design</td>
<td>Country</td>
<td>Sample Size</td>
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<td>Paradoxic TB-IRIS cases (n)</td>
<td>Paradoxical TB-IRIS incidence (%)</td>
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<td>Leutkeymeyer et al (2014)</td>
<td>J Acquir Immune Defic Syndr</td>
<td>Tuberculosis Immune Reconstitution Inflammatory Syndrome in A5221 STRIDE: Timing, Severity and Implications for HIV-TB Programs</td>
<td>To compare ART started earlier (within 2 weeks after TB treatment initiation) vs. later (8-12 weeks after TB treatment initiation) in HIV-infected participants with CD4+ cell counts &lt; 250 cells/mm³ receiving treatment for suspected tuberculosis</td>
<td>Open label, randomized study</td>
<td>Multicountry</td>
<td>806</td>
<td>806</td>
<td>61</td>
<td>7.6</td>
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</tbody>
</table>

*: IRIS specific study objective
IRIS associated with TB occurs in 2 distinctive circumstances (72, 73). “Paradoxical” IRIS occurs in HIV-infected patients with known TB that are improving while either receiving or having recently completed TB treatment but who develop a paradoxical worsening of symptoms, signs, and or radiological manifestations of TB, after commencing ART (72, 82). “Unmasking” IRIS occurs when HIV infected patients who have no clinical evidence of TB initiate ART and subsequently develop clinical manifestations of TB where the inflammatory component is often pronounced (72). In the latter group, occult TB infection becomes unmasked following ART induced immune restoration (Figure 5). Clinical features of IRIS in TB HIV co-infected patients range from mild clinical presentations, to more severe morbidity, or recurrent, new, or deteriorating clinical and radiological manifestations to mortality (83).

Figure 5: Paradoxical tuberculosis-associated IRIS, ART-associated tuberculosis, and Unmasking tuberculosis-associated IRIS (72) Reproduced with permission from Elsevier (License no. 3738170833211)

Other atypical and more severe manifestations include new or progressive serositis, tuberculoma, acute renal failure, airway compression, with respiratory failure (70, 72, 73, 84-91). Although IRIS can occur in HIV uninfected patients and in the absence of ART, the vast majority of all reported cases occur in HIV infected patients after the commencement of ART (70, 72, 73, 84-91). Most reports show that paradoxical IRIS occurs within 6 weeks of ART initiation. Risk factors for development of paradoxical IRIS include disseminated TB, ART initiation close to tuberculosis treatment initiation, low pre-ART CD4 cell count, high baseline viral load and a greater decrease in viral load and larger CD4 cell count increase or increase in CD4:CD8 cell ratio from baseline on ART (70-74). IRIS remains a diagnostic challenge as it is important to exclude poor adherence to ART or TB treatment, the presence of another
opportunistic infection, multidrug resistant TB, or a suspected adverse drug reaction as the underlying reason for clinical deterioration, before the diagnosis of TB–IRIS can be made. Treatment of IRIS includes the use of corticosteroids and non-steroidal anti-inflammatory agents, both strategies as yet poorly defined, and implemented to varying degrees in available published literature (86, 92). Mortality associated with TB-IRIS is relatively uncommon overall, however when IRIS affects the CNS, it is likely to be life-threatening (67). Concerns about the frequency, severity and clinical outcomes resulting from immune reconstitution inflammatory syndrome (IRIS) remained an obstacle to antiretroviral therapy (ART) initiation during TB treatment in co-infected patients (Table 5).

“Unmasking” TB occurs when undiagnosed active TB present at ART initiation (72, 73, 85, 91), becomes overtly symptomatic after ART initiation. This new, “unmasked” presentation of TB, usually occurs in the weeks following initiation of ART, and when accompanied by an exaggerated inflammatory clinical presentation, is termed unmasking tuberculosis-associated IRIS. This phenomenon, leading to increased numbers of new TB cases diagnosed in newly initiated ART patients, may be as a result of restoration of TB-specific immune responses generated by the use of antiretroviral therapy (84, 91, 93). The incidence of unmasking TB in programs may vary, dependent on the efficiency of screening for clinical and sub-clinical TB in patients preparing for ART initiation. Severity of unmasking TB reported in published literature varies. Severe and fatal outcomes of unmasking TB IRIS have been reported in a few studies (90, 94), others have shown that this contributes to high mortality during the initial months of ART (95), however most published data demonstrate an unremarkable clinical presentation (91, 93). The use of ART in HIV-infected patients is a key strategy recommended by the World Health Organization (WHO) to prevent TB (96) as it has been shown to reduce the risk of developing TB by approximately 70–90% (42, 97-99). While studies from resource-limited settings show a decline in TB incidence rates in HIV-infected patients with longer duration on ART (16, 100, 101), the challenge of the burden of newly diagnosed tuberculosis among rural patients initiating ART in a HIV and TB endemic setting has not been fully quantified.

1.5.2 Impact of TB-HIV integration on overlapping drug toxicities

The TB treatment regimen requires daily intake of either 4 drugs (intensive phase) or 2 drugs (continuation phases), whilst HIV treatment requires daily intake of 3 drugs. Each regimen contain drugs that may be associated with overlapping and additive side effects and toxicities including gastrointestinal intolerance, drug induced liver injury, renal impairment, hypersensitivity reactions, peripheral neuropathy, rash and neuro-psychiatric effects (Table 6) (1, 102).
Table 6: Shared side effects of antiretroviral and anti-tuberculosis drugs (1)

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Antiretroviral Drugs</th>
<th>Antituberculosis drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disturbance and/or pain</td>
<td>AZT, ddl, PIs, INSTI</td>
<td>RIF, PZA, INH, ethionamide, PAS, clofazamine, linezolid</td>
</tr>
<tr>
<td>Liver injury</td>
<td>NNRTIs, PIs, NRTIs*, ABC, Entry inhibitors</td>
<td>RIF, INH, PZA, second line drugs including PAS, ethionamide, flouroquinolones</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>D4T, ddl</td>
<td>INH, terizidone/cycloserine, ethionamide, linezolid</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>EFV</td>
<td>INH, Terizidone/cycloserine, ethionamide,</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>TDF, Indinivir</td>
<td>Aminoglycosides and capreomycin</td>
</tr>
<tr>
<td>Rash</td>
<td>NVP, EFV, ABC, Fusion Inhibitors, Entry inhibitors</td>
<td>RIF, INH, PZA, ethambutol, streptomycin second line drugs including flouroquinolones, clofazamine</td>
</tr>
<tr>
<td>Blood dyscrasias</td>
<td>AZT, 3TC, Fusion Inhibitors</td>
<td>Linezolid, rifabutin, INH, rifampicin</td>
</tr>
<tr>
<td>Cardiac conduction abnormalities</td>
<td>PIs, Entry inhibitors</td>
<td>Bedaquiline, flouroquinolones, clofazamine</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>D4T, ddl, Lop/Rit</td>
<td>Linezolid</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>D4T, ddl</td>
<td>Linezolid</td>
</tr>
</tbody>
</table>

NRTIs (especially D4T and ddl) can cause steato-hepatitis.

\[3TC\] 2’, 3’-dideoxy-3’-thiacytidine, \[ABC\] abacavir, \[AZT\] zidovudine, \[D4T\] stavudine, \[ddl\] didanosine, \[EFV\] efavirenz, \[INH\] isoniazid, \[NRTIs\] nucleoside reverse transcriptase inhibitors, \[NVP\] nevirapine, \[PAS\] para-aminosalicylic acid, \[PIs\] protease inhibitors, \[PZA\] pyrazinamide, \[RIF\] rifampicin, \[TDF\] tenofovir, \[INSTI\] Integrase strand transfer inhibitor, \[Fusion Inhibitors\] eg. Enfuvirtide, \[Entry inhibitor\] eg. maraviroc.
Some studies suggest that HIV-infected patients have a higher rate of adverse events whilst other studies do not support these findings (103, 104). Few studies assessed the extent of additive side effects and toxicities as well as tolerability of co-treating TB and HIV. For instance, one retrospective study conducted in South Africa demonstrated that there was no association between co-administration of antiretroviral drugs among TB patients and the manifestations of serious and life-threatening adverse events (105). Conversely, retrospective studies conducted elsewhere in patients with CD4 cell counts < 100 cells/mm³, found 66.1% of co-treated patients experienced drug-related adverse events in the first 2 months (106), with an almost two-fold increase risk of an adverse events (OR: 1.88) with concomitant use of ART and TB treatment (44). However, these findings represent data from two small studies where two thirds of patients received an ART regimen containing nevirapine (NVP).

Several retrospective studies also found increased risk of adverse events among co-infected vs mono-infected patients and in those receiving co-treatment vs those receiving ART or TB treatment only. It is however important to note that the antiretroviral regimen used in these studies contained stavudine and didanosine - drugs no longer in wide usage. In contrast, regimens containing EFV were found to be better tolerated. It is unsurprising that peripheral neuropathy which was reported in nearly half of all patients, and hepatotoxicity, were the most common reported toxicities in patients receiving TB-HIV co-treatment (107-110). This study showed that the risk of hepatotoxicity increased when ART was introduced during the intensive phase of TB treatment (109). In addition, while some studies show that concomitant TB treatment in patients on a non-nucleoside reverse transcriptase inhibitors (NNRTI) based ART regimen has been associated with an increased risk of drug induced liver injury (DILI) (109, 111, 112) other studies show otherwise (113). These studies cite elevated baseline transaminases and hepatitis B antigenaemia as likely risk factors (114-123) for increased risk of drug induced liver injury (DILI). Hoffman et al, showed an 8.5-fold increased risk of hepatotoxicity with ART initiation in TB therapy (109).

One cohort study demonstrated low morbidity and mortality in HIV-infected patients with DILI (109), however in another South African study, approximately one third of all HIV infected patients admitted to hospital with DILI, died. This occurred either during TB treatment only, ART only, or in concurrent therapy (124), with sepsis and liver failure cited as reasons for death. Renal dysfunction reported in isolated case reports resulting from overlapping toxicity with use of tenofovir, rifampicin and aminoglycosides, has however not been confirmed in cohort studies (88).

In a meta-analysis (125), of six randomized control trials, 50.7 % of patients receiving early ART initiation vs. 51.5 % of patients receiving delayed ART initiation during TB treatment, experienced grade 3–4 drug-related adverse events, pooled IRR = 0.99, noting high quality of evidence and no observed limitations. Extensive literature review shows a general paucity of prospectively collected
data within RCTs describing the frequency of ART drug changes from treatment-limiting toxicity or virological failure in TB-HIV co-infected patients.

1.5.3 Cost effectiveness of TB HIV treatment Integration

In resource constrained settings, strategic prioritization of efforts to integrate services for co-occurring endemic diseases are essential. The management of HIV associated TB presents an opportunity to assess the cost-effectiveness of an integrated approach to care in comparison to the treatment of HIV and TB at separate care sites. The costs of screening for TB range from large, e.g. GeneXpert which costs between $15-32; to moderate e.g., chest x-ray which costs about $9-17 and small e.g. TB symptom screen via history (126) (127). The costs of TB treatment also range widely with a 6-month course of first-line therapy costing approximately $6, second-line MDR-TB therapy costing $120, and treatment for XDR-TB costing $180 (126). The additional costs of providing TB care include infrastructure for provision of services, personnel, and training (127). Costs of integrated HIV/TB care have been less well-described, with the actual differences in overall costs of integrated screening and treatment for TB with HIV needing further evaluation.

Published studies have examined cost-effectiveness of various TB diagnosis strategies of TB in HIV-infected patients, and of HIV in TB patients (128-133). One study from India suggested that integrating HIV testing into TB treatment clinics was “very cost-effective,” with an incremental cost-effectiveness ratio of $730/year of life saved (YLS), well below the Indian per capita annual GDP of $1,500 (134). Modelling data from South Africa comparing specific TB screening methods in HIV-infected patients (14, 129) found that Xpert MTB/RIF tests used in routine TB screening among HIV-infected patients were cost-effective when compared to symptom screening and sputum smear or sputum culture. Nevertheless to our knowledge, no studies have assessed the comparative effectiveness and cost of fully integrated HIV/TB programs.

Cost and cost-effectiveness of ART has been extensively researched in SSA, including provision of ART, treatment monitoring strategies, and regimen choices (135-142). However, no studies have studied comparative costs or cost-effectiveness of different timing of ART initiation in TB therapy for co-infected patients (143).
CHAPTER 2
METHODS

Data for this dissertation is drawn from two CAPRISA studies: The CAPRISA 003 Starting Antiretrovirals in Three Points in Tuberculosis Therapy Trial (SAPIT); and the CAPRISA AIDS Treatment (CAT) Programme.

2.1. The SAPiT Trial

Setting: The SAPiT trial, a three-arm, prospective, randomized, open-label clinical trial, was conducted at the CAPRISA eThekwini Clinical Research Site (ECRS), from June 28, 2005, to July 11, 2010. Patients recruited for participation into the SAPiT trial were drawn from the Prince Cyril Zulu Communicable Disease Centre (PCZCDC), a Primary Health Care Clinic dedicated to treating ambulatory patients with TB and sexually transmitted infections which is located alongside the CAPRISA ECRS. This municipal facility is conveniently located in central Durban in the transport hub for public commuters by rail, bus or minibus taxis. It is across from the central train station with the commuter taxi ranks on the one side and Durban’s central fresh produce farmer’s market with its linked main bus terminus on the other side. The PCZCDC is one of the largest out-patient TB facilities in South Africa with a sophisticated computerized patient record system. The PCZCDC provides care to patients from North and South Central Durban, a city with a population of about 3 million inhabitants, with over 10,000 cases of TB annually. PCZCDC notifies approximately 3,500 new TB cases per annum. Patients who present to the facility for TB screening and treatment are mostly unemployed (53%), with a median age of 33 years (range: 5-72), 39% are women and 69% are HIV co-infected (personal communication Dr Surie Chinappa, Medical Manager, PCZCDC).

Background therapy: Management of tuberculosis followed the National Tuberculosis programme guidelines which recommended that all first episode tuberculosis cases be treated with a 2-month intensive phase of a combination-drug regimen of rifampicin, isoniazid, ethambutol, and pyrazinamide, with doses based on pre-treatment weight. Thereafter, patients receive the 4-month continuation phase regimen consisting of isoniazid and rifampicin. Patients with retreatment tuberculosis receive a 3-month intensive phase regimen, which also includes streptomycin for the first 2 months, followed by a 5-month continuation phase regimen consisting of isoniazid and rifampicin. All patients were also routinely provided with cotrimoxazole prophylaxis.

SAPiT Trial Methods: Adult patients at least 18 years or older with confirmed HIV infection (based on two rapid HIV tests) with sputum smear positive tuberculosis diagnosed using auramine and Ziehl–Neelsen staining methods, and a screening CD4 count < 500 cells/mm³ were recruited for possible trial
participation. Patient eligibility criteria for study participation included independent microbiologic confirmation of positive tuberculosis status and absence of clinical contraindications to initiation of standard tuberculosis treatment or antiretroviral therapy. All female patients enrolled needed to agree to use dual contraception while taking efavirenz.

**Randomisation:** Patients provided written informed consent, and were thereafter randomly assigned in a 1:1:1 ratio, with the use of sealed envelopes, to one of three study arms in permuted blocks of six or nine with no stratification, as per a random allocation sequence generated by the study statistician. Patients were randomly assigned to initiate ART within 4 weeks of tuberculosis treatment initiation (early integrated treatment arm), within 4 weeks after intensive phase of tuberculosis treatment completion (late integrated treatment arm), or within 4 weeks after tuberculosis therapy completion (sequential treatment arm) (Figure 6). The standard first-line ART regimen consisting of once daily didanosine (250 mg for patients with a body weight of <60 kg and 400 mg for a body weight ≥60 kg), lamivudine (300 mg), and efavirenz (600 mg). Placebos were not used in this trial. All patients received adherence counselling, and adherence to the antiretroviral regimen was assessed via monthly pill counts. In addition, patients could be started on ART on clinical grounds, based on clinician’s discretion regardless of arm assignment.

![Figure 6: SAPiT Trial Schema (77)](image)

**Follow-up:** Follow-up visits were scheduled monthly for 24 months, for monitoring of patient safety and clinical status. All clinical and laboratory related adverse events were graded with the use of the National Institute of Allergy and Infectious Diseases Division of AIDS Table for Grading the Severity
of Adult and Paediatric Adverse Events, version 1.0, (December 28, 2004). CD4+ cell counts and HIV RNA measurements were performed at screening, randomization, and 6 monthly thereafter. Chest radiographs and sputum microbiologic examination was performed at screening, at the end of the intensive phase of TB therapy, 1 month before the end of TB therapy, and on clinical indication.

The SAPiT trial sample size calculated as 649 patients, was based on the primary mortality outcome of the study. Statistical analyses were done using SAS (version 9.2; SAS Institute Inc., Cary, NC, USA). All statistical tests were two sided. All reported P values are 2-sided. TB incidence was calculated as number of new TB cases after ART initiation per 100 person-years (py) of follow-up. The primary outcome was analysed with the use of Kaplan–Meier curves and the log-rank test. Poisson approximations were used to calculate confidence intervals (CIs) and incidence rate ratios (IRRs). Cox proportional-hazards regression was used to adjust for confounding variables. Fisher’s exact test or Fisher-Freeman-Halton test was used for analysis of categorical data, and unpaired t-tests or Wilcoxon two-sample, one way ANOVA, or the Kruskal-Wallis tests were used for the analysis of continuous data.

The trial was approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee, reference number: E107/05 and the Medicines Control Council of South Africa reference number. N2/19/8/2 (2137).

2.2. The CAPRISA AIDS Treatment (CAT) Programme

A prospective cohort study was conducted among 969 adult HIV-positive patients, a subset of patients from the rural Vulindlela CAT programme that initiated ART between 2007 and 2010. Vulindlela, located in the province of KwaZulu-Natal, is a rural village of about 400 000 predominantly Zulu speaking people. Free ART provided through PEPFAR supported HIV services, was offered as per current South African National HIV treatment guidelines (144). Ambulant HIV infected patients, predominantly ART naïve patients were initiated on ART if eligible as per guideline criteria. All patients were screened for TB by health care workers using a standardized TB clinical symptom checklist that screened patients for symptoms of drenching night sweats, fever, prolonged cough, and weight loss at every clinical visit. All TB suspects were referred for TB smear testing to the neighbouring government Primary Health Care Clinic. All patients that were tuberculosis sputum smear-positive were initiated onto anti-TB therapy upon receipt of microbiologic results while smear-negative patients routinely received sputum culture testing and a trial of antibiotic therapy. Diagnosis and treatment of TB followed South African National TB Control Program guidelines (30). Smear- and culture-negative TB suspects, showing poor response to antibiotic therapy, and those patients in whom extra-pulmonary TB was suspected, were referred to the nearest local hospital for further investigation and management. Patient follow-up data was censored at twenty four months for this analysis.
This study was approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee, ref no: E248/05.
Chapters 3, 4 and 5 highlight important contributions to understanding the impact of timing of ART initiation in TB treatment on mortality. These studies conclude that early ART initiation in TB patients with low CD4 cell counts significantly improved AIDS-free survival. This holds true for all co-infected patients except those with TB meningitis. This was, however, accompanied by a significant increase in the number and severity of IRIS events.
CHAPTER 3

WHEN TO START ANTIRETROVIRAL THERAPY DURING TUBERCULOSIS TREATMENT?

AUTHORS: Naidoo K, Baxter C, Abdool Karim SS.

When to start antiretroviral therapy during tuberculosis treatment

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Abstract

Purpose of review—Effective treatment exists for TB and for HIV but treating both diseases simultaneously presents several challenges. This review assessed the evidence for timing of antiretroviral therapy (ART) initiation in patients co-infected with TB.

Recent findings—Published evidence clearly demonstrates that TB HIV integration is essential for improved survival, but the question of when to start ART during TB treatment is more complex. Five randomised controlled trials assessed this question; four trials showed no difference in incidence rates of AIDS or death between TB patients initiating ART within 2 months compared to later during TB therapy, while one trial showed a significant survival gain with ART initiation within 2 weeks of TB therapy start. All five studies found improved AIDS-free survival with earlier ART initiation in TB patients with low CD4+ T-cell counts, except among patients with TB meningitis. The survival benefit was however, accompanied by increased immune reconstitution inflammatory syndrome events.

Summary—The trial data support the World Health Organisation recommendations on when to start ART in TB-HIV co-infected patients including earlier ART initiation in severely immune-compromised patients. However, several challenges remain in integrating TB and HIV treatment in public health care services. Additional research on timing of ART is needed for patients with drug-resistant and extra-pulmonary TB, notably TB meningitis.

Keywords
HIV; tuberculosis; antiretroviral therapy; immune reconstitution inflammatory syndrome (IRIS)

Introduction

Globally, an estimated 34.2 million people were living with HIV in 2011[1] and 8.8 million new tuberculosis (TB) cases occurred in 2010[2]. The two diseases are closely intertwined and the number of co-infected patients continues to grow rapidly[3]. Globally, an estimated 13% of TB patients are co-infected with HIV, while in sub-Saharan Africa, up to 82% of patients with TB are also co-infected with HIV.

Tuberculosis is the most common presenting opportunistic disease [4] and cause of mortality in AIDS patients in developing countries [5], accounting for approximately 25% of all HIV
associated deaths each year [6]. In the presence of HIV, TB is associated with substantially higher case fatality rates [7] and is the commonest notified cause of death [8]. The mortality in TB-HIV co-infected patients is usually due to complications from overwhelming TB disease or to impaired immunity from advancing AIDS [9, 10]. Effective treatment for TB and HIV exists but treating both diseases simultaneously is challenging. Despite World Health Organisation (WHO) guidelines supporting TB-HIV co-treatment [11], ART initiation is often deferred until TB treatment completion due to concerns of potential drug interactions between rifampicin and specific antiretroviral drugs [12], clinical deterioration from immune reconstitution inflammatory syndrome (IRIS) [13, 14], overlapping side effects [15], high pill burden compromising treatment adherence and programmatic challenges [16]. However, delays in ART initiation may result in AIDS-related illness and death. The goal of managing TB-HIV co-infected patients is to strike an optimal balance between the risks and benefits of increased mortality associated with delaying ART initiation to later in the course of TB therapy; against the morbidity and mortality burden associated with early ART initiation (Figure 1).

Before 2011, the only data available on guiding when to initiate ART during TB therapy was from observational reports [17–20] and a randomised controlled trial, the SAPIT (Starting Antiretroviral therapy at three Points in Tuberculosis) trial. The SAPIT Trial showed that initiating ART during TB treatment in patients with HIV co-infection significantly improves survival [21]. Patients who received ART during the course of TB therapy demonstrated a 56% (95% CI: 21 to 75) reduction in mortality compared to patients initiating ART after tuberculosis therapy completion.

This review examines clinical trial evidence published over the past year of exactly when during TB therapy ART should be initiated. Specifically, the impact of initiating HIV treatment at various points during TB treatment is evaluated in relation to mortality, incidence of IRIS and IRIS-associated mortality, adherence to treatment and drug interactions. Specific analyses among the sub-group of patients known to be most vulnerable to increased mortality from delayed ART and IRIS-related complications with earlier ART were also conducted. Studies published from 2011 onwards were searched using PubMed, Scopus and Google Scholar using the key words “tuberculosis” and “antiretroviral therapy” and “treatment of TB HIV co-infection” and “complications from treatment of TB HIV co-infection”. AIDS Conference proceedings were also searched.

**Impact of TB HIV Integration on mortality**

Four recent randomised clinical trials [22–25] have shown that initiating ART early during TB treatment in patients with very low CD4+CD4+ T-cell counts improved survival.

The Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPIT) trial which compared ART initiation within 4 weeks of TB treatment initiation (early group) to later ART initiation within 4 weeks after completion of the intensive phase of TB treatment (late group), among 642 HIV-infected South African patients with smear-positive pulmonary TB and CD4+ T-cell counts < 500 cells/mm², showed no difference in incidence rate of AIDS death in the early and late integrated treatment groups (6.9 vs 7.8 cases per 100 person-years; incidence-rate ratio, 0.89; 95% CI, 0.44 to 1.79; p = 0.73). However, among patients with CD4+ T-cell counts < 500 cell/mm³, the incidence rate of AIDS or death was 8.5 and 26.3 cases per 100 person-years; (incidence-rate ratio, 0.32; 95% CI, 0.07 to 1.13; p = 0.06) in the early and late groups, respectively.

Similar findings were demonstrated in the AIDS Clinical Trials Group (ACTG) Study 5221 (A5221) [25], which compared immediate (within 2 weeks) and early (between 8–12 weeks) ART in 809 HIV infected patients with suspected TB initiating TB therapy with...
CD4+ T-cell counts < 250 cells/mm³ showed no difference in mortality or AIDS defining illness between patients randomized to the immediate or early study group (12.9% vs 16%; p=0.45; 95% CI: 1.8%, 8.1%). However, in patients with CD4+ T-cell counts < 50 cells/mm³, the rate of AIDS or death was significantly lower in the immediate compared to the early group (15.5% vs. 26.6%; p=0.02). No differences were seen in rates of AIDS or death among patients with CD4+ T-cell counts ≥ 50 cells/mm³ (p=0.67).

Another trial in Ethiopia among 512 patients, presented at the 2012 Conference on Retroviruses and Opportunistic Infections, compared the efficacy and safety of ART when initiated 1 week, 4 weeks, and 8 weeks after anti-TB therapy initiation [24]. Results from this trial showed that although mortality was always higher in those with CD4 ≤ 50 cells/mm³, a better survival trend was observed among patients with CD4+ T-cell T-cell counts ≤ 50 cells/mm³ who initiated ART as early as 1 week. The overall incidence rate of mortality among patients in this study was 36.4 per 100 person-years, 26 per 100 person-years, and 20.8 per 100 person-years, among patients randomized to ART initiation at week 1, week 4, and week 8, respectively, p = 0.4. The relative risk of mortality among patients with baseline CD4+ T-cell ≤ 50 cells/mm³ versus CD4+ T-cell > 50 cells/mm³ was 1.5 in week 1 (95% CI 0.6 to 3.9), 2.0 in week 4 (95% CI 0.7 to 5.2), and 2.9 in week 8 (95% CI 0.8 to 9.9).

In contrast, the Cambodian Early versus Late Introduction of Antiretroviral Therapy (CAMELLA) study [23] did show a significant reduction in mortality among 332 patients who initiated ART within 2 weeks after TB treatment initiation compared with 329 patients who initiated ART within 8 weeks after TB treatment initiation (18% vs 27%; hazard ratio [HR], 0.62; 95% confidence interval [CI]: 0.44 to 0.86; p = 0.006). There was a more advanced degree of immunosuppression in this study cohort; patients had a median baseline CD4+ T-cell count of 25 cells/mm³ (Table 1), may account for this discrepancy.

A model, developed to predict 2-year survival rates under different ART initiation strategies, i.e., 15, 30, 60, or 180 days after TB treatment initiation or if ART was never initiated, in TB patients from Rwanda has also shown that early ART initiation reduced mortality among individuals with low CD4+ T-cell counts and improved retention in care [26].

Taken together, the data provide clarification on optimal timing of ART initiation in patients with HIV associated pulmonary TB. Specifically, these studies indicate that TB-HIV co-infected patients with advanced immunosuppression (CD4+ T-cell count < 50 cells/mm³) benefit from initiating ART earlier during (within 2–4 weeks) TB treatment initiation. In patients with higher CD4+ T-cell counts, however, the incidence of AIDS and or death were similar irrespective of whether ART was initiated early or later during TB treatment. Consideration of other clinical factors may therefore be necessary when determining the optimal timing of ART initiation in TB-HIV co-infected patients with higher CD4+ T-cell counts.

Impact of integrated TB-HIV treatment among patients with extra-pulmonary tuberculosis

Most clinical trials completed to date have predominantly focused on patients infected with drug susceptible pulmonary TB. It is not known if similar survival benefits observed among patients infected with pulmonary TB will also apply to patients infected with either drug resistant or extra-pulmonary TB.

Indeed, severe forms of tuberculosis like disseminated or extreme-pulmonary TB have been associated with much higher rates of mortality and fatal complications after ART initiation, suggesting that the optimal time to initiate ART in these patients may differ. A double blinded placebo controlled trial, the OXTEC 023–04 trial, conducted in Vietnam among 253 HIV infected patients with mean baseline CD4+ T-cell counts of 41 cells/mm³.

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diagnosed with TB meningitis showed no survival benefit for patients randomised to immediate (within 7 days) compared to deferred (within 2 months) ART initiation after TB treatment start (hazard ratio [HR], 1.12; 95% CI, 0.81–1.55; p = 0.50). There was high overall mortality and no difference in time to new AIDS event or death between the two groups (HR, 1.16; 95% CI, 0.87–1.55; p = 0.34) suggesting the need to delay ART initiation in patients with severe forms of TB [27]. While the high overall mortality precludes a definitive conclusion; early initiation of ART in patients with TB meningitis did not appear to lead to poorer outcomes.

The spectrum of IRIS relative to Timing of ART in TB HIV Co-infected patients

Data from retrospective and observational studies indicate that TB-associated IRIS occurs in approximately 11% to 71.4% of TB HIV co-infected patients starting ART [28, 29]. Reports of high IRIS rates from various settings is a key reason for delaying the initiation of ART in patients receiving TB treatment. Data from the CAMELIA, SAPIT and ACTG 5221 studies [22, 23, 25] provided some insights into this complex clinical situation.

The risk of TB-associated IRIS in all three studies was higher among patients randomized to receive ART earlier during TB treatment. The CAMELIA trial reported 110 versus 45 IRIS events in the early and late-ART groups (HR: 2.51; 95% CI, 1.78 to 3.59; p < 0.001); while ACTG 5221, found two-fold higher IRIS rates in the immediate compared to late ART groups (11% vs 5% p = 0.002), respectively. IRIS incidence rates in the SAPIT trial were 20.1 and 7.7 cases per 100 person-years in the early vs late groups (incidence-rate ratio (IRR): 2.62; 95% CI, 1.48 to 4.82; p < 0.001). A detailed analysis of IRIS incidence by CD4+ T-cell count in the SAPIT trial show that patients with CD4+ T-cell counts < 50 cells/mm³ had 4.7 times higher IRIS incidence rates in the earlier compared to later-ART group (p = 0.01) [29]. Moreover, patients with baseline CD4+ T-cell counts ≥ 50 cells/mm³ randomised to earlier ART, experienced 2-fold higher IRIS rates than patients randomised to later ART. TB-IRIS events occurred in 44% of patients with CD4 < 50 cells/mm³ receiving immediate ART in the ACTG 5221 study; while 155 (26%) of patients experienced IRIS events in the CAMELIA trial.

The overall IRIS incidence rates in all trials described above were not as high as previous reports. As patients with advanced immunosuppression are at higher risk of developing IRIS, the trade-off between improved survival and increased IRIS risk needs to be considered when initiating ART earlier during TB treatment.

IRIS-associated mortality

IRIS-associated mortality varied between studies but was low overall, despite heterogeneity in baseline characteristics and setting. All IRIS-associated deaths reported by CAMELIA (6) and SAPIT (2) occurred among patients randomised to earlier-ART initiation [23, 29]. Although the ACTG 5221 study, which was conducted across 26 sites in four continents, reported no IRIS associated deaths, extremely high mortality rates likely due to fatal intracranial IRIS was reported in both study groups in the COTREC 023–04 trial [27]. Overall the low rates of IRIS-associated mortality and IRIS-related hospitalisations observed in these studies indicate that scale-up of TB-HIV integration can be done without fear of overburdening secondary and tertiary level resources for IRIS management, or of worsening the morbidity and mortality burden experienced by TB-HIV co-infected patients. Future research efforts need to focus on finding a reliable diagnostic marker of IRIS in routine clinical and laboratory settings to assist with efficient IRIS diagnosis and management.
These studies were all conducted in resource limited settings with high background burden of TB and HIV with similar capacity for IRIS investigation and management. These study settings are comparable to centres scaling up TB-HIV integration. Prior to these studies being conducted, one of the biggest challenges anticipated was that co-treated patients experiencing IRIS would require intensive management at secondary and tertiary level facilities. However, the low IRIS associated mortality and IRIS-related hospitalisation rates seen in these studies indicate that the resource burden for secondary and tertiary level IRIS diagnosis and management will be limited. Until a reliable diagnostic tool is available to distinguish IRIS from clinical complexities such as TB or ART treatment failure and drug resistant TB, resource allocation for IRIS diagnoses at a primary care level will be necessary.

Impact of TB-HIV integration on ART outcomes

Concerns that the increased pill burden created by treating TB and HIV simultaneously will potentiate treatment related toxicity and undermine TB and HIV treatment outcomes was also addressed in the CAMELIA, ACTG 5221 and SAPIT trials. The trials all demonstrated similar virologic suppression rates, similar CD4+ T-cell count gains, and similar adverse event rates, irrespective of treatment group assignment.

Impact of TB-HIV integration on drug interactions

The resulting pharmacokinetic effect from drug interactions between the rifamycins and efavirenz among patients taking both agents concurrently remains controversial. The US Food and Drug Administration attempted to resolve this issue by releasing an updated package insert revising efavirenz dosing when co-administered with rifampin [30]. While data that informed this recommendation supports a once daily efavirenz dose of 800 mg instead of 600 mg for HIV-infected patients weighing ≥50 kg, other studies show that the efavirenz-rifamycin interaction could result in reduced efavirenz clearance, creating increased efavirenz exposure and potential toxicity [31]. While all trials described above showed clinical benefit with standard efavirenz dosing, conflicting pharmacokinetic interaction data requires further research and understanding [32]. Unfortunately, nevirapine, a potential alternate to efavirenz, has been shown to increase virologic failure and death [32] and the optimal dosing of protease inhibitors and rifabutin requires clarification. Uncertainty about potential drug interactions, cross class resistance and reduced efficacy of NNRTIs, such as delavirdine and newer generation NNRTIs such as etravirine has made the suitability of these drugs for co-administration with TB therapy questionable. There is extremely limited published clinical experience documenting use of newer classes of drugs such as integrase inhibitors and CCR5 co-receptor antagonists, nonetheless, the recently updated package insert for raltegravir (RDI) now recommends a dose increase of RGR to 800 mg twice daily if co-administered with rifampicin [33].

Challenges in scaling up the integration of TB and HIV treatment in public health settings

The recent clinical trials on the optimal time to initiate ART in patients on TB treatment have provided empirical evidence for improving TB and HIV outcomes. These clinical trial findings have also been incorporated into local and international guidelines and have been used to inform TB-HIV integration policy for patient and public health benefit [34]. However, it is important to acknowledge that these studies were carried out under controlled conditions and several challenges need to be overcome in order to translate the clinical trial evidence into public health benefit within diverse operational settings [35].
Logistics of integrating TB and HIV treatments

Firstly, the burden of the dual epidemics of TB and HIV is most severe in sub-Saharan Africa. This is also the region with limited health budgets, infrastructure, human resources, and suboptimal TB infection control practices. HIV and TB clinics are also often in different localities, which introduces logistical challenges in trying to integrate the treatments. One study has shown that delays in starting ART were almost three times as high in patients referred between non-integrated TB services and ART clinics as in those with TB that was diagnosed in ART clinics, with only 11% of TB HIV co-infected patients with CD4+ T-cell counts <200 cells/mm³ initiated on ART within 4 weeks of a TB diagnosis [36].

Secondly, in resource-limited settings, CD4+ T-cell count testing is not readily available making the determination of treatment initiation based on CD4+ T-cell count almost impossible in such settings. Alternate approaches to estimate disease severity such as the patients' general clinical condition, Karnofsky score, body mass index, haemoglobin, albumin, and evidence of organ system dysfunction, will need to be considered when making patient level decisions of timing of ART in TB patients. Conversely, the cost-effectiveness of ART initiation at any CD4+ T-cell count may need to be weighed against the risks and benefits of this strategy, especially in resource-limited settings. One immediate benefit is that HIV testing in TB patients could promptly triage co-infected patients into a TB HIV care continuum.

Although global policy makers have been responsive in translating these findings into TB HIV integration policy and recommendations, the benefit of this research can only be realised if effectively adapted to health care settings. Research on how best to implement the clinical trial findings is now warranted to help identify barriers to effective adaptation of TB HIV integration evidence. Measurements of metrics such as HIV testing of TB patients, CD4+ T-cell count measurement, referral for ART, initiation of ART, and access to TB therapy and ART, notably efavirenz, in facilities can provide key information on the level of TB HIV integration in facilities and in programs.

Applicability of results for extra-pulmonary TB patients and infants

While it is likely that these findings apply to patients with drug resistant, disseminated or sputum smear negative TB, this still needs empirical confirmation. In addition, little clinical trial evidence exists for guiding the optimal timing of ART initiation in infants and children with HIV-associated TB. One study has shown that early commencement of ART, from about 6 weeks of age, irrespective of CD4 lymphocyte threshold or HIV disease stage, would confer a significant survival benefit and reduce the risk of TB in HIV-infected children [37]. While this approach has been adopted by the World Health Organisation as standard of care for infants born to HIV-infected mothers [38], this study was not done in HIV TB co-infected infants, underscoring the need for more evidence to guide clinical decision making in this special group of patients.

Conclusion

Recent clinical trials consolidate the evidence-base underpinning recommendations on when to start ART in HIV infected patients who are co-infected with pulmonary TB and provide support for earlier initiation of ART in severely immune-compromised patients. Further research is, however, needed on the optimal time for initiating ART during TB treatment in patients with extra-pulmonary and drug resistant TB as well as in infants and children.

While these studies have provided the necessary impetus to advance TB and HIV integration efforts, several limitations need to be considered when scaling up TB-HIV treatment integration into public health settings.

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References


Figure 1.
Risks and benefits of early versus late antiretroviral therapy initiation in tuberculosis patients.
### Table 1

Comparison of recent randomized controlled trials evaluating co-initiation of antiretroviral therapy and anti-TB therapy

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>SAPIT</th>
<th>ACTG 5221</th>
<th>CAMELLIA</th>
<th>OXARTO 023-04</th>
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<tbody>
<tr>
<td>CD4+ T-cell count (cell/mm³)</td>
<td>≤ 200</td>
<td>200</td>
<td>&lt; 200</td>
<td>≤ 200</td>
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<tr>
<td>TB status</td>
<td>Known</td>
<td>Unknown</td>
<td>Known</td>
<td>Known</td>
</tr>
<tr>
<td>Early ART</td>
<td>Within 4 weeks of TB treatment initiation</td>
<td>Within 2 weeks of TB treatment initiation</td>
<td>Within 2 weeks of TB treatment initiation</td>
<td>Within 7 days of TB treatment initiation</td>
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<tr>
<td>Late ART</td>
<td>Within 8 weeks of TB treatment initiation</td>
<td>8-12 weeks of TB treatment initiation</td>
<td>Within 8 weeks of TB treatment initiation</td>
<td>After 8 weeks of TB treatment initiation</td>
</tr>
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<td>ART regimen</td>
<td>d4T, lamivudine, efavirenz</td>
<td>d4T, lamivudine, efavirenz</td>
<td>d4T, lamivudine, efavirenz</td>
<td>Zidovudine, lamivudine, efavirenz</td>
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<tr>
<td>Setting</td>
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<td>Cambodia, Vietnam</td>
<td>South Africa, Asia, North America, South America</td>
<td>Cambodia, Vietnam</td>
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<tr>
<td>Mean age</td>
<td>34</td>
<td>38</td>
<td>35</td>
<td>28.5</td>
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<td>Median CD4+ T-cell count</td>
<td>150</td>
<td>77</td>
<td>23</td>
<td>41</td>
</tr>
<tr>
<td>Median Vladek load</td>
<td>5.21 log₁₀</td>
<td>5.43 log₁₀</td>
<td>5.64 log₁₀</td>
<td>5.4 log₁₀</td>
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<tr>
<td>Number enrolled</td>
<td>429</td>
<td>809</td>
<td>65</td>
<td>253</td>
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<tr>
<td>Median Follow up (months)</td>
<td>17.7</td>
<td>11</td>
<td>23</td>
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### Outcomes

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<tr>
<th></th>
<th>Early (Event rate/100 p. y)</th>
<th>Late (Event rate/100 p. y)</th>
<th>HR (95% CI; p value)</th>
<th>Early (%)</th>
<th>Late (%)</th>
<th>95% CI for difference in proportion p value</th>
<th>Early (%)</th>
<th>Late (%)</th>
<th>Hazard Ratio (95% CI; p value)</th>
<th>Early (%)</th>
<th>Late (%)</th>
<th>Hazard Ratio (95% CI; p value)</th>
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<tr>
<td>All patients</td>
<td>5.7</td>
<td>6.0</td>
<td>0.96 (0.64-1.43)</td>
<td>0.09</td>
<td></td>
<td></td>
<td>18.0</td>
<td>27.5</td>
<td>0.62 (0.41-0.90); P=0.06</td>
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<td>0.31 (0.18-0.55); P=0.05</td>
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<tr>
<td>CD4+ count &lt; 50 cell/mm³</td>
<td>0.3</td>
<td>0.3</td>
<td>0.99 (0.46-1.76)</td>
<td>0.77</td>
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<tr>
<td>CD4+ count ≥ 50 cell/mm³</td>
<td>5.6</td>
<td>3.8</td>
<td>1.40 (0.55-4.19)</td>
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<td><strong>AIDS defining events/death</strong></td>
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<tr>
<td>All patients</td>
<td>6.9</td>
<td>7.1</td>
<td>0.99 (0.44-1.79)</td>
<td>0.77</td>
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<td>CD4+ count &lt; 50 cell/mm³</td>
<td>8.3</td>
<td>26.3</td>
<td>0.22 (0.01-1.31)</td>
<td>0.59</td>
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<tr>
<td>CD4+ count ≥ 50 cell/mm³</td>
<td>0.6</td>
<td>4.4</td>
<td>1.51 (0.61-3.96)</td>
<td>0.54</td>
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<td><strong>Ibbs</strong></td>
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<tr>
<td>Outcome</td>
<td>Early (Count rate/100p-y)</td>
<td>Late (Count rate/100p-y)</td>
<td>HR (95% CI), p value</td>
<td>Early (%)</td>
<td>Late (%)</td>
<td>95% CI for difference in prob, p value</td>
<td>Early (%)</td>
<td>Late (%)</td>
<td>Hazard Ratio (95% CI), p value</td>
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<td>Late (%)</td>
<td>Hazard Ratio (95% CI), p value</td>
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<tr>
<td>All patients</td>
<td>20.1</td>
<td>7.7</td>
<td>2.61 (1.40-4.53), p=0.001</td>
<td>10.6</td>
<td>4.7</td>
<td>p=0.002 (HR 3.56 per 100p-y)</td>
<td>8.1</td>
<td>5.5</td>
<td>2.51 (1.75-3.95), p=0.001</td>
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<td>-</td>
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<tr>
<td>CD4+ count &lt;500</td>
<td>46.8</td>
<td>9.8</td>
<td>4.71 (1.88-15.66), p=0.001</td>
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<tr>
<td>CD4+ count ≥500</td>
<td>15.8</td>
<td>7.2</td>
<td>2.18 (1.17-4.17), p=0.033</td>
<td>-</td>
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HR: hazard ratio

Data for all CD4 T cell count states ≤500 cells/mm³ were combined but no HR could be calculated as no person-time of follow-up was provided.
p-y: person-years
p: p-value
CHAPTER 4

TIMING OF INITIATION OF ANTIRETROVIRAL DRUGS DURING TUBERCULOSIS THERAPY


Timing of Initiation of Antiretroviral Drugs during Tuberculosis Therapy


BACKGROUND
The rates of death are high among patients with coinfection with tuberculosis and the human immunodeficiency virus (HIV). The optimal timing for the initiation of antiretroviral therapy in relation to tuberculosis therapy remains controversial.

METHODS
In an open-label, randomized, controlled trial in Durban, South Africa, we assigned 642 patients with both tuberculosis and HIV infection to start antiretroviral therapy either during tuberculosis therapy (in two integrated-therapy groups) or after the completion of such treatment (in one sequential-therapy group). The diagnosis of tuberculosis was based on a positive sputum smear for acid-fast bacilli. Only patients with HIV infection and a CD4+ cell count of less than 500 per cubic millimeter were included. All patients received standard tuberculosis therapy, prophylaxis with trimethoprim-sulfamethoxazole, and a once-daily antiretroviral regimen of didanosine, lamivudine, and efavirenz. The primary end point was death from any cause.

RESULTS
This analysis compares data from the sequential-therapy group and the combined integrated-therapy groups up to September 1, 2008, when the data and safety monitoring committee recommended that all patients receive integrated antiretroviral therapy. There was a reduction in the rate of death among the 429 patients in the combined integrated-therapy groups (5.4 deaths per 100 person-years, or 25 deaths), as compared with the 213 patients in the sequential-therapy group (12.1 per 100 person-years, or 27 deaths); a relative reduction of 56% (hazard ratio in the combined integrated-therapy groups, 0.44; 95% confidence interval, 0.25 to 0.79; P=0.008). Mortality was lower in the combined integrated-therapy groups in all CD4+ count strata. Rates of adverse events during follow-up were similar in the two study groups.

CONCLUSIONS
The initiation of antiretroviral therapy during tuberculosis therapy significantly improved survival and provides further impetus for the integration of tuberculosis and HIV services. (ClinicalTrials.gov number, NCT00398896.)
In 2007, it was estimated that there were about 33 million persons living with human immunodeficiency virus (HIV) infection\(^1\) and 9.2 million persons with newly diagnosed tuberculosis worldwide.\(^2\) The two diseases are closely intertwined, and the number of patients with coinfection continues to grow rapidly.\(^3\) Tuberculosis is the most common opportunistic disease\(^4\) and the most common cause of death in patients with HIV infection in developing countries.\(^5\) Notwithstanding effective tuberculosis chemotherapy, in the presence of HIV infection, tuberculosis is associated with substantially increased case fatality rates\(^6\) and is also the most commonly reported cause of death in South Africa.\(^7\) In 2007 in South Africa, an estimated 5.3 million people were infected with HIV and 341,165 with tuberculosis, of whom approximately 73% were coinfected with HIV.\(^8\)

The optimal timing for the initiation of antiretroviral therapy in patients with HIV and tuberculosis coinfection remains unclear. Current guidelines are based on observational studies and expert opinion.\(^9\) Despite World Health Organization (WHO) guidelines supporting concomitant treatment of the two diseases and urging more aggressive management,\(^10\) the initiation of antiretroviral therapy is often deferred until completion of tuberculosis therapy because of concern about potential drug interactions between rifampin and some classes of antiretroviral drugs,\(^11\) the immune reconstitution inflammatory syndrome,\(^12,13\) overlapping side effects,\(^14\) a high pill burden, and programmatic challenges.\(^15\) This study, called the Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPIT) trial, was designed to determine the optimal time to initiate antiretroviral therapy in patients with HIV and tuberculosis coinfection who were receiving tuberculosis therapy.

**METHODS**

**STUDY DESIGN**

The study was an open-label, randomized, controlled trial conducted at the eThekwini HIV-Tuberculosis clinic, which is operated by the Centre for the AIDS Programme of Research in South Africa (CAPRISA) in Durban, South Africa. This clinic adjoins one of the largest outpatient tuberculosis facilities in South Africa, the Prince Cyril Zulu Communicable Disease Centre.

Guidelines of the South African National Tuberculosis Control Programme stipulate that a first episode of tuberculosis be treated with a 2-month intensive combination-drug regimen of rifampin, isoniazid, ethambutol, and pyrazinamide, with doses determined according to pretreatment weight. Thereafter, patients receive a 4-month continuation regimen of isoniazid and rifampin. Patients with a history of tuberculosis receive a 3-month intensive regimen (including the addition of streptomycin for the first 2 months), followed by a 5-month continuation phase. In our study, patients were routinely offered therapy that was directly observed by clinic-based nurses. Some patients selected community-based supervisors, heads of households, and treatment supporters in workplaces who supervised and recorded the taking of medication.

**PATIENTS**

From June 28, 2005, to July 11, 2008, we recruited patients who were at least 18 years of age and who had confirmed HIV infection (on the basis of two rapid HIV tests) and a positive smear for tuberculosis acid-fast bacilli (with the use of auramine and Ziehl–Neelsen staining methods). Inclusion in the study required independent confirmation of positive tuberculosis status at the Department of Medical Microbiology at the Nelson R. Mandela School of Medicine, initiation of treatment with the standard tuberculosis regimen at the Communicable Disease Centre, a CD4+ cell count of less than 500 per cubic millimeter at screening, and an absence of clinical contraindications to the initiation of antiretroviral therapy. Female patients were required to agree to use contraception while receiving efavirenz.

**STUDY PROCEDURES**

After providing written informed consent, patients with confirmed HIV and tuberculosis coinfection were randomly assigned in a 1:1:1 ratio (with the use of sealed envelopes) to one of three study groups in permuted blocks of six or nine with no stratification. In the first group, antiretroviral therapy was to be initiated within 4 weeks after the start of tuberculosis therapy (early integrated-therapy group). In the second group, antiretroviral therapy was to be initiated within 4 weeks after the completion of the intensive phase of tuberculosis therapy (late integrated-therapy group). In the third group, antiretroviral therapy was to be initiated within 4 weeks after the completion of tuberculosis therapy (sequential-therapy group).
All patients received adherence counseling, prophylaxis with trimethoprim-sulfamethoxazole against HIV-related opportunistic infections, and the same once-daily three-drug antiretroviral therapy regimen, consisting of didanosine (250 mg for a body weight of <60 kg and 400 mg for a weight 60 kg), lamivudine (300 mg), and efavirenz (600 mg). Adherence to the antiretroviral regimen was assessed monthly according to pill counts (pills issued minus pills returned as a percentage of anticipated pill consumption). Regardless of the study-group assignment, patients could be started on antiretroviral therapy at any time by clinicians at the Communicable Disease Centre, by study clinicians, or by personal physicians at their discretion.

Follow-up visits for the monitoring of safety and clinical status were scheduled monthly for the first 24 months. Adverse events were graded with the use of the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 1.0, as recommended by the National Institute of Allergy and Infectious Diseases (December 28, 2004). Measurements of CD4+ cell counts with the use of flow cytometry (FACSCalibur, Becton Dickinson) and HIV RNA (Cobas Amplicor HIV-1 Monitor, version 1.5, Roche) were performed at the time of screening, at randomization, and every 6 months thereafter. Monitoring for radiologic changes and sputum conversion was performed at the time of screening, at the end of the intensive phase of tuberculosis therapy, 1 month before the end of tuberculosis therapy, and whenever clinically indicated.

END POINTS
The primary end point was death from any cause. Secondary end points included discontinuation because of side effects, toxic effects, HIV RNA levels, tuberculosis outcomes, and the occurrence of the immune reconstitution inflammatory syndrome. Discontinuation because of side effects was documented as study-initiated treatment interruptions in the pharmacy records. Toxic effects were assessed by means of a clinical checklist and standard laboratory tests for hematologic, hepatic, and renal abnormalities. The immune reconstitution inflammatory syndrome was defined as a paradoxical deterioration in clinical status or laboratory findings after the initiation of antiretroviral or antituberculosis therapy without another attributable cause.

INTERIM MONITORING
After a planned interim analysis, on September 1, 2008, almost 2 months after completion of enrollment, the data and safety monitoring committee recommended that all patients in the sequential-therapy group be started on antiretroviral therapy as soon as possible but continue in follow-up until study completion. The committee also recommended continuation of the two integrated-therapy groups with no changes. The patients in the sequential-therapy group were contacted within a week after the committee's meeting, and almost all of them started antiretroviral therapy within a month. We present data up to September 1, 2008, comparing the sequential-therapy group with the combined early and late integrated-therapy groups, which are hereafter referred to as the integrated-therapy group.

STUDY OVERSIGHT
The trial was approved by the Biomedical Research Ethics Committee at the University of KwaZulu-Natal and the South African government's Medicines Control Council.

STATISTICAL ANALYSIS
We estimated that we would need to enroll 649 patients (factoring in an anticipated loss to follow-up) in order to have a power of 80% and an alpha level of 0.05 to detect a 60% reduction in mortality on the basis of a predicted death rate of 10% in the study group with the worst outcome. All analyses were performed according to the intention-to-treat principle. The primary outcome was analyzed with the use of Kaplan-Meier curves and the log-rank test. The duration of time in the study was calculated as the time from randomization to death, withdrawal from the study, or the cutoff date of September 1, 2008, whichever occurred first. Poisson approximations were used to calculate confidence intervals for the rate of death. Proportional-hazards regression models were used to adjust for confounding variables. Fisher's exact test was used for the analysis of categorical data, and unpaired t-tests or the Wilcoxon two-sample test for the analysis of continuous data.

RESULTS

PATIENTS
A total of 642 patients with HIV and tuberculosis coinfection were enrolled: 429 in the combined
integrated-therapy group and 213 in the sequential-therapy group (Fig. 1). At baseline, patients in the two groups had similar demographic and clinical characteristics, including age, CD4+ cell counts, and HIV RNA levels (Table 1).

**Follow-up**

At the time of the data cutoff, on September 1, 2008, a total of 338 of the 642 patients (52.6%) were still in active follow-up, 52 (8.1%) had died during follow-up, 134 (20.9%) had completed follow-up, and 56 (8.7%) had withdrawn before study completion. Of the 62 patients (9.7%) who were regarded as lost to follow-up (9.6% in the integrated-therapy group and 9.9% in the sequential-therapy group), 35 were known to be alive, and the clinical status of the remaining 27 was unknown. (Patients were considered to be lost to follow-up if they went 4 months without a visit.) The median duration of follow-up in the trial was 12.1 months (interquartile range, 6.1 to 21.6).

**Initiation of Antiretroviral Therapy**

The median duration of tuberculosis therapy was similar among patients who completed such therapy: 210 days for 271 patients in the integrated-therapy group and 207 days for 137 patients in the sequential-therapy group. At the time of this analysis, 102 patients in the integrated-therapy group and 48 patients in the sequential-therapy group were still receiving tuberculosis therapy. Of the 350 patients in the integrated-therapy group who started antiretroviral therapy, 338 did so while they were receiving tuberculosis therapy. Patients in this group started antiretroviral therapy at a mean (±SD) of 70±72 days after the start of tuberculosis therapy. Of the 100 patients in the sequential-therapy group who started antiretroviral therapy, 7 did so while they were receiving tuberculosis therapy. In this group, antiretroviral therapy was initiated a mean of 260±71 days after the initiation of tuberculosis therapy. Thus, patients in the sequential-therapy group started antiretroviral therapy, on average, 190 days later than those in the integrated-therapy group.

**Primary End Point**

There were 25 deaths in the integrated-therapy group, for a death rate of 5.4 per 100 person-years, as compared with 27 deaths in the sequential-therapy group, for a death rate of 12.1 per 100 person-years (hazard ratio in the integrated-therapy group, 0.44; 95% confidence interval [CI], 0.25 to 0.79; P=0.003) (Table 2 and Fig. 2). After adjustment for baseline WHO status of HIV infection (stage 4 vs. stage 3), CD4+ cell count, age, sex, the presence or absence of a history of tuberculosis, the presence or absence of extrapulmonary tuberculosis, and baseline HIV RNA level, the hazard ratio was 0.43 (95% CI, 0.25 to 0.77; P=0.004).

Information on the 52 deaths was based on hospital chart notes for 28 patients, a death certificate for 1 patient, and two independent oral reports of death for 23 patients. On the basis of the chart notes and death certificate for 29 patients, causes of death in the integrated-therapy group were tuberculosis (including tuberculous meningitis) for 2 patients, respiratory distress or Pneumocystis jiroveci pneumonia for 6 patients, and metabolic acidosis, cardiomyopathy, and a motor-vehicle accident for 1 patient each; causes of death in the sequential-therapy group were tuberculosis (including tuberculous meningitis) for 6 patients, respiratory distress or P. jiroveci pneumonia for 3 patients, and non-tuberculous meningitis, gastroenteritis, renal failure, hepatic failure, and glioma for 1 patient each. The cause of death was unclear in the chart notes of four patients.

The baseline CD4+ cell count independently predicted mortality in the two study groups. Mortality was lower in the integrated-therapy group in all CD4+ count strata (Table 2). The median baseline CD4+ count was similar in the two study groups. There was no interaction between the CD4+ count and the study groups (P=0.57).

**Treatment Outcomes**

The rate of adherence to antiretroviral therapy according to pill counts was 92.2% in the integrated-therapy group and 97.6% in the sequential-therapy group. Outcomes with respect to tuberculosis therapy were similar in the two study groups, regardless of whether patients were receiving first-episode therapy or repeated therapy (Table 3). At 12 months after randomization, the proportion of patients with a suppressed HIV RNA level was higher in the integrated-therapy group than in the sequential-therapy group (90.0% vs. 77.8%; P=0.006). However, the proportion of patients with a suppressed HIV RNA level 6 months after the initiation of antiretroviral therapy was similar in the two groups (Table 4).

**Adverse Events**

The immune reconstitution inflammatory syndrome was diagnosed in 53 of 429 patients (12.4%);
Figure 1. Enrollment and Outcomes.
Table 1. Baseline Characteristics of the Patients. 

<table>
<thead>
<tr>
<th>Variable</th>
<th>Integrated Therapy (N=429)</th>
<th>Sequential Therapy (N=213)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>34.4±8.38</td>
<td>33.9±8.18</td>
<td>0.48</td>
</tr>
<tr>
<td>Range</td>
<td>19–72</td>
<td>19–60</td>
<td></td>
</tr>
<tr>
<td>Male sex — %</td>
<td>48.7</td>
<td>52.1</td>
<td>0.45</td>
</tr>
<tr>
<td>Educational level — no./total no. (%)</td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Primary school or less</td>
<td>92/427 (21.5)</td>
<td>48 (22.5)</td>
<td></td>
</tr>
<tr>
<td>Some secondary school</td>
<td>205/427 (48.0)</td>
<td>80 (37.6)</td>
<td></td>
</tr>
<tr>
<td>Completed secondary school</td>
<td>130/427 (30.4)</td>
<td>85 (39.9)</td>
<td></td>
</tr>
<tr>
<td>Employed — no./total no. (%)</td>
<td>251/428 (58.6)</td>
<td>116 (54.5)</td>
<td>0.35</td>
</tr>
<tr>
<td>History of tuberculosis — no. (%)</td>
<td>144 (33.6)</td>
<td>64 (30.0)</td>
<td>0.42</td>
</tr>
<tr>
<td>Karnofsky score — no./total no. (%)</td>
<td></td>
<td></td>
<td>0.44</td>
</tr>
<tr>
<td>90 or 100</td>
<td>251/425 (59.1)</td>
<td>132/209 (63.2)</td>
<td></td>
</tr>
<tr>
<td>70 or 80</td>
<td>165/425 (38.8)</td>
<td>75/209 (35.9)</td>
<td></td>
</tr>
<tr>
<td>&lt;70</td>
<td>9/425 (2.1)</td>
<td>2/209 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Median CD4+ count (interquartile range) — cells/mm³†</td>
<td>150 (77–254)</td>
<td>140 (69–247)</td>
<td>0.32</td>
</tr>
<tr>
<td>Median log viral load (interquartile range) — copies/ml‡</td>
<td>3.2 (4.5–5.6)</td>
<td>5.2 (4.7–5.6)</td>
<td>0.22</td>
</tr>
<tr>
<td>WHO stage 4 HIV infection — no. (%)‡‡</td>
<td>21 (4.9)</td>
<td>10 (4.7)</td>
<td>1.00</td>
</tr>
<tr>
<td>Presence of extrapulmonary tuberculosis — no. (%)</td>
<td>24 (5.6)</td>
<td>10 (4.7)</td>
<td>0.71</td>
</tr>
<tr>
<td>Median no. of days of tuberculosis therapy at randomization (interquartile range)</td>
<td>9 (1–14)</td>
<td>9 (7–16)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

† Patients underwent randomization on the basis of the CD4+ count at screening (criterion for study enrollment, <300 cells per cubic millimeter). However, for 16 patients, the CD4+ count at enrollment was more than 500 cells per cubic millimeter.
‡ The viral load at baseline was measured in 397 patients in the integrated-therapy group and in 201 patients in the sequential-therapy group.
‡‡ The remainder of patients had stage 3 infection, according to criteria of the World Health Organization (WHO).

95% CI, 9.5 to 15.9, in the integrated-therapy group and in 8 of 213 patients (3.8%; 95% CI, 1.8 to 7.5) in the sequential-therapy group (P<0.001). Six patients required the use of corticosteroids (five in the integrated-therapy group and one in the sequential-therapy group). No changes in the antiretroviral regimen were needed because of immune-reconstitution events. None of the deaths were determined to be related to the immune reconstitution inflammatory syndrome. Among grade 3 or 4 adverse events that were not regarded as immune reconstitution, 140 occurred in the integrated-therapy group (30 per 100 person-years) and 71 in the sequential-therapy group (32 per 100 person-years) (P=0.09) (see the table in the Supplementary Appendix, available with the full text of this article at NEJM.org).

DISCUSSION

This trial showed that the initiation of antiretroviral therapy during tuberculosis therapy in patients with confirmed tuberculosis and HIV co-infection reduced mortality by 56% (95% CI, 21 to 75). The death rate rose from 5.4 per 100 person-years to 12.1 per 100 person-years when initiation of antiretroviral therapy was delayed until the completion of tuberculosis therapy. The interval between the completion of tuberculosis therapy and the initiation of antiretroviral therapy is important; a considerable number of deaths in the sequential-therapy group occurred during this time (Fig. 2). Once antiretroviral therapy was initiated, however, it was associated with similarly high levels of viral suppression in the two study
groups, findings that are similar to those observed in other HIV treatment programs in South Africa.\textsuperscript{13}

Mortality among patients with HIV and tuberculosis coinfection is known to be high despite the use of effective tuberculosis therapy.\textsuperscript{7} Observational studies have indicated that the initiation of antiretroviral therapy during tuberculosis therapy improves treatment outcomes in such patients. A meta-analysis of studies involving 6934 patients at five hospitals in Madrid showed a significant improvement in survival (63\% increase) among patients who began antiretroviral therapy while they were receiving tuberculosis therapy.\textsuperscript{18} In Thailand, an analysis of 1003 patients showed an increase by a factor of 20 in the rate of death among patients who did not receive simultaneous antiretroviral and tuberculosis therapies, as compared with those who did receive the two therapies.\textsuperscript{19} A Thai review of studies involving 626 patients showed a hazard ratio for death of 0.17 for patients who started antiretroviral therapy during tuberculosis treatment, as compared with patients who did not receive antiretroviral therapy.\textsuperscript{20} Although the selection of patients for integrated treatment by clinicians may have led to bias in these studies, the trials show a consistent association between antiretroviral therapy and survival in coinfected patients. The randomized design of our trial validates and extends the findings from these retrospective observational data.

Among patients with CD4\(^+\) counts of less than 200 cells per cubic millimeter, the rate of death was 46\% lower in the integrated-therapy group than in the sequential-therapy group (P=0.04). Although the number of deaths was small in the subgroup of patients who had CD4\(^+\) counts between 200 and 500 cells per cubic millimeter, there was a trend toward lower mortality in the
Table 3. Clinical Outcomes of Tuberculosis Therapy.\(^a\)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Integrated Therapy (N=345)</th>
<th>Sequential Therapy (N=171)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Repeated Therapy of Tuberculosis (N=116)</td>
<td>First Episode of Tuberculosis (N=227)</td>
<td>Repeated Therapy of Tuberculosis (N=58)</td>
</tr>
<tr>
<td>Tuberculosis cure(^c)</td>
<td>67 (37.8)</td>
<td>131 (57.7)</td>
<td>31 (53.4)</td>
</tr>
<tr>
<td>Successful completion(^d)</td>
<td>16 (13.8)</td>
<td>42 (18.5)</td>
<td>5 (8.6)</td>
</tr>
<tr>
<td>Therapy success (cure plus successful completion)</td>
<td>83 (71.6)</td>
<td>173 (76.2)</td>
<td>36 (62.1)</td>
</tr>
<tr>
<td>Died before completion of therapy</td>
<td>3 (2.7)</td>
<td>12 (5.3)</td>
<td>3 (5.2)</td>
</tr>
<tr>
<td>Therapy interruption</td>
<td>3 (2.7)</td>
<td>12 (5.3)</td>
<td>3 (5.2)</td>
</tr>
<tr>
<td>Therapy failure(^f)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>13 (11.2)</td>
<td>13 (5.7)</td>
<td>6 (10.3)</td>
</tr>
<tr>
<td>Therapy outcome unknown because of transfer to another clinic</td>
<td>1 (0.9)</td>
<td>5 (2.2)</td>
<td>2 (3.4)</td>
</tr>
<tr>
<td>Other outcome</td>
<td>1 (0.9)</td>
<td>1 (0.4)</td>
<td>0</td>
</tr>
<tr>
<td>Outcome pending (still receiving therapy at time of analysis)</td>
<td>9 (7.8)</td>
<td>20 (8.8)</td>
<td>1 (1.6)</td>
</tr>
</tbody>
</table>

\(^a\) Only patients who were enrolled in the study at least 7 months before the date of the analysis are included. Percentages may not total 100% because of rounding.

\(^c\) Tuberculosis cure was defined as a sputum smear that was negative for acid-fast bacilli close to the time of therapy completion.

\(^d\) Successful completion of therapy was defined as the use of more than 85% of the prescribed medication.

\(^f\) Therapy failure was defined as the presence of a positive smear or culture for Mycobacterium tuberculosis obtained at least 5 months after the initiation of tuberculosis therapy.

integrated-therapy group. This finding has implications for treatment guidelines and policies. Current WHO guidelines for the treatment of patients with HIV and tuberculosis coinfection recommend the deferment of antiretroviral therapy until the completion of tuberculosis therapy in patients with WHO stage 3 HIV infection and CD4+ counts of more than 200 cells per cubic millimeter.\(^3,5,10\) Our findings suggest that this guideline should be expanded to include cotreatment of HIV infection and tuberculosis in patients with CD4+ counts of less than 500 cells per cubic millimeter.

There is increasing evidence that even among patients with HIV infection who do not have tuberculosis, earlier initiation of antiretroviral therapy is associated with improved outcomes.\(^10,12,23\) In a study involving 9562 asymptomatic patients with HIV infection in the United States and Canada,\(^22\) mortality was 69% lower among patients in whom antiretroviral therapy was initiated when the CD4+ count was between 350 and 500 cells per cubic millimeter than in those in whom such therapy was deferred until the CD4+ count was less than 350 cells per cubic millimeter. Similarly, data from 18 prospective cohort studies have shown that deferring antiretroviral therapy was associated with higher rates of the acquired immunodeficiency syndrome (AIDS) and death than starting therapy when the CD4+ count was more than 350 cells per cubic millimeter.\(^23\)

However, there are major concerns regarding the early initiation of antiretroviral therapy during tuberculosis treatment, including the increased risk of the immune reconstitution inflammatory syndrome, additive toxic effects, and the potential adverse effect on outcomes of tuberculosis therapy. We found similar rates of grade 3 and 4 adverse events in the two study groups and similar outcomes of tuberculosis therapy. Since many of the deaths occurred after the completion of tuberculosis therapy, the providers of such therapy were unaware of the benefits of coterapy of tuberculosis and HIV infection. Although the incidence of immune-reconstitution events was significantly higher in the integrated-therapy group, this finding was not unexpected, since such events have been associated with the early initiation of antiretroviral therapy in patients with tuberculosis.\(^24,25\) The incidence of such events in the integrated-therapy group was similar to that observed in studies of other cohorts.
Table 4. Clinical Outcomes of HIV Therapy.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Integrated Therapy</th>
<th>Sequential Therapy</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viral load &lt;400 copies/ml</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 12 mo after randomization</td>
<td>199/221</td>
<td>70/90</td>
<td>0.006</td>
</tr>
<tr>
<td>No./total no.</td>
<td>90.0 (85.1–93.5)</td>
<td>77.6 (67.6–85.6)</td>
<td></td>
</tr>
<tr>
<td>Percent (95% CI)</td>
<td>174/191</td>
<td>39/45</td>
<td>0.40</td>
</tr>
<tr>
<td>Mean increase in CD4+ count from baseline</td>
<td>207</td>
<td>148.7 (105.5–169.9)</td>
<td>100.7 (77.5–124.8)</td>
</tr>
<tr>
<td>At 12 mo after randomization</td>
<td>84</td>
<td>14.2 (105.4–143.3)</td>
<td>116.3 (88.0 to 144.6)</td>
</tr>
<tr>
<td>No. of patients</td>
<td>124</td>
<td>116.3 (88.0 to 144.6)</td>
<td>100.7 (77.5–124.8)</td>
</tr>
<tr>
<td>No. of cells/mm³ (95% CI)</td>
<td>187</td>
<td>41</td>
<td>0.21</td>
</tr>
</tbody>
</table>

in developing countries, including a retrospective analysis of hospitalized Thai patients receiving both antiretroviral and tuberculosis therapies, which showed that 21 of 167 patients (12.5%) had an immune-reconstitution event. Furthermore, none of the deaths in our trial, in which data regarding the cause of death were available, were considered attributable to the immune reconstitution inflammatory syndrome. It is reassuring that recent studies of tuberculosis-associated immune reconstitution inflammatory syndrome indicate that this complication is rare and that severe episodes can be successfully managed with corticosteroids. Thus, the concern about increasing the likelihood of such episodes must be tempered by the survival benefit shown in our study. Nevertheless, the paradoxical deterioration in the clinical status is sufficiently common to warrant close clinical monitoring in the first few months after the initiation of antiretroviral therapy in patients coinfected with tuberculosis. We acknowledge several limitations of our study. The use of death from any cause as the primary end point might underestimate the potential effect of integrated HIV–tuberculosis treatment on the rates of death specifically from tuberculosis or HIV infection. Since we were not able to obtain reliable information on the causes of all deaths in the trial, we were not able to estimate the effect on the rate of deaths that were related only to tuberculosis or HIV infection. Since our trial included only patients who had a positive sputum smear for acid-fast bacilli and whose disease was diagnosed and treated in an outpatient tuberculosis clinic, the results may not be directly generalizable to all forms and severity levels of tuberculosis. Since a retrospective analysis of 549 patients with AIDS and extrapulmonary tuberculosis showed that the introduction of highly active antiretroviral therapy significantly improved survival, the early initiation of antiretroviral therapy may have similar benefits in patients with extrapulmonary tuberculosis. Although we have no reason to believe that our findings do not apply to sputum-smear-negative tuberculosis, our findings require empirical confirmation in this group. It should be noted that the judgment of study and nonstudy care providers took precedence over protocol-defined timing of the initiation of antiretroviral therapy, which led to early initiation of such therapy in some patients in the sequential-therapy group and delayed initiation in some patients in the integrated-therapy group. Another limitation was the delay in the initiation of antiretroviral therapy after the completion of tuberculosis therapy in the sequential-therapy group because of clinical issues (e.g., elevated levels of liver enzymes) or missed visits. Furthermore, the question of when antiretroviral therapy should be initiated during tuberculosis therapy awaits completion of the study.

In summary, our findings provide compelling...
Evidence of the benefit of initiating antiretroviral therapy during tuberculosis therapy in patients with HIV coinfected. The findings also support recommendations by the WHO and others for the integration of tuberculosis and HIV care.

Supported by the U.S. President’s Emergency Plan for AIDS Relief for the care of patients, the Global Fund to Fight AIDS, Tuberculosis and Malaria for drugs used in the trial, and the Comprehensive International Program of Research on AIDS for the research infrastructure (including data management and laboratory and pharmacy facilities) to conduct the trial.

An overview of the results was presented at the 16th Conference on Retroviruses and Opportunistic Infections, Montreal, February 9, 2009.

Dr. S. Abdul Karim reports being listed as a co-investigator on two patents (08003457 and PC17802604590) that are part of the development of clade C HIV vaccines, and Mr. Gray receiving lecture fees from AstraZeneca, Aspen Pharmacare, and Prin- naxa Kids. No other potential conflict of interest relevant to this article was reported.

We thank the patients for their participation in this study.

Professor Willem Steyn of the Nelson R. Mandela School of Medicine for the confirmatory tuberculosis testing; Drs. Surir Chinnappa and Sr. Jeanne Lieberman of the Prince Cyril Zaki Communicable Disease Centre; Drs. Gray Hendey, Ed Tramont, Kidd Hoff, Sandi Lehrman, and Richard Hafer of the Division of AIDS at the National Institutes of Health; Drs. Gavin Chamberyard, Douglas Taylor, and Mark Weaver for serving on the data and safety monitoring committee; Ms. Anushka Naidoo for serving as the on-site study pharmacist; members of the Community Advisory Board; Ms. Neelam Narang of the CAPRISA Community Programme; Ms. Natsuka Samander and Mr. Keith Coeter for laboratory analysis; Ms. Nandishla Vedie for statistical support; Ms. Lene Delden for data management; and all the other members of the study team.

REFERENCES


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CHAPTER 5

INTEGRATION OF ANTIRETROVIRAL THERAPY WITH TUBERCULOSIS TREATMENT


Integration of Antiretroviral Therapy with Tuberculosis Treatment


ABSTRACT

BACKGROUND
We previously reported that integrating antiretroviral therapy (ART) with tuberculosis treatment reduces mortality. However, the timing for the initiation of ART during tuberculosis treatment remains unresolved.

METHODS
We conducted a three-group, open-label, randomized, controlled trial in South Africa involving 642 ambulatory patients, all with tuberculosis (confirmed by a positive spum smear for acid-fast bacillus), human immunodeficiency virus infection, and a CD4+ T-cell count of less than 500 per cubic millimeter. Findings in the earlier-ART group (ART initiated within 4 weeks after the start of tuberculosis treatment, 214 patients) and later-ART group (ART initiated during the first 4 weeks of the continuation phase of tuberculosis treatment, 215 patients) are presented here.

RESULTS
At baseline, the median CD4+ T-cell count was 150 per cubic millimeter, and the median viral load was 161,000 copies per milliliter, with no significant differences between the two groups. The incidence rate of the acquired immunodeficiency syndrome (AIDS) or death was 6.9 cases per 100 person-years in the earlier-ART group (18 cases) as compared with 78 per 100 person-years in the later-ART group (10 cases) (incidence-rate ratio, 0.89; 95% confidence interval [CI], 0.44 to 1.79; P = 0.73). However, among patients with CD4+ T-cell counts of less than 50 per cubic millimeter, the incidence rates of AIDS or death were 8.3 and 26.3 cases per 100 person-years, respectively (incidence-rate ratio, 0.32; 95% CI, 0.07 to 1.19; P = 0.06). The incidence rates of the immune reconstitution inflammatory syndrome (IRIS) were 20.1 and 77 cases per 100 person-years, respectively (incidence-rate ratio, 2.62; 95% CI, 1.48 to 4.82; P < 0.001). Adverse events requiring a switching of antiretroviral drugs occurred in 10 patients in the earlier-ART group and 1 patient in the later-ART group (P = 0.006).

CONCLUSIONS
Early initiation of ART in patients with CD4+ T-cell counts of less than 50 per cubic millimeter increased AIDS-free survival. Deferral of the initiation of ART to the first 4 weeks of the continuation phase of tuberculosis therapy in those with higher CD4+ T-cell counts reduced the risks of IRIS and other adverse events related to ART without increasing the risk of AIDS or death. (Funded by the U.S. President's Emergency Plan for AIDS Relief and others; SAPIT ClinicalTrials.gov number, NCT00398996.)
IN PATIENTS WHO HAVE INFECTION WITH the human immunodeficiency virus (HIV) and tuberculosis, antiretroviral therapy (ART) may be initiated at the same time as or soon after the initiation of tuberculosis treatment. However, antiretroviral agents are often deferred until after the intensive phase of tuberculosis treatment because of concern about the immune reconstitution inflammatory syndrome (IRIS), a high pill burden, and overlapping side effects when three antiretroviral agents are added to the standard four antituberculosis drugs. These challenges may result in interruption or discontinuation of treatment for the acquired immunodeficiency syndrome (AIDS) or tuberculosis, which can lead to drug resistance and potentially limit future therapeutic options, but the disadvantages must be weighed against the risk of increased mortality early in the treatment of tuberculosis.

The Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPIT) trial was designed to determine the clinical consequences of the time to the start of ART in patients with HIV infection and tuberculosis. We previously reported that integrating ART with tuberculosis treatment reduces mortality. Here, we report on the initiation of ART at two points during tuberculosis treatment.

METHODS

STUDY DESIGN, PATIENTS, AND PROCEDURES
We conducted a prospective, open-label, randomized trial in South Africa. A total of 642 ambulatory patients with both pulmonary tuberculosis and HIV infection, 18 years of age or older, were enrolled after providing written informed consent. The diagnosis of pulmonary tuberculosis was confirmed by a positive sputum smear for acid-fast bacilli. HIV infection was confirmed by two rapid screening tests for HIV. All patients had a CD4+ T-cell count of less than 500 per cubic millimeter at screening and were started on a standard tuberculosis treatment regimen. All patients with a first episode of tuberculosis were treated with a fixed combination of rifampin, isoniazid, ethambutol, and pyrazinamide, with doses determined according to pretreatment weight, for 2 months (intensive phase) and a subsequent fixed combination of isoniazid and rifampicin for 4 months (continuation phase). Patients who had previously received treatment for tuberculosis received a 60-day intensive regimen that included streptomycin, followed by a 100-day continuation regimen.

The once-daily ART regimen consisted of entecavir-coated didanosine (250 mg if the patient’s weight was ≤60 kg, and 400 mg if the weight was ≥60 kg), lamivudine (300 mg), and efavirenz (600 mg). Adherence to ART was assessed monthly by means of pill counts. Notwithstanding the study-group assignments, patients could be started on ART at any time at the discretion of the study clinicians or the patients’ primary care physicians. Details of the study design and procedures have been described previously and are provided in the protocol and Supplementary Appendix, available with the full text of this article at NEJM.org.

The outcome of the sequential-therapy group (ART initiated after the completion of tuberculosis treatment) has been reported previously. The analysis reported here includes complete follow-up data on the 214 patients in the early-integrated-therapy group (ART initiated within 4 weeks after the start of tuberculosis treatment) and the 215 patients in the late-integrated-therapy group (ART initiated within 4 weeks after completion of the intensive phase of tuberculosis treatment).

STUDY OVERSIGHT
The trial was approved by the Biomedical Research Ethics Committee at the University of KwaZulu-Natal and by the Medicines Control Council of the South African government. Study data were reviewed periodically by a data and safety monitoring committee. All authors vouch for the completeness and accuracy of the data and analyses presented.

STATISTICAL ANALYSIS
All analyses were performed in the intention-to-treat population. The primary outcome, the incidence rate of AIDS or death, was analyzed with the use of Kaplan–Meier curves. The duration of time in the study was calculated as the time from randomization to death or AIDS-defining illness, withdrawal from the study, or 18 months after randomization, whichever occurred first. Poisson approximations were used to calculate confidence intervals for the incidence-rate ratios. Cox proportional-hazards regression was used to adjust for confounding variables. Fisher’s exact test was used for the analysis of categorical data, and unpaired t-tests or the Wilcoxon two-sample test was used.
for the analysis of continuous data. Interactions between therapy group and CD4+ T-cell count were evaluated by fitting a proportional-hazards model with therapy group, CD4+ T-cell count, and the interaction between therapy group and CD4+ T-cell count.

RESULTS

STUDY PARTICIPANTS
A total of 429 patients were enrolled in the two integrated-therapy groups. 214 were randomly assigned to receive early integrated therapy (hereafter referred to as the earlier-ART group), and 215 were assigned to receive late integrated therapy (hereafter referred to as the later-ART group). At baseline, the two groups had similar demographic and clinical characteristics (Table 1). The median CD4+ T-cell count was 150 per cubic millimeter, and the median viral load was 161,000 copies per milliliter. The median duration of follow-up in the trial was 17.7 months (interquartile range, 14.0 to 17.8). At study completion, the retention rates were 76.9% and 71.5% in the earlier-ART and later-ART groups, respectively (information on retention and causes of death is provided in the Supplementary Appendix).

INITIATION OF ART
Among patients who completed tuberculosis therapy, the median treatment duration was 210 days in the earlier-ART group (207 participants) and 205 days in the later-ART group (210 participants). A total of 92.5% of the patients in the earlier-ART group (198 of 214) and 76.3% in the later-ART group (164 of 215) started ART during the study (P<0.001). The longer period from randomization to the initiation of ART in the later-ART group meant that more patients in this group were lost to follow-up, withdrew, or died before the start of ART, as compared with the earlier-ART group (Fig. 1). However, there were no significant differences between the earlier-ART and later-ART groups in the overall rates of loss to follow-up (12.1% [26 of 214] and 15.8% [34 of 215], P=0.33) and withdrawal (0.3% [2 of 214] and 10.7% [23 of 215], P=0.75).

The 198 patients in the earlier-ART group who started ART did so at a median of 21 days (interquartile range, 15 to 29) after the initiation of tuberculosis therapy. Of the 31 patients who started ART after the 4-week window, 9 missed the study-clinic visit for the initiation of ART, 8 had abnormal liver function, 2 had other laboratory abnormalities, 4 declined ART, and 10 had clinical conditions that precluded ART initiation.

The 164 patients in the later-ART group who started ART did so at a median of 97 days (interquartile range, 77 to 126) after the initiation of tuberculosis therapy. One patient started ART during the intensive phase of tuberculosis treatment. Of the 47 patients who started ART more than 4 weeks after completion of the intensive phase of tuberculosis treatment, 29 missed the study-clinic visit for the initiation of ART, 1 had abnormal liver function, 6 declined ART, and 11 had clinical conditions that precluded ART initiation.

INCIDENCE RATES OF AIDS OR DEATH
The incidence rate of AIDS or death was 6.9 cases per 100 person-years in the earlier-ART group (38 cases as compared with 7.8 per 100 person-years in the later-ART group [19 cases] incidence-rate ratio, 0.88; 95% confidence interval [CI], 0.44 to 1.79; P=0.73). After adjustment for baseline World Health Organization (WHO) disease stage (4 vs. stage 3), age, sex, history of tuberculosis (yes or no), presence or absence of extrapulmonary tuberculosis, and baseline CD4+ T-cell count and HIV RNA level, the hazard ratio with earlier ART was 0.86 (95% CI, 0.42 to 1.85; P=0.72). The probability of observing 18 AIDS cases or deaths in the earlier-ART group and 10 cases in the later-ART group was 5.6%, 1.5%, and 0.4%, if the true difference in AIDS cases or deaths between the groups was 40%, 50%, and 60%, respectively. In a sensitivity analysis in which all participants lost to follow-up were classified as having died, the incidence was 170 cases per 100 person-years (95% CI, 12.3 to 22.8) in the earlier-ART group and 21.7 per 100 person years (95% CI, 16.3 to 28.4) in the later-ART group (incidence-rate ratio, 0.78; 95% CI, 0.51 to 1.19; P=0.23).

INCIDENCE RATES OF AIDS OR DEATH ACCORDING TO CD4+ T-CELL COUNT
A significant interaction between therapy group and CD4+ T-cell count was observed for AIDS or death (P=0.03), indicating heterogeneity across the two CD4+ strata in the effect of time to initiation of ART on the incidence of AIDS or death. The incidence rates of AIDS or death among the 72 patients with CD4+ T-cell counts of less than 50 per cubic millimeter were 8.5 cases per 100 person-years (95% CI, 2.3 to 21.9) in the earlier-ART group as compared with 26.3 per 100 person-years (95% CI, 12.6 to 48.4) in the later-ART group (incidence-rate ratio, 3.2; 95% CI, 0.07 to 1.13; P=0.06) (Table 2).
Table 1. Baseline Characteristics of the Patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Earlier ART (N=214)</th>
<th>Later ART (N=215)</th>
<th>Total (N=429)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td></td>
<td></td>
<td></td>
<td>0.75</td>
</tr>
<tr>
<td>Mean</td>
<td>34.3±8.0</td>
<td>34.5±8.7</td>
<td>34.4±8.4</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>19–63</td>
<td>21–72</td>
<td>19–72</td>
<td></td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>97 (45.3)</td>
<td>112 (52.1)</td>
<td>209 (48.7)</td>
<td>0.18</td>
</tr>
<tr>
<td>Educational level — no. (%)†</td>
<td></td>
<td></td>
<td></td>
<td>0.23</td>
</tr>
<tr>
<td>Primary school or less</td>
<td>43 (20.2)</td>
<td>49 (22.9)</td>
<td>92 (21.5)</td>
<td></td>
</tr>
<tr>
<td>Some secondary school</td>
<td>97 (45.5)</td>
<td>108 (50.5)</td>
<td>205 (48.0)</td>
<td></td>
</tr>
<tr>
<td>Completed secondary school</td>
<td>73 (34.3)</td>
<td>57 (26.6)</td>
<td>130 (30.4)</td>
<td></td>
</tr>
<tr>
<td>Employed — no. (%)</td>
<td>135 (63.1)</td>
<td>117 (54.4)</td>
<td>252 (58.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>History of tuberculosis — no. (%)‡</td>
<td>80 (37.4)</td>
<td>68 (31.6)</td>
<td>148 (34.5)</td>
<td>0.22</td>
</tr>
<tr>
<td>Karnofsky performance score — no. (%)</td>
<td>$\leq$ 80 or 100</td>
<td>123 (57.5)</td>
<td>128 (59.5)</td>
<td>251 (58.5)</td>
</tr>
<tr>
<td>WHO stage 4 HIV infection — no. (%)³</td>
<td>80 (37.4)</td>
<td>68 (31.6)</td>
<td>148 (34.5)</td>
<td></td>
</tr>
<tr>
<td>Resistance to tuberculosis drugs — no. (%)</td>
<td>10 (4.7)</td>
<td>9 (4.2)</td>
<td>19 (4.4)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

| Variable                              |                     |                   |               |         |
| Isoniazid                             | 12 (5.6)            | 5 (2.3)           | 17 (3.9)      | 0.08    |
| Rifampin                              | 8 (3.7)             | 4 (1.9)           | 12 (2.7)      | 0.17    |
| Ethambutol                            | 1 (0.5)             | 0 (0.0)           | 1 (0.2)       | 1.00    |
| Multiple drug resistance              | 6 (2.8)             | 3 (1.4)           | 9 (2.1)       | 0.50    |
| CD4+ T-cell count — cells/mm³¶       | 114                  | 149                | 150           | 0.93    |
| Median                                | 75–261              | 77–244            | 77–254        | 0.53    |
| Viral load — log₁₀ copies/ml         | 5.1                  | 5.2                | 5.2           |         |
| Median                                | 4.5–5.6             | 4.5–5.6            | 4.5–5.6       |         |
| No. of days of tuberculosis therapy at randomization | 9                    | 9                  | 9             | 0.49    |

* Plus–minus values are means ±SD.
† Data on educational level were not available for one patient in each group.
‡ The Karnofsky performance score is a measure of the patient’s general condition and degree of autonomy on a scale ranging from 0 to 100, with lower numbers indicating poorer function.
§ Patients underwent randomization on the basis of the CD4+ T-cell count at screening (criterion for study enrollment, $<500$ per cubic millimeter). However, for 16 patients, the CD4+ T-cell count at enrollment was 500 per cubic millimeter or higher.
∥ Data on the viral load at baseline were not available for 16 patients in each group.

and Fig. 2. Among the 357 patients with baseline CD4+ T-cell counts of 50 per cubic millimeter or higher, the incidence rates of AIDS or death were 6.6 cases per 100 person-years (95% CI, 3.6 to 11.0) and 4.4 per 100 person-years (95% CI, 2.6 to 8.3) in the earlier-ART and later-ART groups, respectively (incidence-rate ratio, 1.51; 95% CI, 0.61 to 3.95; P=0.34).

IRIS

Among patients with a CD4+ T-cell count of less than 50 per cubic millimeter, the incidence of IRIS was 4.7 times as high in the earlier-ART group as in the later-ART group (P=0.01) (Table 2). Among patients with a CD4+ T-cell count of 50 per cubic millimeter or higher, the incidence of IRIS was 2.2 times as high in the earlier-ART group as in the
Figure 1. Enrollment and Outcomes.
Loss to follow-up was defined as no visit during the previous 4 months: ART denotes antiretroviral therapy.
ADHERENCE TO THERAPY AND SWITCHING OF DRUGS

Nineteen patients in each of the two study groups were considered to have defaulted tuberculosis therapy (8.9% and 8.8% in the earlier-ART and later-ART groups, respectively), either if they chose to interrupt therapy or if they did not attend the clinic for any further scheduled study visits before treatment completion. According to monthly pill counts, patients in the earlier-ART and later-ART groups took 98.0% and 98.8% of their assigned antiretroviral tablets, respectively, during the trial.

Ten patients in the earlier-ART group and one patient in the later-ART group needed to switch antiretroviral drugs because of adverse events (P=0.006). Among patients with CD4+ T-cell counts of 50 per cubic millimeter or higher, seven patients in the earlier-ART group and one patient in the later-ART group switched antiretroviral drugs (P=0.04).

A total of 15 patients (6 in the earlier-ART group and 9 in the later-ART group) changed their ART regimens because of virologic failure (defined as a viral load >1000 copies per milliliter on two occasions at least 4 weeks apart). The instances of drug switching occurred an average of 9.6 months (95% CI, 5.9 to 12.2) and 11.9 months (95% CI, 9.1 to 14.6) after the initiation of ART in the earlier-ART and later-ART groups, respectively (P=0.18).

OUTCOMES OF TUBERCULOSIS AND HIV TREATMENT

There was no significant difference between the study groups in resistance to tuberculosis drugs at baseline (Table 1). Outcomes of tuberculosis treatment did not differ significantly between the groups (Table 3, and Table 2 in the Supplementary Appendix); this finding did not change after adjustment for the presence or absence of multidrug resistance. At 6 and 12 months after randomization, the proportions of participants with a suppressed HIV RNA level did not differ significantly between the earlier-ART and later-ART groups (P=0.15).
the earlier-ART and later-ART groups. However, the mean increases from baseline in the CD4+ T-cell count at 12 and 18 months were significantly higher in the earlier-ART group than in the later-ART group (Table 4).

ADVERSE EVENTS
Grade 3 or 4 non-IRIS adverse events occurred in 112 patients in the earlier-ART group and in 107 patients in the later-ART group (42.8 and 42.6 events per 100 person-years, respectively; P=0.98); serious adverse events occurred in 56 and 50 patients in the respective groups. Table 3 in the Supplementary Appendix provides details of the adverse events.

DISCUSSION
Overall, the rates of AIDS or death did not differ significantly between the patients who received early integrated ART and those who received late integrated ART, but the earlier-ART group had higher rates of IRIS and switching of antiretroviral drugs because of adverse events. However, the findings in severely immunocompromised patients differed. In the subgroup of patients with CD4+ T-cell counts of less than 50 per cubic millimeter, earlier ART was associated with a rate of AIDS or death that was about two thirds lower than the rate with later ART; this benefit outweighs the significantly higher rates of IRIS (incidence-rate ratio, 4.7) and of switching of antiretroviral drugs associated with earlier ART. For patients with CD4+ T-cell counts of less than 50 per cubic millimeter, our findings support the 2009 WHO recommendation8 to start ART as soon as possible after the initiation of tuberculosis treatment.

Our findings suggest a different approach for patients with tuberculosis and HIV who have a CD4+ T-cell count of 50 per cubic millimeter or higher. The initiation of ART during the first 4 weeks of the continuation phase of tuberculosis treatment versus initiation during the first 4 weeks of the intensive phase of tuberculosis treatment was not associated with an increased risk of AIDS or death but was associated with about half the risk of IRIS and a significantly lower risk of the need to switch antiretroviral drugs because of adverse events. Thus, for this subgroup of patients, ART can be deferred until the start of the continuation phase of tuberculosis treatment. However, a longer delay should be avoided, in light of our previous finding that sequential ART (after the completion of tuberculosis treatment) was associated with 50% higher mortality, as compared with its initiation during tuberculosis treatment.5

Some limitations of our study need to be considered. First, the observed 68% lower rate of AIDS or death among severely immunocompromised patients as compared with the rate among other patients (incidence-rate ratio, 0.32), although substantial, was not significant (P=0.06). However, it is unlikely that this finding was due to chance, because a survival benefit in severely immunocompromised patients was also observed in the Cam-
### Table 3. Clinical Outcomes of Tuberculosis Treatment.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baseline CD4+ T-Cell Count &lt;50/μl</th>
<th>Baseline CD4+ T-Cell Count ≥50/μl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Earlier ART (N=177)</td>
<td>Later ART (N=180)</td>
</tr>
<tr>
<td>Tuberculosis cured[4]</td>
<td>23 (62)</td>
<td>24 (69)</td>
</tr>
<tr>
<td>Tuberculosis treatment successfully completed[4]</td>
<td>8 (22)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Treatment successful</td>
<td>31 (84)</td>
<td>28 (80)</td>
</tr>
<tr>
<td>Patient died before tuberculosis treatment completed</td>
<td>3 (9)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Treatment interruption</td>
<td>0 (0)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Treatment failure with first-line regimen</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Patient lost to follow-up before tuberculosis treatment completed</td>
<td>1 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Patient transferred to other clinic, tuberculosis treatment outcome not known</td>
<td>1 (3)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

[4] Tuberculosis cured was defined in accordance with the South African National Tuberculosis Control Programme Practical Guidelines 2004, which states, “Patient who is smear-negative at, or one month prior to, the completion of treatment and also on at least one previous occasion.” Most study patients were unable to produce sputum after the first few months of tuberculosis treatment, making demonstration of a cure difficult.

[5] Successful completion of treatment was defined as the use of more than 85% of the prescribed medication.

[6] Treatment success was defined as tuberculosis cure and successful completion of tuberculosis treatment.

[5] Treatment failure was defined as a positive smear or culture for Mycobacterium tuberculosis that was obtained at least 5 months after the initiation of tuberculosis therapy.

In the Cambodian study, among patients coinfected with tuberculosis and HIV who had a median CD4+ T-cell count of 25 per cubic millimeter, those who started ART 2 weeks after the initiation of tuberculosis treatment had 38% lower mortality than those who waited 8 weeks to start ART (P = 0.006). Among patients with CD4+ T-cell counts below 50 per cubic millimeter in the AIDS Clinical Trials Group Study A5221 (NCT00108862), 15.5% of patients in the earlier-ART group versus 26.6% in the later-ART group had an AIDS-defining illness or died (95% CI, 1.5 to 20.5; P = 0.02). Second, the lack of a survival benefit in patients with CD4+ T-cell counts of 50 per cubic millimeter or higher may be due to the sample size (357 patients) and the small number of deaths observed. There would be only a 2.2% probability of observing these rates of death if the true difference in mortality between the earlier-ART and later-ART groups was 34% or greater. Furthermore, the limited observational data available show similar trends. In a pilot study of the initiation of ART involving 70 patients with a median CD4+ T-cell count of 103 per cubic millimeter, there were 2 deaths in the early-therapy group (within 2 weeks after the start of tuberculosis treatment) versus 1 death in the delayed-therapy group (8 weeks after the start of tuberculosis treatment) (P = 0.001). Third, inaccuracies in the diagnosis of HIV, and therefore in the reported incidence of the syndrome, may have affected the study outcome. The incidence rate of 14.2% observed in this study is consistent with findings from other South African studies. In one study of patients coinfected with tuberculosis and HIV, the incidence of IRIS was 12% overall, yet 32% of patients who started ART within 2 months after receiving a diagnosis of tuberculosis had an IRIS event. The risk of IRIS remained elevated if ART was started within 3 months after the initiation of tuberculosis treatment, but it was highest during the first month of tuberculosis treatment. A retrospective analysis of 627 patients from India showed that 7.6% of patients with tuberculosis (18 of 237) had paradoxical tuberculosis-associated IRIS, and 3.1% of patients without tuberculosis (12 of 390) had IRIS associated with ART. A low CD4+ T-cell count at baseline and early initiation of ART...
Table 4. Clinical Outcomes of ART.

<table>
<thead>
<tr>
<th>Outcome and Baseline CD4+ T-Cell Count</th>
<th>Earlier ART</th>
<th>Later ART</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no./total no.</td>
<td>% (95% CI)</td>
<td>no./total no.</td>
</tr>
<tr>
<td>Viral load &lt;400 copies/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6 mo after initiation of ART</td>
<td>166/179</td>
<td>92.9 (84.3–99.8)</td>
<td>166/179</td>
</tr>
<tr>
<td>CD4+ count &lt;50/mm³</td>
<td>30/34</td>
<td>88.2 (71.6–96.2)</td>
<td>32/35</td>
</tr>
<tr>
<td>CD4+ count ≥50/mm³</td>
<td>131/145</td>
<td>90.3 (84.0–94.4)</td>
<td>134/144</td>
</tr>
<tr>
<td>At 12 mo after randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>147/159</td>
<td>92.5 (86.9–95.9)</td>
<td>130/147</td>
</tr>
<tr>
<td>CD4+ count &lt;50/mm³</td>
<td>30/32</td>
<td>93.8 (77.8–98.9)</td>
<td>21/27</td>
</tr>
<tr>
<td>CD4+ count ≥50/mm³</td>
<td>117/127</td>
<td>92.1 (85.6–96.0)</td>
<td>107/120</td>
</tr>
<tr>
<td>At 18 mo after randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>144/153</td>
<td>94.1 (88.8–97.1)</td>
<td>135/143</td>
</tr>
<tr>
<td>CD4+ count &lt;50/mm³</td>
<td>28/30</td>
<td>93.3 (76.5–98.8)</td>
<td>25/26</td>
</tr>
<tr>
<td>CD4+ count ≥50/mm³</td>
<td>116/123</td>
<td>94.3 (88.2–97.5)</td>
<td>110/117</td>
</tr>
</tbody>
</table>

Mean increase in CD4+ count

<table>
<thead>
<tr>
<th></th>
<th>no. of patients</th>
<th>mean increase</th>
<th>no. of patients</th>
<th>mean increase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(95% CI)</td>
<td></td>
<td>(95% CI)</td>
</tr>
<tr>
<td>At 6 mo after initiation of ART</td>
<td>178</td>
<td>0.122 (0.113–0.152)</td>
<td>179</td>
<td>0.132 (0.111–0.152)</td>
</tr>
<tr>
<td>CD4+ count &lt;50/mm³</td>
<td>34</td>
<td>0.224 (0.143–0.354)</td>
<td>35</td>
<td>0.104 (0.81–0.124)</td>
</tr>
<tr>
<td>CD4+ count ≥50/mm³</td>
<td>144</td>
<td>0.134 (0.110–0.157)</td>
<td>144</td>
<td>0.138 (0.113–0.152)</td>
</tr>
<tr>
<td>At 12 mo after randomization</td>
<td>159</td>
<td>0.183 (0.162–0.204)</td>
<td>147</td>
<td>0.125 (0.105–0.145)</td>
</tr>
<tr>
<td>CD4+ count &lt;50/mm³</td>
<td>32</td>
<td>0.170 (0.157–0.213)</td>
<td>27</td>
<td>0.111 (0.016–0.241)</td>
</tr>
<tr>
<td>CD4+ count ≥50/mm³</td>
<td>127</td>
<td>0.186 (0.163–0.210)</td>
<td>120</td>
<td>0.128 (0.104–0.152)</td>
</tr>
<tr>
<td>At 18 mo after randomization</td>
<td>152</td>
<td>0.217 (0.192–0.243)</td>
<td>142</td>
<td>0.172 (0.150–0.194)</td>
</tr>
<tr>
<td>CD4+ count &lt;50/mm³</td>
<td>30</td>
<td>0.207 (0.166–0.248)</td>
<td>26</td>
<td>0.173 (0.134–0.212)</td>
</tr>
<tr>
<td>CD4+ count ≥50/mm³</td>
<td>122</td>
<td>0.220 (0.189–0.251)</td>
<td>116</td>
<td>0.172 (0.146–0.198)</td>
</tr>
</tbody>
</table>

were significantly associated with paradoxical tuberculosis-associated IRIS.

The rates of adverse events in the earlier-ART and later-ART groups were not substantially different. Published data on additive treatment-related toxic effects in patients receiving treatment for both tuberculosis and HIV infection are limited. A retrospective study in India showed that concomitant use of ART and tuberculosis treatment was a predictor of adverse events (odds ratio, 1.88). Furthermore, a study from Thailand showed that 44.6% of patients receiving treatment for tuberculosis and HIV had adverse events due to antituberculosis drugs or ART. Of these patients, 66% had adverse events within the first 2 months after the start of tuberculosis treatment, and 76.8% had to stop or change either antituberculosis or antiretroviral drugs. In contrast, a retrospective study from South Africa showed that the occurrence of serious adverse events was unrelated to the use of antiretroviral drugs in patients with tuberculosis. In our study, there were no significant differences between the earlier-ART and later-ART groups in the outcomes of tuberculosis treatment.
or in the proportion of participants with a suppressed viral load. However, significant increases in the CD4+ T-cell count at 12 and 18 months were observed in the earlier-ART group, probably as a result of the longer duration of ART, as compared with the duration in the later-ART group. This finding may have implications for longer-term survival, for which long-term follow-up would be needed.

These results of the SAPIT study further support the integration of treatment for tuberculosis and HIV infection. The current WHO recommendation to initiate ART as soon as possible after the start of tuberculosis treatment, regardless of the CD4+ T-cell count, may need to be revisited in view of the findings of this study. We found that early initiation of ART in patients with CD4+ T-cell counts of less than 50 per cubic millimeter increased AIDS-free survival, whereas deferral of the initiation of ART to the first 4 weeks of the continuation phase of tuberculosis therapy in those with higher CD4+ T-cell counts reduced the risks of IRIS and other adverse events related to ART without increasing the risk of AIDS or death.

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Disclosure forms provided by the authors are available with the full text of this article on NEJM.org.

We thank the patients for their participation in this study. Prof. William Stead of the Nelson R. Mandela School of Medicine for confirmatory tuberculosis testing; the management and staff of the Prince Cyril Zulu Communicable Disease Clinic, Ethekwini Municipality, for support of the study; Drs. Cara Hanley, Ed Trumore, Ruedi Noss, and Richard Hadler of the Division of AIDS at the National Institute of Health for study support; Drs. Gavin Churchyard, Douglas Taylor, and Mark Wainberg for serving on the data and safety monitoring committee; members of the Community Advisory Board for their advice regarding the conduct of the trial; Ms. Nonzupa Ntshonalu of the CAPRISA Community Programme (for overseeing community involvement in the trial); Ms. Matsuso Sansumod and Mr. Keith Cooper for laboratory analysis; Mr. Ntshonalu Vemla for statistical support; Ms. Irene van Rensburg for data management; and all the other members of the SAPIT study team for their commitment to high-quality study conduct.

REFERENCES


Chapter 6 presents secondary analysis of SAPiT trial data, addressing important concerns about incidence, severity, and outcomes of IRIS relative to timing of ART initiation in TB-HIV co-infected patients. This study highlighted significantly higher IRIS rates, more severe cases of IRIS, longer time to resolution, and more frequent hospitalization among patients receiving early integrated ART in TB therapy. Chapter 7 addresses the other distinct form of ART induced TB associated IRIS. This paper highlights the high rates of unmasking TB in a rural ART programme, irrespective of baseline CD4 counts or duration on ART.
CHAPTER 6
THE IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME AFTER ANTIRETROVIRAL THERAPY INITIATION IN PATIENTS WITH TUBERCULOSIS: FINDINGS FROM THE SAPIT TRIAL.


The Immune Reconstitution Inflammatory Syndrome After Antiretroviral Therapy Initiation in Patients With Tuberculosis: Findings From the SAPIT Trial

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Background: Concerns about the immune reconstitution inflammatory syndrome (IRIS) remain a barrier to antiretroviral therapy (ART) initiation during antituberculosis treatment in co-infected patients.

Objective: To assess IRIS incidence, severity, and outcomes relative to the timing of ART initiation in patients with HIV-related tuberculosis.

Design: Randomized, open-label clinical trial. (ClinicalTrials.gov registration number: NCT00398906)

Setting: An outpatient clinic in Durban, South Africa.

Patients: 642 patients co-infected with HIV and tuberculosis.

Measurements: In a secondary analysis of the SAPIT (Starting Antiretroviral Therapy at Three Points in Tuberculosis) trial, IRIS was assessed in patients randomly assigned to initiate ART within 4 weeks of tuberculosis treatment initiation (early integrated treatment group), within 4 weeks of completion of the intensive phase of tuberculosis treatment (late integrated treatment group), or within 4 weeks after tuberculosis therapy completion (sequential treatment group). The syndrome was defined as new-onset or worsening symptoms, signs, or radiographic manifestations temporally related to treatment initiation, accompanied by a treatment response. Severity of IRIS, hospitalization, and time to resolution were monitored.

Results: Incidence of IRIS was 19.5 (n = 43), 7.5 (n = 18), and 8.1 (n = 19) per 100 person-years in the early integrated, late integrated, and sequential treatment groups, respectively. Incidence of IRIS was higher in the early integrated treatment group than in the late integrated incidence rate ratio, 2.6 [95% CI, 1.5 to 4.8; P < 0.001] or sequential incidence rate ratio, 2.4 [95% CI, 1.4 to 4.4; P < 0.001] treatment groups. More severe IRIS cases occurred in the early integrated treatment group than in the other 2 groups (35% vs. 19%; P = 0.179), and patients in the early integrated treatment group had significantly higher hospitalization rates (62% vs. 14%; P = 0.007) and longer time to resolution (70.5 vs. 29.0 days; P = 0.007) than patients in the other 2 groups.

Limitations: It was not possible to assess IRIS in more patients in the sequential treatment group (n = 56) than in the late integrated (n = 90) and early integrated (n = 33) treatment groups because of loss to follow-up, withdrawal, or death within 6 months of scheduled ART initiation. This study did not assess IRIS risk in nonambulatory patients or in those with extrapulmonary and smear-negative tuberculosis.

Conclusion: Initiation of ART in early stages of tuberculosis treatment resulted in significantly higher IRIS rates, longer time to resolution, and more severe cases of IRIS requiring hospitalization. These findings are particularly relevant to patients initiating ART with a CD4+ count less than 0.050 x 10^6 cells/L, given the increased survival benefit of early ART initiation in this group.

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For author affiliations, see end of text.

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among patients with a CD4\(^+\) count of 0.050 \times 10^5 \text{cells/L} or greater (10–13). Previous studies in patients with HIV and tuberculosis have shown IRIS incidence rates that varied from 11% to 71.4% (14–17). Beginning ART around the start of tuberculosis treatment in patients with a baseline CD4\(^+\) count less than 0.050 \times 10^5 \text{cells/L} has been associated with higher risk for IRIS (11–13, 16, 18–21).

Evidence for improved clinical outcomes is compelling in co-infected patients with a CD4\(^+\) count less than 0.050 \times 10^5 \text{cells/L} (11–15). However, data from the SAPIT trial show that incidence of IRIS among patients with a CD4\(^+\) count less than 0.050 \times 10^5 \text{cells/L} was 4.7 times higher in patients who started ART within 4 weeks of the start of tuberculosis treatment than in patients who started ART within 4 weeks after completion of the intensive phase of tuberculosis treatment (P = 0.004). In addition, incidence of IRIS among patients with a CD4\(^+\) count of 0.050 \times 10^5 \text{cells/L} or greater was 2.2 times higher in the former group than in the latter group (P = 0.010).

Prospective data for the systematic examination of incidence, severity, risk factors, and outcome of IRIS events relative to timing of ART initiation in patients with HIV and tuberculosis are limited. The purpose of this study was to compare IRIS risks and outcomes in patients initiating ART within a month of tuberculosis treatment initiation with those of patients initiating ART later to better guide patient-level decision making about the timing of ART initiation in patients with HIV and tuberculosis.

**METHODS**

**Design Overview**

The SAPIT trial was a 3-group, randomized, open-label clinical trial in 642 patients conducted from June 2005 to July 2010. The primary outcome, which has been reported elsewhere (10), was to determine the optimal timing of ART initiation in patients co-infected with HIV and tuberculosis. In this review, we present one of the secondary objectives of the SAPIT trial: an analysis of IRIS data by trial group.

**Setting and Participants**

The study was conducted at the Centre for the AIDS Programme of Research in South Africa (CPRAD) in Durban, South Africa. Study nurses and clinicians recruited and enrolled HIV-infected patients aged 18 years or older with sputum smear-positive tuberculosis and a screening CD4\(^+\) count less than 0.050 \times 10^5 \text{cells/L}. All patients received standard antiretroviral prophylaxis and antituberculosis therapy; the latter was administered in a fixed drug combination of rifampicin, isoniazid, ethambutol, and pyrazinamide for 2 months (intensive phase), followed by isoniazid and rifampicin for 4 months (continuation phase). Per South African treatment guidelines (22), patients who had had tuberculosis in the past and were being re-treated also received streptomycin during a longer intensive phase of tuberculosis treatment. The study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal and the Medicines Control Council of South Africa.

**Randomization and Interventions**

Patients were randomly assigned to initiate ART within 4 weeks of tuberculosis treatment initiation (early integrated treatment group), within 4 weeks after completion of the intensive phase of tuberculosis treatment (late integrated treatment group), or within 4 weeks after completion of tuberculosis therapy (sequential treatment group) (Figure 1). The study statistician generated a random allocation sequence to assign patients to one of the intervention groups. Patients were randomly assigned in a 1:1:1 ratio (with the use of sealed envelopes) to one of three study groups in permuted blocks of 6 or 9 with no stratiﬁcation. The standard first-line ART regimen comprised lamivudine, 300 mg/d; efavirenz-coated didanosine, 250 mg/d (for patients weighing <60 kg) or 400 mg/d (for patients weighing >60 kg); and efavirenz, 600 mg/d. Because placebos were not used in this trial, study clinicians were not blinded to treatment group allocation when they assessed possible IRIS.

**Outcomes and Follow-up**

Study patients were evaluated for features of suspected IRIS by using a standardized set of criteria at every study visit, regardless of group allocation. We deﬁned IRIS as the occurrence of new-onset or worsening symptoms, signs, or radiographic features temporally related to initiation of antiretroviral or tuberculosis treatment; an increase in CD4\(^+\) cell count; and exclusion of confirmed tuberculosis or antiretroviral treatment failure, toxicity, nonadherence, or new
concurrent opportunistic infection or other complication. This definition is in accordance with other published case definitions (23, 24) in the following respects: occurrence of IRIS after diagnosis of an underlying opportunistic infection (in this instance, tuberculosis); inclusion of an ART treatment response; presence of new-onset or worsening clinical features consistent with an inflammatory process; timing of IRIS onset relative to tuberculosis and ART initiation; and exclusion of ART and tuberculosis treatment failure, toxicity, and concurrent infections. The IRIS definitions used in this study varied from published case definitions where it was not required that patients have an initial response to tuberculosis treatment or that the results of tuberculin skin tests convert from positive to negative.

Presentation of specific signs and symptoms indicative of IRIS (as per a standardized checklist) triggered a detailed IRIS assessment, which included clinical examination; urine and sputum evaluation; blood microscopy, culture, and sensitivity testing; and chest radiograph evaluation. A CD4+ cell count was not always measured at the time of development of IRIS symptoms; however, we used CD4+ cell response to ART in the presence of other protocol-defining criteria of IRIS when assessing suspected IRIS. All patients presenting with clinical grade 3 and 4 IRIS events (graded according to the Table for Grading the Severity of Adult and Pediatric Adverse Events [version 1.0, December 2004], which was developed by the National Institute of Allergy and Infectious Diseases Division of AIDS) or IRIS events of a lower grade that warranted further investigation and management were referred for tertiary care to the infectious diseases unit at a local hospital. All cases of IRIS identified during the trial were retrospectively assessed and found to meet the 2008 International Network for the Study of HIV-Associated IRIS (INSHI) definition of 1 major clinical criterion or 2 minor clinical criteria (7). All IRIS events were followed, either until resolution or, if unresolved, until the end of study follow-up. An experienced independent clinician conducted a detailed chart review of suspected cases once all clinical and radiographic information became available to verify the IRIS diagnosis for inclusion in this analysis. We determined the severity of IRIS on the basis of IRIS-associated deaths, life-threatening events, IRIS-associated hospitalization and duration of hospitalization, number of events warranting steroid use, and proportion of IRIS events that did not resolve or resolved with sequelae at study conclusion. Every adverse event elicited by the IRIS assessment tool was graded for severity by using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.

Statistical Analysis

The sample size for the SAPIT trial was calculated as 649, which was based on the primary mortality outcome. The study was not powered for the secondary IRIS outcome. After the second planned interim review on 1 September 2008, the study’s safety monitoring committee recommended, on the basis of superior survival in the early and late integrated treatment groups, that all participants in the sequential treatment group initiate ART as soon as possible and that the 2 integrated treatment groups complet...
### Table 1. Baseline Characteristics of Participants in the SAPIT Trial

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early Integrated Treatment Group (n = 214)</th>
<th>Late Integrated Treatment Group (n = 215)</th>
<th>Sequential Treatment Group (n = 213)</th>
<th>Patients Who Developed IRIS (n = 80)</th>
<th>Patients Who Did Not Develop IRIS (n = 562)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), y</td>
<td>34.4 (8.0)</td>
<td>34.5 (8.7)</td>
<td>33.9 (8.2)</td>
<td>34.3 (6.4)</td>
<td>34.2 (8.5)</td>
<td>0.97</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>97 (45.3)</td>
<td>112 (52.3)</td>
<td>110 (51.6)</td>
<td>39 (48.8)</td>
<td>280 (49.8)</td>
<td>0.91</td>
</tr>
<tr>
<td>BMI &lt; 18.5 kg/m², n (%)</td>
<td>25 (11.7)</td>
<td>28 (13.0)</td>
<td>29 (13.4)</td>
<td>10 (12.5)</td>
<td>72 (12.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>History of tuberculosis, n (%)</td>
<td>80 (37.4)</td>
<td>68 (31.6)</td>
<td>66 (31.0)</td>
<td>31 (38.8)</td>
<td>183 (32.6)</td>
<td>0.31</td>
</tr>
<tr>
<td>Extra-pulmonary tuberculosis, n (%)</td>
<td>10 (4.7)</td>
<td>8 (4.2)</td>
<td>9 (4.3)</td>
<td>5 (6.3)</td>
<td>23 (4.1)</td>
<td>0.38</td>
</tr>
<tr>
<td>WHO stage 4, n (%)</td>
<td>14 (6.5)</td>
<td>11 (5.1)</td>
<td>13 (6.1)</td>
<td>6 (7.5)</td>
<td>32 (5.7)</td>
<td>0.46</td>
</tr>
<tr>
<td>Median CD4⁺ count (IQR), × 10⁹ cells/L</td>
<td>0.195 (0.075 to 0.261)</td>
<td>0.149 (0.077 to 0.244)</td>
<td>0.140 (0.069 to 0.247)</td>
<td>0.091 (0.036 to 0.177)</td>
<td>0.159 (0.078 to 0.261)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with CD4⁺ count &lt; 0.050 × 10⁹ cells/L, n (%)</td>
<td>37 (17.3)</td>
<td>35 (16.3)</td>
<td>41 (19.2)</td>
<td>26 (32.5)</td>
<td>87 (15.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median viral load (IQR), copies/mL</td>
<td>5.0 (0.9)</td>
<td>5.0 (0.9)</td>
<td>5.1 (0.7)</td>
<td>5.0 (0.7)</td>
<td>5.0 (0.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMI = body mass index; IQR = interquartile range; IRIS = immune reconstitution inflammatory syndrome; SAPIT = Starting Antiretroviral Therapy at Three Points in Tuberculosis; WHO = World Health Organisation.

* P value for the comparison of patients who developed IRIS with those who did not develop IRIS.

† Four patients in the sequential treatment group had missing BMI data, which were not included in the percentage calculation.

‡ One patient in the late integrated treatment group and 5 patients in the sequential treatment group had missing extra-pulmonary tuberculosis data, which were not included in the percentage calculation.

§ Baseline viral load data were not available for 16 patients in the early integrated treatment group, 16 in the late integrated treatment group, and 12 in the sequential treatment group.

### Results

Of 1331 patients screened for eligibility, 642 were enrolled and randomly assigned (Figure 2). Patients in the early integrated (n = 214), late integrated (n = 215), and sequential (n = 213) treatment groups had similar baseline demographic and clinical characteristics (Table 1). Retention rates (the number of patients who completed their scheduled study exit visit divided by the number of enrolled patients who did not die during follow-up) at 18 months were 76.9%, 71.5%, and 70.9% in the early integrated, late integrated, and sequential treatment groups, respectively. Although retention rates are similar across the 3 treatment groups, we could not assess some patients for IRIS because of the timing of ART initiation in the 3 groups. Thirty-two patients in the early integrated treatment group, 50 in the late integrated treatment group, and 74 in the sequential treatment group withdrew from the study or died within 6 months after ART initiation. These 156 patients were younger overall, and most were men (Appendix Tables 1 and 2, available at www.annals.org).

### IRIS Incidence

Of the 642 patients evaluated at every study visit, 85 had suspected IRIS. Five patients with pulmonary infiltrates, respiratory symptoms, thoracic lymphadenopathy, cervical lymphadenopathy, abdominal pain, and fever were subsequently found to have undiagnosed multidrug-resistant tuberculosis at the time of the IRIS event and were therefore not regarded as having IRIS. Seventy-four of the remaining 80 patients with suspected IRIS had an in-
**Figure 2. Study flow diagram.**

ART = antiretroviral therapy; ARV = antiretroviral drug; TB = tuberculosis.
Table 2. IRIS incidence in the SAPIT Trial, by Study Group

<table>
<thead>
<tr>
<th>CD4&lt;sup&gt;+&lt;/sup&gt; Count</th>
<th>Early Integrated Treatment Group</th>
<th>Late Integrated Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRIS Events, n</td>
<td>Deaths or AIDS-Defining Illnesses, n</td>
</tr>
<tr>
<td>Observed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>43</td>
<td>28</td>
</tr>
<tr>
<td>&lt;0.050 × 10&lt;sup&gt;9&lt;/sup&gt; cells/L</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>≥0.050 × 10&lt;sup&gt;9&lt;/sup&gt; cells/L</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>Scenario 1†</td>
<td>52</td>
<td>2</td>
</tr>
<tr>
<td>&lt;0.050 × 10&lt;sup&gt;9&lt;/sup&gt; cells/L</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>≥0.050 × 10&lt;sup&gt;9&lt;/sup&gt; cells/L</td>
<td>36</td>
<td>20</td>
</tr>
<tr>
<td>Scenario 2‡</td>
<td>65</td>
<td>2</td>
</tr>
<tr>
<td>&lt;0.050 × 10&lt;sup&gt;9&lt;/sup&gt; cells/L</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>≥0.050 × 10&lt;sup&gt;9&lt;/sup&gt; cells/L</td>
<td>46</td>
<td>20</td>
</tr>
<tr>
<td>Scenario 3§</td>
<td>55</td>
<td>2</td>
</tr>
<tr>
<td>&lt;0.050 × 10&lt;sup&gt;9&lt;/sup&gt; cells/L</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>≥0.050 × 10&lt;sup&gt;9&lt;/sup&gt; cells/L</td>
<td>38</td>
<td>20</td>
</tr>
<tr>
<td>Scenario 4¶</td>
<td>74</td>
<td>2</td>
</tr>
<tr>
<td>&lt;0.050 × 10&lt;sup&gt;9&lt;/sup&gt; cells/L</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>≥0.050 × 10&lt;sup&gt;9&lt;/sup&gt; cells/L</td>
<td>51</td>
<td>20</td>
</tr>
<tr>
<td>Scenario 5‖</td>
<td>95</td>
<td>2</td>
</tr>
<tr>
<td>&lt;0.050 × 10&lt;sup&gt;9&lt;/sup&gt; cells/L</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>≥0.050 × 10&lt;sup&gt;9&lt;/sup&gt; cells/L</td>
<td>39</td>
<td>20</td>
</tr>
</tbody>
</table>

IRIS = immune reconstitution inflammatory syndrome; SAPIT = Starter Antiretroviral Therapy at Three Points in Tuberculosis.
* Data are different from those reported previously (1) because of changes in the calendar time used for counting.
† Assumes patients who withdraw before initiation of antiretroviral therapy and within 3 mo after initiation of antiretroviral therapy had IRIS rates 2 times those of patients who did not withdraw.
‡ Assumes patients who withdraw before initiation of antiretroviral therapy and within 6 mo after initiation of antiretroviral therapy had IRIS rates 5 times those of patients who did not withdraw.
§ Assumes patients who withdraw or die before initiation of antiretroviral therapy and within 6 mo after initiation of antiretroviral therapy had IRIS rates 2 times those of patients who completed the study.
¶ Assumes patients who withdraw or die before initiation of antiretroviral therapy and within 6 mo after initiation of antiretroviral therapy had IRIS rates 5 times those of patients who completed the study.
‖ Composite end point of death or IRIS.

created CD4<sup>+</sup> cell count. The remaining 6 patients (5 in the early integrated treatment group and 1 in the late integrated treatment group) did not have available CD4<sup>+</sup> cell count data at or after the IRIS diagnosis. Because their exclusion did not materially change the results, we included these 6 patients in the analysis.

There were 43 patients with IRIS in the early integrated treatment group, 18 in the late integrated treatment group, and 19 in the sequential treatment group (Table 2). Incidence of IRIS was significantly higher in the early integrated treatment group (19.5 per 100 person-years) than in the late integrated group (7.5 per 100 person-years; P < 0.001) or sequential (8.1 per 100 person-years; P < 0.001) treatment groups (Table 2). The median number of days to IRIS from ART initiation was 17.5 in the early integrated treatment group, 17 in the late integrated treatment group, and 28 in the sequential treatment group (P = 0.32) (Figure 3). The median CD4<sup>+</sup> count at or near the IRIS event was 0.101 × 10<sup>9</sup> cells/L in the early integrated treatment group, 0.117 × 10<sup>9</sup> cells/L in the late integrated treatment group, and 0.132 × 10<sup>9</sup> cells/L in the sequential treatment group (P = 0.52). Our results hold even if the 6 patients who did not have a CD4<sup>+</sup> cell count at or after the diagnosis of IRIS are excluded from the analysis (Appendix Table 3, available at www.anahs.org).

Incidence of IRIS in the subset of patients enrolled with a CD4<sup>+</sup> count less than 0.050 × 10<sup>9</sup> cells/L was 45.5 per 100 person-years in the early integrated treatment group, 9.7 per 100 person-years in the late integrated treatment group, and 19.7 per 100 person-years in the sequential treatment group (P = 0.008) (Table 2). Incidence of IRIS in patients with a CD4<sup>+</sup> count less than 0.050 × 10<sup>9</sup> cells/L was higher in the early integrated treatment group than in the late integrated (P = 0.004) or sequential (P =
<table>
<thead>
<tr>
<th>IRIS Events, n</th>
<th>Deaths or AIDS-Defining Illnesses, n</th>
<th>Person-Years</th>
<th>IRIS Incidence Rate per 100 Person-Years (95% CI)</th>
<th>Early Integrated Treatment Group vs. Late Integrated Treatment Group</th>
<th>Early Integrated Treatment Group vs. Sequential Treatment Group</th>
<th>Late Integrated Treatment Group vs. Sequential Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>47</td>
<td>235.4</td>
<td>8.1 (4.9 to 12.6)</td>
<td>2.6 (1.5 to 4.8) : 0.001</td>
<td>2.4 (1.4 to 4.4) : 0.001</td>
<td>0.9 (0.5 to 1.5) : 0.18</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>-20.8</td>
<td>19.7 (9.9 to 38.8)</td>
<td>4.7 (1.7 to 19.6) : 0.004</td>
<td>2.1 (0.9 to 4.4) : 0.05</td>
<td>0.9 (0.1 to 1.8) : 0.18</td>
</tr>
<tr>
<td>11</td>
<td>27</td>
<td>194.8</td>
<td>5.6 (2.8 to 10.1)</td>
<td>2.2 (1.1 to 4.5) : 0.010</td>
<td>2.7 (1.3 to 6.0) : 0.003</td>
<td>1.3 (0.3 to 5.0) : 0.59</td>
</tr>
<tr>
<td>26</td>
<td>-</td>
<td>235.4</td>
<td>11.0 (4.8 to 15.3)</td>
<td>2.4 (1.5 to 3.8) : 0.001</td>
<td>2.2 (1.3 to 3.4) : 0.002</td>
<td>0.9 (0.5 to 1.5) : 0.73</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>-60.6</td>
<td>24.8 (9.3 to 59.5)</td>
<td>5.4 (1.8 to 15.6) : 0.003</td>
<td>2.1 (0.5 to 4.4) : 0.064</td>
<td>0.4 (0.1 to 1.2) : 0.13</td>
</tr>
<tr>
<td>16</td>
<td>-</td>
<td>194.8</td>
<td>8.2 (4.2 to 12.2)</td>
<td>1.9 (1.1 to 3.3) : 0.023</td>
<td>2.3 (1.3 to 4.4) : 0.008</td>
<td>1.2 (0.6 to 2.4) : 0.54</td>
</tr>
<tr>
<td>36</td>
<td>-</td>
<td>235.4</td>
<td>15.3 (10.3 to 20.3)</td>
<td>2.1 (1.4 to 3.3) : 0.001</td>
<td>1.9 (1.3 to 2.9) : 0.001</td>
<td>0.9 (0.4 to 1.6) : 0.56</td>
</tr>
<tr>
<td>13</td>
<td>-</td>
<td>-60.6</td>
<td>32.0 (14.5 to 48.5)</td>
<td>6.4 (2.2 to 18.7) : 0.001</td>
<td>1.9 (0.9 to 3.5) : 0.069</td>
<td>0.3 (0.1 to 0.9) : 0.37</td>
</tr>
<tr>
<td>23</td>
<td>-</td>
<td>194.8</td>
<td>11.8 (5.0 to 18.6)</td>
<td>1.7 (1.1 to 2.6) : 0.032</td>
<td>2.1 (1.3 to 3.5) : 0.005</td>
<td>1.3 (0.7 to 2.3) : 0.44</td>
</tr>
<tr>
<td>31</td>
<td>-</td>
<td>235.4</td>
<td>13.2 (9.5 to 17.8)</td>
<td>2.5 (1.5 to 3.7) : 0.001</td>
<td>1.9 (1.2 to 3.0) : 0.004</td>
<td>0.8 (0.5 to 1.4) : 0.47</td>
</tr>
<tr>
<td>14</td>
<td>-</td>
<td>-60.6</td>
<td>34.5 (16.2 to 52.2)</td>
<td>4.6 (1.7 to 12.4) : 0.003</td>
<td>1.6 (0.8 to 3.2) : 0.192</td>
<td>0.4 (0.1 to 1.2) : 0.44</td>
</tr>
<tr>
<td>17</td>
<td>-</td>
<td>194.8</td>
<td>6.7 (6.6 to 12.5)</td>
<td>1.3 (0.1 to 3.2) : 0.018</td>
<td>2.3 (1.3 to 4.3) : 0.004</td>
<td>1.2 (0.6 to 2.3) : 0.55</td>
</tr>
<tr>
<td>43</td>
<td>-</td>
<td>235.4</td>
<td>18.3 (12.8 to 23.8)</td>
<td>2.2 (1.5 to 3.2) : 0.001</td>
<td>1.8 (1.3 to 2.7) : 0.001</td>
<td>0.8 (0.5 to 1.3) : 0.45</td>
</tr>
<tr>
<td>26</td>
<td>-</td>
<td>-60.6</td>
<td>61.6 (47.1 to 84.9)</td>
<td>9.1 (2.7 to 12.6) : 0.001</td>
<td>1.2 (0.7 to 2.1) : 0.001</td>
<td>0.2 (0.1 to 0.6) : 0.002</td>
</tr>
<tr>
<td>28</td>
<td>-</td>
<td>194.8</td>
<td>14.4 (9.0 to 19.7)</td>
<td>1.7 (1.1 to 2.7) : 0.017</td>
<td>1.9 (1.2 to 3.5) : 0.007</td>
<td>1.1 (0.7 to 1.8) : 0.73</td>
</tr>
<tr>
<td>52</td>
<td>-</td>
<td>235.4</td>
<td>22.1 (16.5 to 29.0)</td>
<td>1.9 (1.2 to 3.0) : 0.003</td>
<td>1.1 (0.8 to 1.7) : 0.44</td>
<td>0.6 (0.4 to 1.0) : 0.25</td>
</tr>
<tr>
<td>22</td>
<td>-</td>
<td>-60.6</td>
<td>54.2 (31.9 to 82.6)</td>
<td>2.1 (0.9 to 3.3) : 0.068</td>
<td>1.0 (0.5 to 1.9) : 0.98</td>
<td>0.4 (0.2 to 0.9) : 0.09</td>
</tr>
<tr>
<td>30</td>
<td>-</td>
<td>194.8</td>
<td>15.4 (10.4 to 22.6)</td>
<td>1.9 (1.1 to 3.3) : 0.020</td>
<td>1.3 (0.8 to 2.2) : 0.20</td>
<td>0.7 (0.4 to 1.3) : 0.28</td>
</tr>
</tbody>
</table>

0.051) treatment groups. By comparison, in patients with a CD4+ count of 0.050 × 10^3 cells/L or greater, incidence of IRIS was 15.3 per 100 person-years in the early integrated treatment group, 7.1 per 100 person-years in the late integrated treatment group, and 5.6 per 100 person-years in the sequential treatment group (P = 0.002). The incidence rate in patients enrolled with a CD4+ count of 0.050 × 10^3 cells/L or greater was significantly higher in the early integrated treatment group than in the late integrated (P = 0.010) or sequential (P = 0.003) treatment groups (Table 2). Overall, in patients with a CD4+ count of 0.050 × 10^3 cells/L, the median time to IRIS from ART initiation was double that of patients with a CD4+ count of 0.050 × 10^3 cells/L or greater (28 days [interquartile range [IQR], 15 to 56 days] vs. 14 days [IQR, 13 to 28 days]; P = 0.009). The combination of treatment group and CD4+ cell count status (greater than or less than 0.050 × 10^3 cells/L) did not have a statistically significant effect on the risk for IRIS (P = 0.97), indicating homogeneity across the 2 CD4+ cell count strata in the effect of time to ART initiation on the risk for IRIS. Results from various sensitivity analyses, which assumed that patients who were lost to follow-up, withdrew, or died within 6 months after their scheduled ART initiation had IRIS rates 2 or 5 times those observed in patients who completed follow-up, were consistent with the primary results. In a sensitivity analysis that used the composite end point of death or IRIS, outcome rates were higher in the early integrated treatment group than in the late integrated treatment group (Table 2). New-onset or worsening respiratory symptoms (59 of 80) was the most common clinical presentation of IRIS (Figure 4). Fever was uncommon (2 of 80), whereas 22.5% (18 of 80) of patients with IRIS presented with new-onset or worsening lymphadenopathy. In the sequential treatment group, 2 participants who had completed tuberculosis treatment when ART was initiated developed active tuberculosis within 3 months of ART initiation and met the provisional INSHI case definition of unmasking tuberculosis-associated IRIS.

**Severity of IRIS Events**

Severe or life-threatening IRIS events occurred in 35%, 22%, and 16% of patients with IRIS in the early integrated, late integrated, and sequential treatment groups, respectively (Table 3). Forty-two percent of patients with IRIS in the early integrated treatment group were hospitalized for IRIS-related conditions, compared with 22% in
Figure 3. Kaplan–Meier estimates of cumulative probability of IRIS, by study group.

<table>
<thead>
<tr>
<th>IRIS Events/Patients in Follow-up (Deaths; Withdrawals)</th>
<th>Early integrated treatment</th>
<th>Late integrated treatment</th>
<th>Sequential treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early treatment</td>
<td>214 (48/156)</td>
<td>43/145</td>
<td>42/141</td>
</tr>
<tr>
<td>(4/14)</td>
<td>(7/20)</td>
<td>(8/23)</td>
<td>(9/25)</td>
</tr>
<tr>
<td>(12/30)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late integrated treatment</td>
<td>215 (6/188)</td>
<td>14/167</td>
<td>16/153</td>
</tr>
<tr>
<td>(1/20)</td>
<td>(5/29)</td>
<td>(9/37)</td>
<td>(11/44)</td>
</tr>
<tr>
<td>(18/50)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequential treatment</td>
<td>213 (0/196)</td>
<td>1/179</td>
<td>6/152</td>
</tr>
<tr>
<td>(2/14)</td>
<td>(12/213)</td>
<td>(32/35)</td>
<td>(32/40)</td>
</tr>
<tr>
<td>(32/51)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IRIS = immune reconstitution inflammatory syndrome.

the late integrated treatment group and 5.0% in the sequential treatment group ($P = 0.009$). A total of 35% (15 of 43) of IRIS cases in the early integrated treatment group were severe, compared with 19% (7 of 37) of IRIS cases in the other 2 treatment groups ($P = 0.179$). Median duration of IRIS-associated hospitalization was 9.5 days (IQR, 3 to 20 days) and 11.5 days (IQR, 6 to 23 days) in the early integrated and late integrated treatment groups, respectively. In the sequential treatment group, only 1 patient was hospitalized for 68 days. Steroid therapy was started in 8 patients with IRIS (4 in the early integrated treatment group, 1 in the late integrated treatment group, and 3 in the sequential treatment group). Baseline CD4+ cell count status (greater than or less than 0.050 × 10^3 cells/L) did not affect the number of unscheduled medical visits that were due to IRIS. Seventy-two of the 80 patients with IRIS had unscheduled medical visits (median, 3 visits; range, 1 to 12 visits), whereas 351 of 562 patients without IRIS had unscheduled medical visits (median, 2 visits; range, 1 to 18 visits). Eighty of the 113 patients with a CD4+ count less than 0.050 × 10^3 cells/L had unscheduled medical visits (median, 2 visits; range, 1 to 16 visits), whereas 343 of 529 patients with a CD4+ count of 0.050 × 10^3 cells/L or greater had unscheduled medical visits (median, 2 visits; range, 1 to 18 visits). There was no statistically significant difference in the rate of single drug switching ($P = 0.54$) or whole regimen change due to virologic failure ($P = 0.21$) between patients with IRIS and those without it.

Seventy-two of the 80 IRIS events resolved completely during follow-up. Time to IRIS resolution was longer in the early integrated treatment group than in the late integrated and sequential treatment groups ($P = 0.001$) (Table 3). Among the unresolved IRIS events, there were 2 deaths (both in the early integrated treatment group) due to respiratory complications. Two events did not resolve by study completion (new onset of pulmonary infiltrates in the early integrated treatment group and worsening pulmonary effusion in the sequential treatment group), and 3 IRIS events resolved with sequelae (tuberculosis meningitis and meningitis, both in the early integrated treatment group, and herpes zoster in the sequential treatment group). The outcome of IRIS in 1 patient was unknown.

Risk Factors Associated With IRIS

CD4+ cell count, viral load, and World Health Organization clinical disease stage were associated with an increased risk for IRIS. Incidence of IRIS was 23.1 per 100 person-years in patients with a CD4+ count less than...
0.050 × 10^9 cells/L (95% CI, 15.1 to 33.8 per 100 person-years), 12.3 per 100 person-years in patients with a CD4^+ count between 0.050 and 0.200 × 10^9 cells/L (CI, 8.7 to 16.8 per 100 person-years), and 5.6 per 100 person-years in patients with a CD4^+ count greater than 0.200 × 10^9 cells/L (CI, 3.2 to 9.4 per 100 person-years). Similarly, IRIS incidence was higher in patients with a baseline viral load greater than 100,000 copies/mL (16.2 per 100 person-years [CI, 12.4 to 20.8 per 100 person-years]) than in those with a baseline viral load less than 100,000 copies/mL (6.0 per 100 person-years [CI, 3.4 to 9.7 per 100 person-years]) (Appendix Table 4, available at www.annals.org).

**DISCUSSION**

Patients with HIV and tuberculosis who started ART in the first 4 weeks of tuberculosis treatment had a more than 2-fold higher rate of IRIS incidence than those who started ART later. Of note, IRIS occurring in patients who initiated ART early was more severe, took longer to resolve, and more often required hospitalization.

Higher IRIS rates in patients who start ART during the early stages of tuberculosis treatment have been shown in clinical trials (11–13) and in retrospective and observational studies (1, 25–27). In the CAMELIA study, IRIS incidence rates were 3.76 per 100 person-months in the early initiation group versus 1.53 per 100 person-months in the late initiation group (12). Another large multicenter trial (ACTG 5221) reported IRIS rates of 11% in patients with immediate ART versus 5% in patients with early ART (13), with 11.5% of patients with a CD4^+ count less than 0.050 × 10^9 cells/L and 5.4% of patients with a CD4^+ count of 0.050 × 10^9 cells/L or greater developing IRIS. This study also showed a substantial interaction between CD4^+ cell count and ART group (P = 0.014).

Time to IRIS from ART initiation was similar in the ACTG 5221 and SAPIT studies. The most common clinical presentation of IRIS in the ACTG 5221 study was lymphadenopathy followed by new-onset constitutional symptoms, whereas fever followed by peripheral lymphadenopathy was the most common clinical presentation of IRIS in the CAMELIA study. In contrast, new-onset or worsening respiratory symptoms followed by pulmonary infiltrates was the most common clinical presentation of IRIS in the SAPIT trial. These different presentations of IRIS are probably due to the different patient profiles in the 3 studies—patients in the SAPIT trial were all ambulatory and had smear-positive tuberculosis; patients in the ACTG 5221 trial were a mix of ambulatory and hospitalized patients with all forms of tuberculosis, and most patients in the CAMELIA trial were hospitalized with a clinically significantly lower baseline CD4^+ cell count than patients in the other 2 trials.

Our study also shows that in severely immunocompromised patients (CD4^+ count <0.050 × 10^9 cells/L), risk for IRIS was almost 5 times higher in those initiating ART early. It is important to note that within this population, studies have shown a substantial decrease in the risk for morbidity and mortality with early ART initiation (11–13). Patients with a CD4^+ count of 0.050 × 10^9 cells/L or

**Figure 4. Proportion of all patients with IRIS who developed clinical signs, symptoms, and radiographic features of IRIS.**

IRIS = immune reconstitution inflammatory syndrome.

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greater did not gain a survival benefit from ART initiation within the first 4 weeks compared with ART initiation at the start of the continuation phase of tuberculosis treatment, but they had a 2-fold higher risk for IRIS (1.53 vs. 7.1 per 100 person-years) (11). Similarly, no discernible survival or decreased morbidity benefit was evident with early ART initiation in patients with a CD4+ count of 0.950 × 10^6 cells/L or greater in the ACTG 5221 study; the incidence rate of AIDS or death was 11.5% in patients who initiated ART within 2 weeks compared with 10.3% in those initiating ART within 8 to 12 weeks of the start of tuberculosis treatment (13).

In addition to being more common, IRIS was more severe in patients initiating ART in the first 4 weeks of tuberculosis treatment. Those who initiated ART early had greater burden of IRIS-related illness, longer duration of illness, more steroid use, and higher rates of hospitalization. Two thirds of all severe or life-threatening IRIS-associated adverse events occurred in patients in the early integrated treatment group. These patients had a disproportionately high number (approximately 80%) of the IRIS-associated hospitalizations in the study. Consistent with previously published data (14, 20, 26, 28), low baseline CD4+ cell count and high baseline viral load were statistically significant risk factors for IRIS in our study. Time to IRIS resolution in the early integrated treatment group was 2-fold higher than that in the late integrated treatment group and 3-fold higher than that in the sequential treatment group. Furthermore, 50% of all patients requiring steroids for management of IRIS were in the early integrated treatment group. Steroid therapy was prescribed in 10% of patients with IRIS in this study to alleviate the clinical course of IRIS when life-threatening, space-occupying lesions or danger of respiratory failure existed. However, the role of corticosteroids in management of IRIS has not been clearly defined. A study has shown that steroids reduced the need for hospitalization and therapeutic procedures and hastened improvement in IRIS symptoms, whereas other studies caution against steroids in patients with IRIS because they have been shown to exacerbate underlying opportunistic infections, including drug-resistant tuberculosis and Kaposi sarcoma (29, 30). There was no difference in the number of unscheduled medical visits or drug switching due to toxicity or virologic failure between patients who developed IRIS and those who did not develop IRIS. It is important to underscore that, overall, we found that the IRIS-associated death rate was relatively low and that IRIS had a relatively benign nature. These findings are clinically relevant on 2 levels: For individual patients, they increase confidence in coadministering tuberculosis and HIV treatment without fear of worsening morbidity and mortality due to IRIS; for public health, they indicate that tuberculosis and HIV integration can occur without increasing the availability of resources for IRIS management, especially in settings where tuberculosis and HIV are endemic.

In light of higher IRIS-associated morbidity with early ART in tuberculosis treatment, the decision on the timing of ART in co-infected patients should be influenced by baseline CD4+ cell counts because of the association between risk for IRIS and reported morbidity and mortality benefit by CD4+ cell count strata. Thus, in patients with a CD4+ count less than 0.950 × 10^6 cells/L, the balance of benefit and risk would favor initiation of ART within 4 weeks of tuberculosis treatment initiation. On the other hand, in patients with a CD4+ count of 0.950 × 10^6 cells/L or greater, the decision of early versus later initiation of ART during tuberculosis treatment must be weighed against the availability of clinical capacity to diagnose and manage IRIS. Hence, careful consideration is required to assess the potential benefits and risks of each strategy in each clinical setting. Of note, in patients with a CD4+ count greater than 0.950 × 10^6 cells/L, although ART initiation may be deferred for 8 to 12 weeks after tuberculosis treatment initiation, every effort should be made to initiate ART no later than 12 weeks after tuberculosis treatment initiation. In addition, early initiation of ART should be strongly considered among patients with a CD4+ count greater than 0.950 × 10^6 cells/L, who also have a clinical disease of major severity; organ system dys-
function; or low Karnofsky performance score, body mass index, hemoglobin level, or albumin level, because these variables are associated with higher mortality rates.

Our study has several limitations. First, because we enrolled ambulatory patients with sputum smear-positive tuberculosis, our results may not be directly generalizable to all forms and severities of tuberculosis in HIV-infected patients. Although the difference in patient retention across the 3 study groups was not statistically significant, it is possible, albeit unlikely, that ascertainment of IRIS was greater in the early integrated treatment group than in the other 2 groups as a result of more patients being retained in that group. In addition, we were unable to assess IRIS in patients who were lost to follow-up, withdrew, or died before or 6 months after their scheduled ART initiation, but results comparing early and late integrated treatments were unchanged in various sensitivity analyses.

Second, in the absence of placebo use in this trial, study clinicians knew when a patient began ART, which could have biased the assessment of whether IRIS was present. We mitigated this bias to some extent by using standard checklists that were followed for clinical assessments and diagnosis of IRIS. It was not possible to prevent treating clinicians from knowing when patients initiated ART, and this may have affected their clinical management decisions, including whether to hospitalize. We attempted to minimize this limitation by a standard procedure that required a second clinician to give an opinion on hospitalization. Decisions on steroid use were made by hospital clinicians unrelated to the study.

Further studies may be necessary to assess IRIS risk in nonambulatory patients and in those with extrapulmonary and smear-negative tuberculosis. Although CD4+ cell count was a strong prog nostic indicator of IRIS risk, CD4+ cell count assays are not always available in many settings. Decisions on the timing of ART in individual patients need to be modified by clinical judgment of disease severity and consideration of capacity to diagnose and manage IRIS. In the absence of a reliable diagnostic test for IRIS, it is possible that misclassification bias occurred. Milder forms of IRIS were probably missed because IRIS diagnosis is dependent on patient self-reporting of specific symptoms and clinician awareness, especially where diagnostic radiography is not routinely available or is inaccessible, even to symptomatic patients. This issue was addressed procedurally through use of a standard IRIS evaluation checklist, which was administered to every patient at each clinical visit. The INS11 criteria for IRIS diagnosis were published 3 years after we commenced our study (7). Despite the lack of a standardized case definition for IRIS at the time, we implemented several steps in the design and conduct of the study to ensure consistency in reporting, recording, and interpreting suspected IRIS.

We address an important and current topic in the management of individuals co-infected with HIV and tuberculosis by using data from a randomized clinical trial that had more cases of IRIS (80 patients) than prior reports and used a single ART regimen in a well-characterized, smear-positive tuberculosis cohort. Because integration of tuberculosis and HIV treatment can reduce mortality by 56% (10), decisions on when to start ART during tuberculosis treatment should take into account the balance of risk and severity of IRIS and potential benefits in relation to morbidity or mortality. Incidence of IRIS is substantially higher in patients starting ART earlier after tuberculosis treatment initiation. Although patients with severe immunosuppression have a clear survival benefit from early ART initiation despite high IRIS risk (11–13), this balance of risks and benefits is different in patients with a higher CD4+ cell count. Deferring ART initiation by as much as 12 weeks after tuberculosis treatment initiation may be an appropriate strategy in stable ambulatory patients with a CD4+ count of 0.050 × 10^9 cells/L or greater because this approach offers lower incidence and severity of IRIS without increasing the risk for AIDS or death. Future research efforts need to focus on finding a reliable diagnostic marker of IRIS in routine clinical and laboratory settings. Furthermore, a randomized, placebo-controlled trial that would investigate whether corticosteroids in patients with a CD4+ count less than 0.050 × 10^9 cells/L initiating highly active ART early in tuberculosis treatment reduce frequency and severity of IRIS events and need for hospitalization is warranted. In addition, validated clinical and laboratory tools to reliably diagnose IRIS will simplify clinical management decisions for patients with HIV and tuberculosis.

From University of KwaZulu-Natal and eThekwini Research Clinic, Durban, South Africa; Columbia University, New York, New York; and Yale University School of Medicine, New Haven, Connecticut.

Disclaimer: All authors had access to the data, commented on drafts, and approved the final report. Dr. Naikoo had final responsibility for the decision to submit the report for publication.

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IRIS After ART Initiation in Patients With Tuberculosis

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Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M12-4847.

Reproducible Research Statement: Study protocol: Available by contacting the authors. Statistical code and data set: Available from Ms. Yenelle Zuma (zuma.yenelle@fudan.ac.jp). Access to all items will be restricted (based on prior ethical approval for data use and on completion of written informed consent from the author or researcher sponsor).

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References

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**Appendix Table 1. Patterns of Patient Withdrawal, by Study Group**

<table>
<thead>
<tr>
<th>Study Duration</th>
<th>Early Integrated Treatment Group</th>
<th>Late Integrated Treatment Group</th>
<th>Sequential Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to &lt; 6 mo</td>
<td>Died (n = 7) Lost to follow-up (n = 13) Withdrawn (n = 7) Requested withdrawal: 1 Could not attend visits: 1</td>
<td>Died (n = 53) Lost to follow-up (n = 21) Withdrawn (n = 8) Requested withdrawal: 5 Unable to adhere to protocol: 1 Relocated: 2</td>
<td>Died (n = 52) Lost to follow-up (n = 15) Withdrawn (n = 6) Requested withdrawal: 1 Unable to adhere to protocol: 7 Relocated: 3 Discontinuing medications in other hospital: 1</td>
</tr>
<tr>
<td>6 to &lt; 12 mo</td>
<td>Died (n = 2) Lost to follow-up (n = 2) Withdrawn (n = 2) Requested withdrawal: 2 Relocated: 1</td>
<td>Died (n = 6) Lost to follow-up (n = 8) Withdrawn (n = 7) Requested withdrawal: 2 Unable to adhere to protocol: 2 Relocated: 3</td>
<td>Died (n = 59) Lost to follow-up (n = 12) Withdrawn (n = 5) Requested withdrawal: 3 Unable to adhere to protocol: 2</td>
</tr>
<tr>
<td>12 to 18 mo</td>
<td>Died (n = 3) Lost to follow-up (n = 6) Withdrawn (n = 7) Requested withdrawal: 5 Relocated: 2</td>
<td>Died (n = 31) Lost to follow-up (n = 4) Withdrawn (n = 7) Requested withdrawal: 2 Unable to adhere to protocol: 2 Relocated: 3</td>
<td>Died (n = 2) Lost to follow-up (n = 7) Withdrawn (n = 6) Unable to adhere to protocol: 5 Relocated: 1</td>
</tr>
</tbody>
</table>

* Deaths or withdrawals that happened after onset of IBS have been removed so that the table matches Figure 3.
### Appendix Table 2. Baseline Characteristics of Patients Who Withdrew, Died, or Could Not Be Assessed for IRIS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lost to Follow-up/Withdrawn (n = 144)</th>
<th>Died (n = 59)</th>
<th>Lost to Follow-up, Withdrew, or Died (n = 203)</th>
<th>Completed (n = 439)*</th>
<th>P Value</th>
<th>Could Not Be Assessed for IRIS (n = 1568)</th>
<th>Assessed for IRIS (n = 486)</th>
<th>P Value$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), y</td>
<td>32.4 (7.4)</td>
<td>34.6 (8.0)</td>
<td>33.1 (7.6)</td>
<td>34.8 (8.6)</td>
<td>0.019</td>
<td>32.3 (7.1)</td>
<td>34.9 (8.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>78 (54.2)</td>
<td>37 (62.7)</td>
<td>115 (56.7)</td>
<td>264 (46.5)</td>
<td>0.018</td>
<td>89 (57.1)</td>
<td>236 (47.3)</td>
<td>0.043</td>
</tr>
<tr>
<td>BMI &lt;18.5 kg/m², n (%)</td>
<td>10 (7.5)</td>
<td>10 (17.5)</td>
<td>30 (15.1)</td>
<td>52 (11.9)</td>
<td>0.31</td>
<td>24 (17.5)</td>
<td>56 (11.5)</td>
<td>0.095</td>
</tr>
<tr>
<td>History of tuberculosis, n (%)</td>
<td>42 (29.2)</td>
<td>21 (35.6)</td>
<td>63 (31.0)</td>
<td>151 (34.4)</td>
<td>0.42</td>
<td>53 (34.0)</td>
<td>161 (33.1)</td>
<td>0.85</td>
</tr>
<tr>
<td>Extrapulmonary tuberculosis, n (%)</td>
<td>3 (2.1)</td>
<td>5 (8.6)</td>
<td>8 (4.0)</td>
<td>20 (4.6)</td>
<td>0.84</td>
<td>4 (2.6)</td>
<td>24 (5.0)</td>
<td>0.26</td>
</tr>
<tr>
<td>WHO stage 4a, n (%)</td>
<td>5 (3.5)</td>
<td>8 (13.6)</td>
<td>13 (6.4)</td>
<td>25 (5.7)</td>
<td>0.72</td>
<td>8 (5.1)</td>
<td>30 (6.2)</td>
<td>0.70</td>
</tr>
<tr>
<td>Median CD4 count (IQR), × 10⁶ cells/lt</td>
<td>0.197 (0.109 to 0.312)</td>
<td>0.073 (0.025 to 0.150)</td>
<td>0.154 (0.074 to 0.282)</td>
<td>0.144 (0.073 to 0.238)</td>
<td>0.27</td>
<td>0.155 (0.074 to 0.297)</td>
<td>0.143 (0.073 to 0.239)</td>
<td>0.163</td>
</tr>
<tr>
<td>Median CD8 count (IQR), × 10⁶ cells/lt</td>
<td>0.663 (0.446 to 1.027)</td>
<td>0.571 (0.334 to 0.821)</td>
<td>0.632 (0.423 to 0.934)</td>
<td>0.668 (0.456 to 1.002)</td>
<td>0.132</td>
<td>0.614 (0.417 to 0.929)</td>
<td>0.665 (0.456 to 1.030)</td>
<td>0.064</td>
</tr>
<tr>
<td>Mean log₂ HIV RNA (SD, copies/ml)</td>
<td>4.9 (0.9)</td>
<td>5.2 (0.8)</td>
<td>5.0 (0.8)</td>
<td>5.1 (0.9)</td>
<td>0.131</td>
<td>5.0 (0.9)</td>
<td>5.1 (0.9)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

BMI = body mass index; IQR = interquartile range; IRIS = immune reconstitution inflammatory syndrome; WHO = World Health Organization.

* Patients with IRIS are regarded as having completed the study. Missing data were not included in the percentage calculation.

P = p value for comparison of patients who were lost to follow-up, who were withdrawn, or who died compared to the study population.

P = p value for comparison of patients who could not be assessed for IRIS with those who could be assessed.

### Appendix Table 3. IRIS Incidence, by Study Group*

<table>
<thead>
<tr>
<th>CD4⁺ Count</th>
<th>Early Integrated Treatment Group</th>
<th>Late Integrated Treatment Group</th>
<th>Sequential Treatment Group</th>
<th>Incidence Rate Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Person-Years</td>
<td>Incidence Rate per 100 Person-Years (95% CI)</td>
<td>Patients</td>
<td>Person-Years</td>
</tr>
<tr>
<td>&lt;0.009 × 10⁶ cells/lt</td>
<td>13</td>
<td>30.6</td>
<td>42.2 (22.9 to 71.2)</td>
<td>4</td>
<td>41.3</td>
</tr>
<tr>
<td>≥0.059 × 10⁶ cells/lt</td>
<td>25</td>
<td>189.9</td>
<td>11.3 (5.5 to 19.4)</td>
<td>13</td>
<td>198.5</td>
</tr>
</tbody>
</table>

IRIS = immune reconstitution inflammatory syndrome.

* Excludes 6 patients with IRIS who had no available CD4⁺ cell count.
### Table 4: IRIS Incidence and Incidence Rate Ratios for Selected Baseline Characteristics, by Study Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early Integrated Treatment Group</th>
<th>Late Integrated Treatment Group</th>
<th>Sequential Treatment Group</th>
<th>All Treatment Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence Rate (95% CI)</td>
<td>Incidence Rate Ratio (95% CI)</td>
<td>Incidence Rate (95% CI)</td>
<td>Incidence Rate Ratio (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;31 y</td>
<td>18/96.0</td>
<td>18.8 (11.1 to 29.6)</td>
<td>0.9 (0.5 to 1.8)</td>
<td>9/107.7</td>
</tr>
<tr>
<td>≥31 y</td>
<td>29/123.6</td>
<td>23.2 (13.1 to 40.3)</td>
<td>1.8 (1.1 to 2.9)</td>
<td>10/127.7</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21/95.2</td>
<td>22.1 (13.7 to 35.7)</td>
<td>1.3 (0.7 to 2.4)</td>
<td>6/122.5</td>
</tr>
<tr>
<td>Female</td>
<td>22/146.6</td>
<td>15.7 (11.1 to 26.7)</td>
<td>1.0 (0.5 to 1.9)</td>
<td>7/126.5</td>
</tr>
<tr>
<td>CD4+ count</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.050 × 10⁹/μl</td>
<td>14/108.0</td>
<td>45.2 (24.9 to 79.6)</td>
<td>4.2 (1.4 to 7.7)</td>
<td>4/41.8</td>
</tr>
<tr>
<td>0.050-0.200 × 10⁹/μl</td>
<td>24/107.9</td>
<td>21.6 (15.7 to 36.6)</td>
<td>1.7 (1.0 to 1.5)</td>
<td>10/108.0</td>
</tr>
<tr>
<td>&gt;0.200 × 10⁹/μl</td>
<td>5/91.2</td>
<td>5.5 (1.8 to 12.8)</td>
<td>0.7 (0.2 to 2.2)</td>
<td>4/90.3</td>
</tr>
<tr>
<td>Log₁₀ HIV RNA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 copies/mL</td>
<td>3/18.6</td>
<td>16.2 (3.3 to 47.2)</td>
<td>0.9 (0.5 to 1.7)</td>
<td>0/20.4</td>
</tr>
<tr>
<td>≥3 copies/mL</td>
<td>8/93.8</td>
<td>8.3 (3.7 to 16.8)</td>
<td>1.2 (0.6 to 2.3)</td>
<td>4/90.4</td>
</tr>
<tr>
<td>Extrapulmonary tuberculosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>3/1.5</td>
<td>6.3 (0.8 to 47.3)</td>
<td>1.0 (0.1 to 1.9)</td>
<td>0/0</td>
</tr>
<tr>
<td>Yes</td>
<td>41/210.7</td>
<td>19.8 (14.2 to 26.4)</td>
<td>1.3 (0.7 to 2.4)</td>
<td>17/226.6</td>
</tr>
<tr>
<td>WHO stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>41/209.8</td>
<td>19.9 (14.3 to 27.7)</td>
<td>1.3 (0.8 to 2.4)</td>
<td>16/237.6</td>
</tr>
<tr>
<td>Stage 2</td>
<td>2/14.0</td>
<td>14.2 (7.1 to 30.1)</td>
<td>1.0 (0.5 to 2.2)</td>
<td>2/13.4</td>
</tr>
</tbody>
</table>

IRIS = immune reconstitution inflammatory syndrome; WHO = World Health Organization.
* Continuous risk factors were split at the median for comparison purposes.
CHAPTER 7

HIGH RATES OF TUBERCULOSIS IN PATIENTS ACCESSING HAART IN RURAL SOUTH AFRICA


High Rates of Tuberculosis in Patients Accessing HAART in Rural South Africa

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Background: The challenge of early tuberculosis (TB) infection among rural patients accessing highly active antiretroviral therapy (HAART), in a resource-limited setting with high HIV and TB burden has not been fully quantified.

Methods: This is a retrospective study nested within a prospective study of 969 patients consecutively initiated onto HAART at the CAPRISA AIDS Treatment programme in rural KwaZulu-Natal between January 2007 and December 2010. Patients were screened for clinical symptoms consistent with TB using a standardized checklist, and routine clinical investigations that included sputum microscopy and chest X-ray diagnosis.

Results: Of 969 HIV-infected patients initiated on HAART, 173 (17.9%); 95% confidence interval (CI): 15.5 to 20.4) had active TB at HAART initiation. TB incidence rates were 3-fold higher in the first 3 months (early incident TB) after HAART initiation [11.5/1000 person-years (py); 95% CI: 7.1 to 17.5] compared with +24 months (late incident TB) post-HAART initiation (3.2/1000 py; 95% CI: 2.2 to 4.5; incidence rate ratio: 3.6; 95% CI: 2.0 to 6.4; P < 0.001). Immune status of patients at HAART initiation did not impact TB incidence rates in patients with CD4+ counts of <50 (15.3/1000 py; P = 0.81) cells per cubic millimeter. CD4+ count gains achieved 12 months post-HAART initiation were significantly different in patients with early incident TB versus late incident TB; P = 0.033.

Conclusions: Rural HIV treatment programmes in TB-endemic settings experience high rates of TB irrespective of immunological status of patients at HAART initiation, or duration on HAART.

Key Words: HIV, TB, tuberculosis, HAART, Africa, KwaZulu-Natal, South Africa

I J Acquir Immune Defic Syndr 2014;65:438-446

Tuberculosis (TB) infection contributes substantially to morbidity and mortality among HIV-positive patients. Globally, HIV-associated TB peaked in 2005 at 1.39 million cases with approximately 15% incident cases and 480,000 deaths. However, 2010 data indicated a continuing burden of HIV-associated TB with 1.1 million cases of TB of which 13% were incident cases and resulting in approximately 350,000 deaths. South Africa is home to approximately 1.2 million HIV-infected individuals with 70% of TB patients coinfected with HIV, and a TB notification rate of 1094 cases per 100,000 population. The use of highly active antiretroviral therapy (HAART) in HIV-infected patients reduces the risk of developing TB by 70%-90% and is therefore a key strategy recommended by the World Health Organization (WHO) to prevent TB. Studies from resource-limited settings show that HIV-infected patients have higher rates of TB compared with HIV-uninfected patients, and with longer duration on HAART there is a decline in TB incidence rates.
Notwithstanding the evidence for TB screening and diagnosis, and HAART initiation early during TB therapy, the burden of undiagnosed TB at HAART initiation and the number of new TB cases diagnosed during HAART in high HIV and TB settings have not been fully measured. In rural districts of KwaZulu-Natal where the TB and HIV epidemics converge most dramatically, the TB burden and its impact on patients at HAART initiation and during treatment remain poorly documented.

The aim of this study was to measure the prevalence and incidence rates of TB among patients accessing HAART in a rural community-based programme in a high TB and HIV prevalence setting in KwaZulu-Natal, South Africa, and explores its impact on therapeutic outcomes.

METHODS

Study Population

We conducted a prospective cohort study among 969 HIV-positive patients initiated onto HAART at the Vulindlela CAPRISA AIDS Treatment programme between January 01, 2007 and December 31, 2010. This rural community outpatient clinic admits and receives patients from one of 7 primary health care clinics in an area serving a community of about 400,000 people. Eligibility criteria were in accordance with South African Government HIV/AIDS treatment guidelines at the time. Patients were screened for clinical symptoms consistent with TB using a standardized checklist that asked about drenching night sweats, prolonged cough, fever, and weight loss by either clinicians or professional nurses at every clinical visit. Patients who screened positive were referred to the adjacent government Primary Health Care Clinic for TB smear testing. Smear-positive patients were initiated onto anti-TB therapy while sputum culture testing and antibiotic therapy was offered to all smear-negative patients. Smear- and culture-negative patients with poor response to antibiotics, and those with suspected extrapulmonary TB were referred to the local district hospital for chest x-ray, abdominal ultrasonography, or other invasive investigations such as lymph node aspirate, tissue biopsy, and others. Access to TB microbiology services was variable and depended on the availability of skilled laboratory staff especially for culture and drug susceptibility testing and timeous communication of results to site staff and patients. Tuberculin skin testing and isoniazid preventive therapy (IPT) was not the currently available standard of care during the study period. Patients were seen monthly for the first 6 months and every 3 months thereafter unless clinically indicated. Routine demographic, laboratory, and clinical data were recorded at baseline and at follow-up visits. On TB diagnosis, the following additional information was collected: date and method of diagnosis, TB type [extrapulmonary TB (EPTB) or pulmonary TB (PTB)]; TB drug susceptibility pattern, and date of TB treatment initiation and completion. Patients who had both PTB and EPTB were then classified as having EPTB. TB was diagnosed and treated as per South African National TB Control Program guidelines. All patients with complications or requiring further investigation and management were referred to the closest district level services about 30 km away.

Statistical Analysis

All reported P values are 2-sided. TB incidence was calculated as number of new TB cases after HAART initiation per 100 person-years (py) of follow-up. Data are presented as proportions, means, or medians where appropriate. Study duration for patients with no prevalent TB was calculated from HAART initiation date to date of TB diagnosis, or programme exit through loss to follow-up, transfer out, or death. Patients with prevalent TB were included in the incidence calculation and their time on study calculated from the date treatment for prevalent TB was discontinued to either the date of a new TB diagnosis, or to programme exit through loss to follow-up, transfer out, or death. All patient data were censored at 24 months of follow-up. Poisson approximations were used to calculate confidence intervals (CIs) for TB incidence. Kaplan-Meier was used to construct survival curves. Incidence rate ratios (IRR) were used to identify factors associated with early and late incident TB. The following baseline covariates were used to assess factors associated with early and late incident TB: age, gender, weight, WHO stage HIV disease, number of previous TB episodes, CD4+ counts, and viral load. Data were extracted from routinely collected data recorded on standardized case report forms captured on a customized database through datafile. Statistical analysis was performed using SAS (version 9.2; SAS Institute Inc., Cary, NC).

This study was approved by the Biomedical Research Ethics Committee, University of KwaZulu-Natal, ref no: E248/05.

RESULTS

Baseline Demographic Characteristics

The study comprised 969 HIV-infected patients consecutively initiated on HAART between January 2007 and December 2010. The demographic and clinical characteristics at baseline are presented in Table 1. Approximately two-thirds of the cohort was women (67.8%). The mean age of patients was 34.3 years (SD ± 9.6 years). The median
TABLE 1. Baseline Characteristics of Patients Enrolled Onto HAART*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall (N = 969)</th>
<th>No TB (N = 745)</th>
<th>Prevalent TB (N = 173)</th>
<th>Early Incident TB (N = 21)</th>
<th>Late Incident TB (N = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs), mean ± SD&lt;sup&gt;†&lt;/sup&gt;</td>
<td>44.3 ± 9.6</td>
<td>44.5 ± 9.8</td>
<td>33.9 ± 8.3</td>
<td>29.3 ± 5.3</td>
<td>15.5 ± 11.3</td>
</tr>
<tr>
<td>No. females, n (%)&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>651 (67.8)</td>
<td>599 (69.2)</td>
<td>103 (59.5)</td>
<td>17 (81.0)</td>
<td>24 (72.7)</td>
</tr>
<tr>
<td>Weight (kg), mean ± SD&lt;sup&gt;§&lt;/sup&gt;</td>
<td>61.0 ± 13.5</td>
<td>62.0 ± 14.1</td>
<td>56.9 ± 10.6</td>
<td>62.4 ± 12.6</td>
<td>58.1 ± 11.4</td>
</tr>
<tr>
<td>BMI (kg/m²) &lt;sup&gt;∥&lt;/sup&gt;</td>
<td>19.4 (18.5–21.3)</td>
<td>20.0 (18.9–21.3)</td>
<td>19.4 (18.3–21.2)</td>
<td>20.0 (18.9–21.2)</td>
<td>19.4 (18.3–21.2)</td>
</tr>
<tr>
<td>CD&lt;sub&gt;4&lt;/sub&gt; cell count (cells/mm&lt;sup&gt;3&lt;/sup&gt;)&lt;sup&gt;‡&lt;/sup&gt;, median (IQR)&lt;sup&gt;∥&lt;/sup&gt;</td>
<td>129 (61–186)</td>
<td>139 (71–198)</td>
<td>97 (41–147)</td>
<td>104 (71–139)</td>
<td>112 (34–204)</td>
</tr>
<tr>
<td>WHO Stage 3 of HIV Disease, n (%)**</td>
<td>567 (59.3)</td>
<td>365 (49.8)</td>
<td>166 (96.0)</td>
<td>16 (76.2)</td>
<td>23 (71.9)</td>
</tr>
<tr>
<td>History of TB at HAART initiation, n (%)</td>
<td>226 (23.2)</td>
<td>133 (18.0)</td>
<td>80 (46.0)</td>
<td>5 (23.8)</td>
<td>9 (28.1)</td>
</tr>
<tr>
<td>Recent TB history, n (%)</td>
<td>139 (14.5)</td>
<td>62 (46.8)</td>
<td>139 (14.5)</td>
<td>62 (46.8)</td>
<td>139 (14.5)</td>
</tr>
<tr>
<td>Recent past TB history, n (%)&lt;sup&gt;∥&lt;/sup&gt;</td>
<td>87 (38.5)</td>
<td>71 (53.4)</td>
<td>87 (38.5)</td>
<td>71 (53.4)</td>
<td>87 (38.5)</td>
</tr>
</tbody>
</table>

BMI, body mass index.
*Three patients who developed late incident TB had prevalent TB.
†Ten patients had missing age.
‡Seven patients had missing gender.
§Seven patients had missing weight.
∥Six hundred seventy-one patients had missing BMI data.
**Eighty-six patients had missing CD<sub>4</sub> cell count data.

Follow-up time was 11 [interquartile range (IQR), 6.7–19.6] months, with 77.3% (749/969) of patients still in active follow-up at 24 months post-HAART initiation. The median baseline CD<sub>4</sub> count among patients with early incident TB, late incident TB, with no TB, and in the entire cohort were 101 (IQR, 71–139), 112 (IQR, 34–204), 131 (IQR, 63–187), and 128 (IQR, 61–186) cells per cubic millimeter, respectively. The median baseline CD<sub>4</sub> count overall, among patients with early incident TB, late incident TB, and with no TB was 128 (IQR, 61–186), 101 (IQR, 71–139), and 128 (IQR, 61–186) cells per cubic millimeter, respectively. Approximately 50% of the cohort presented with clinically evident WHO stage 3 HIV disease.

TB Status at HAART Initiation
At baseline, all 969 patients were offered a TB symptom-screening checklist. The diagnosis of active TB (prevalent TB group) was made in 173/969 patients (17.9%; 95% CI: 15.5 to 20.4). Two-thirds of patients with baseline prevalent TB (68.6% had PTB, 24.9% had EPTB, 4.0% had both PTB and EPTB, and 2.3% had TB with the site unspecified). Diagnosis of prevalent PTB (n = 119) was made through sputum smear (n = 54/119), chest x-ray (n = 54/65), clinical grounds only (n = 9/11), and missing data on method of diagnosis (n = 2). The diagnosis of prevalent EPTB (n = 43) was made through diagnostic radiology (n = 25), lymph node aspirate (n = 4), joint aspirate (n = 1), histology from biopsy specimen (n = 2), on clinical grounds (n = 5), and unknown (n = 6). Seven patients had both PTB and EPTB at baseline, diagnosed on sputum smear (n = 1), chest x-ray (n = 2), clinical grounds only (n = 2/7), diagnostic radiology (n = 1/7), and pleural tap (n = 1/7). There were 226 patients with a history of TB (80 in the prevalent TB group and 146 in the group without prevalent TB at baseline) of which 61.5% had an episode of TB within the year before HAART initiation (recent history) (Fig. 1). TB prevalence stratified by immune status is presented in Table 2. Prevalent TB was highest among patients with CD<sub>4</sub> counts of <500 cells per cubic millimeter (25.1%, 47/187; 95% CI: 19.2 to 32.1).

**Incident TB Infections**
There were 54 new clinical TB cases identified after HAART initiation giving an overall TB incidence rate of 4.5 per 100 py (95% CI: 3.3 to 5.8). There were 3 cases of incident TB in the group with prevalent TB at the time of HAART initiation. Early incident TB was 3-fold higher (11.5/100 py; 95% CI: 7.1 to 17.5) compared with late incident TB (3.2/100 py, 95% CI: 2.2 to 4.5; IRR, 3.6; 95% CI: 2.0 to 6.4; P < 0.001) (Fig. 2). Diagnosis of incident PTB (n = 29) was made through sputum smear (n = 7/29), chest x-ray (n = 19/29), sputum culture (n = 1/3), and clinical grounds only (n = 2/29). Diagnosis of incident EPTB (n = 23) was made through diagnostic radiology (n = 13/23), pleural tap (n = 1/1), histology from biopsy specimen (n = 1/1), clinical grounds only (n = 5/23), and unknown (n = 5). Two patients with incident TB had both PTB and EPTB, which was diagnosed by diagnostic radiology.

**Risk Factors for Early and Late Incident TB**
The rate of early incident TB was almost 2-fold higher among female; 13.3/100 py; (95% CI: 7.6 to 21.3) compared with male patients; 7.3/100 py; (95% CI: 2.0 to 18.8; IRR, 1.8; 95% CI: 0.6 to 7.4; P = 0.21), and almost 5-fold higher among patients aged between 24 and 34 years (17.8/100 py, 95% CI: 10.0 to 29.4) compared with ≥35 years (3.8/100 py, 95% CI: 0.8 to 11.1; IRR, 4.7; 95% CI: 1.3 to 25.2; P = 0.01) (Table 3). However, interaction between gender and age was
FIGURE 1. Flowchart depicting TB burden in a community-based HAART programme. History of TB information was available for 947 individuals. Cohort included all patients enrolled onto HAART between January 2007 and December 2010, with patient follow-up time from enrolment date up until June 2011, when database was closed. History of TB: patient who completed TB treatment before HAART initiation; recent history of TB: episode of TB within the year before HAART initiation; remote history of TB: TB episode more than a year before HAART initiation; prevalent TB: patient for whom treatment was ongoing during HAART initiation; incident TB: new cases of TB diagnosed after HAART initiation, which was further divided into early incident TB defined as a new TB diagnosis within 3 months of HAART initiation, and late incident TB defined as a new TB diagnosis 4–24 months post-HAART initiation. PTB, pulmonary TB; EPTB, extrapulmonary TB, including cases of both PTB and EPTB; CAT, The Centre for the AIDS Programme of Research in South Africa (CAPRISA) AIDS Treatment Programme.

not statistically significant \( (P = 0.10) \). No other factors were found to be associated with incident TB.

Baseline immune status of patients did not impact overall TB incidence rates; patients with CD4\(^+\) counts of <50 cells per cubic millimeter had TB incidence rates of 5.3/100 py (95% CI: 2.7 to 9.3) compared with 4.9/100 py (95% CI: 2.4 to 9.0) in patients with CD4\(^+\) counts of >200 cells per cubic millimeter (\( P = 0.81 \)). Additionally, baseline immune status did not impact rates of incident TB.

TB incidence rates 3 months post-HAART initiation among patients with CD4\(^+\) counts of < 50, between 50 and 200, and >200 cells per cubic millimeter were 4.6 (95% CI: 2.1 to 8.8), 2.4 (95% CI: 1.3 to 4.0), and 4.7 (95% CI: 2.0 to 9.2) per 100 py (Table 2).

Impact on Therapeutic Outcomes

There were 51 incident cases of TB among patients with no prevalent TB at baseline (26 PTB, 25 EPTB), and 3 incident cases of PTB among patients with prevalent TB at baseline. There was one case of multidrug-resistant TB in this cohort. Patients with incident PTB and EPTB had similar median baseline CD4\(^+\) counts, 106 versus 129 cells per cubic millimeter (\( P = 0.57 \)), and baseline log viral loads, 5.2 versus 6.2.

<table>
<thead>
<tr>
<th>Baseline CD4(^+) Count (Cells/mm(^3))</th>
<th>Overall (N = 969)</th>
<th>No TB (N = 745)</th>
<th>Prevalent TB (N = 173)</th>
<th>Early Incident TB (N = 21)*</th>
<th>Late Incident TB (N = 33)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing</td>
<td>80 (8.9)</td>
<td>63 (8.5)</td>
<td>17 (10.0)</td>
<td>4.14 (9.1)</td>
<td>2.6 (3.2 to 9.6)</td>
</tr>
<tr>
<td>CD4(^+) count &lt; 50 cells/mm(^3)</td>
<td>187 (19.1)</td>
<td>129 (17.2)</td>
<td>47 (27.4)</td>
<td>26.9 (7.3 to 68.8)</td>
<td>2.75 (6.2 to 28.2)</td>
</tr>
<tr>
<td>CD4(^+) count 50–200 cells/mm(^3)</td>
<td>553 (55.2)</td>
<td>425 (56.8)</td>
<td>87 (50.3)</td>
<td>11.5 (5.9 to 26.1)</td>
<td>4.86 (1.3 to 4.0)</td>
</tr>
<tr>
<td>CD4(^+) count &gt; 200 cells/mm(^3)</td>
<td>161 (16.6)</td>
<td>130 (17.4)</td>
<td>22 (12.8)</td>
<td>6.0 (0.7 to 21.8)</td>
<td>4.7 (2.0 to 9.2)</td>
</tr>
</tbody>
</table>

*Number of patients.
**New TB diagnosis in the first 3 months after HAART initiation.

†TB incidence between 4 and 24 months post-HAART initiation.
FIGURE 2. Kaplan-Meier estimates of cumulative probability of developing early incident TB.

5.0 (P = 0.19); and similar mean CD4⁺ count increases (P = 0.17) and viral load decreases (P = 0.16) from baseline to 12 months post-HAART initiation. The median (IQR) months on HAART to a new episode of TB was 3.7 (0.8–10.9) and 5.2 (1.6–10.8) in the PTB and EPTB groups, respectively. Median CD4⁺ count change from baseline to 12 months post-HAART initiation was significantly higher in patients experiencing early incident 167 (IQR, 141–235) versus late incident 76 (IQR, 32–187) cells per cubic millimeter TB (P = 0.03) (see Table S1, Supplemental Digital Content, http://links.lww.com/QAI/A486).

Mortality Rates

There were 57 deaths in this cohort with an overall mortality rate of 4.3 per 100 py (95% CI: 3.3 to 5.6). There were 7 deaths among patients with baseline prevalent TB, mortality rate of 2.7 (95% CI: 1.1 to 5.6) per 100 py compared with 50 deaths among 796 patients with no baseline prevalent TB, mortality rate of 4.7 (95% CI: 3.5 to 6.3) per 100 py (P = 0.20) of follow-up. Patients with at least 1 episode of TB (either history, prevalent or incident TB) had a lower mortality rate 3.4 (95% CI: 2.0 to 5.4) compared with patients with no TB, 4.5 (95% CI: 3.1 to 6.3) per 100 py (IRR, 0.8; 95% CI: 0.5 to 1.4; P = 0.42) of follow-up. There was 1 death each in the early and late incident TB groups. The causes of death for 29 of 57 patients was known, and this included PTB (n = 4), EPTB (n = 5), complications from severe gastroenteritis (n = 6), trauma (n = 2), natural causes (n = 5), meningitis-unknown cause (n = 2), lower respiratory tract infection (n = 2), cerebrovascular accident (n = 1), intracranial lesion (n = 1), and complications from hyperlactatemia (n = 1). Causes of death were not available in 28 patients as many of them died at home.

DISCUSSION

In a rural HIV treatment programme in a TB endemic setting, we found unacceptably high TB incidence rates irrespective of baseline immunologic status of patients at HAART initiation, or duration on HAART. We document TB incidence rates of 4.5/100 py of follow-up among HIV-infected patients receiving community-based HAART care in a rural setting. This incidence is higher than reports from other sub-Saharan countries and most other high TB burden settings and nearly 10-fold higher than reported among HIV-negative patients from a setting with similar TB notification rates. Thus, we provide further evidence for continued susceptibility of HAART-accessing patients to TB infection in a hyper-endemic TB setting sustained over 2 years post-HAART initiation. This continued susceptibility to TB despite HAART likely points to ongoing community-level and possibly nosocomial TB transmission.

We demonstrate an alarmingly high and consistent TB incidence (Table 2) among all baseline CD4⁺ count strata during study follow-up. The data show an inverse relationship between time on HAART and TB incidence, corroborating past studies, and likely because of greater TB-specific immune restoration with time spent on HAART. Furthermore, we highlight the need for close clinical observation in the first few months post-HAART initiation by demonstrating highest rates of incident TB, likely because of “unmasked” infection, in the


<table>
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<th>Risk Factor</th>
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<tr>
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*Early incident TB is defined as a new TB diagnosis within 3 months of HAART initiation.

Late incident TB is defined as new TB diagnosis 4-24 months post HAART initiation.

first 3 months post-HAART initiation. Additionally, the continued high rate of new TB infections even at 24 months post-HAART initiation is in keeping with published reports showing that, despite its decline with time on HAART, TB incidence among a HAART-accessing HIV population remains higher than in the general HIV-uninfected population. We speculate that the high TB incidence rates observed in this study may be because of either impaired restoration of TB specific immunity when patients are severely immune compromised (baseline CD4+ counts ≤200 cells/mm³) at HAART initiation, or because of high ongoing community-level TB transmission. The incidence rates observed are most likely because of a combination of both these factors. Interestingly, although women carry a disproportionate burden of HIV in sub-Saharan Africa, and despite finding a 2-fold higher rate of early incident TB in women compared with men, further analysis stratified by age and gender showed no statistically significant difference in risk for either early or late incident TB. Notwithstanding lower pre-HAART CD4+ counts among patients who developed early incident TB, therapeutic outcomes among patients at 12 months post-HAART initiation was similar in all groups. In contrast to our study, published literature demonstrates a far more substantial time-dependent reduction in TB incidence among patients on HAART. These studies report highest TB incidence during the first 3 months of HAART with a progressive reduction of all forms of TB during the first year of follow-up from 5.77/100 to 2.23/100 py. Published meta-analysis data from developed country cohorts estimate a comparable effect of HAART on TB incidence despite differences in background risk of
Mycobacterium tuberculosis infection. These data provide an estimated TB incidence of 3 cases per 1000 py among patients accessing HAART, 10-fold lower compared with the TB incidence rates we found. Findings similar to ours were reported in only 1 other study, conducted in a densely populated urban informal settlement with an HIV seroprevalence of 28% and TB notification rate of >1000/100,000 population. In this study, TB incidence was reduced from 22.1 to 4.5/100 py among patients with a median baseline CD4+ count of 96 cells per cubic millimeter (IQR, 46–156), after approximately 3 years of HAART.

The vast majority of TB episodes among patients with a previous TB history occurred in the 5-year period immediately before HAART initiation, a likely clinical feature of symptomatic HIV disease. We demonstrated a TB prevalence rate of 17.9% among HIV-infected patients initiating HAART, lower than previous reports from a South African community-based HAART program. Other published studies from resource-limited settings report a high TB prevalence at HAART enrollment, primarily among patients with CD4+ count <50 cells per cubic millimeter. However, data from this study show high rates of prevalent TB especially in lower baseline CD4+ count strata and not only among those severely immune compromised. Among patients enrolling on HAART, 1 in 4 with CD4+ counts of <100 cells per cubic millimeter and 1 in 7 patients with CD4+ counts of ≥100 cells per cubic millimeter had active TB. It is important to note, however, that excluding active TB among HIV-infected patients is usually complex owing to high rates of smear-negative TB and difficulty distinguishing subclinical TB, common among patients accessing HAART.

Unsurprisingly, there was no statistically significant difference in mortality rates among cases with known TB at baseline compared with those without. Mortality studies among HIV-infected patients conducted in this setting have repeatedly demonstrated high rates of undiagnosed TB responsible for as much as 79% of all deaths in HIV-infected patients. Mortality rates were similar among patients with new episodes of EPTB as compared with those with new episodes of PTB: 2.3 (95% CI: 0.1 to 13.1) versus 2.1 (95% CI: 0 to 11.6) per 100 py of follow-up. Interestingly, the mortality rate at 24 months in this study among patients with and without prevalent TB at baseline was very different to 5-year mortality rates of 4.84 and 2.62 per 100 py of follow-up among prevalent TB and TB-free patients initiating antiretroviral therapy in Cape Town, South Africa.

Although it may be likely that most cases of early incident TB was due to immune reconstitution inflammatory syndrome (IRIS), it remains unclear as to what proportion of incident TB was due to “unmasking” versus “paradoxical” TB incidence versus new TB infections. It is well understood that IRIS embodies an interpretive crisis because its clinical diagnosis is similar to TB treatment failure, drug toxicities, TB relapse, or new AIDS-defining illness, and cannot be diagnosed by available clinical parameters. Mortality rates were similar among patients with and without prevalent TB at baseline and were very different to 5-year mortality rates of 4.84 and 2.62 per 100 py of follow-up among prevalent TB and TB-free patients initiating antiretroviral therapy in Cape Town, South Africa.

CONCLUSIONS
Our study on the prevalence and incidence of TB in a rural, community-based HIV treatment programme has described a disproportionately high TB burden in patients accessing HAART. Our findings highlight the urgent need to implement TB-preventive therapy and TB infection control practices in HAART programmes in endemic settings. TB incidence by baseline CD4+ count is highest among patients with CD4+ count of <50 cells per cubic millimeter; however, we also observed high TB incidence rates at higher CD4+ counts. Therefore, despite apparent immunologic recovery among HAART-accessing HIV patients, high TB incidence is still a potent threat, possibly reflecting community and nosocomial TB transmission. The availability of point-of-care diagnostic assays such as GeneXpert that
readily diagnose TB while patients queue for services will facilitate TB case finding before the start of HAART, thereby reducing TB-related morbidity and mortality commonly found among patients newly enrolled into HAART programs in TB-endemic setting.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of the CAPRISA AIDS Treatment team for providing clinical care of study patients. The authors thank the KwaZulu-Natal Department of Health, the staff of the Umgungundlovu district office, and the nurses at the Majekhulu Primary Care Clinic for their professional support and for clinical care of patients. The mentorship and oversight provided by Professor Salim Abdool Karim and Quarraisha Abdool Karim of CAPRISA was invaluable, without which this project would not have been possible.

REFERENCES


Chapter 8 presents secondary analysis of SAPiT trial data and assesses the impact of TB HIV co-treatment on additive toxicity and virologic failure. There were low rates of drug switching due to toxicity in all study arms, with virologic failure commoner in those with CD4 counts < 50 cells/mm³.
CHAPTER 8

CHANGES TO ANTIRETROVIRAL DRUG REGIMENS DURING INTEGRATED TB-HIV TREATMENT: RESULTS OF THE SAPIT TRIAL


Changes to antiretroviral drug regimens during integrated TB-HIV treatment: Results of the SAPIT trial

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Abstract

Background—Frequency of drug changes in combination antiretroviral therapy among patients starting both tuberculosis (TB) and human immunodeficiency virus (HIV) therapy, as a result of treatment-limiting toxicity or virological failure, is not well established.

Methods—Patients in the Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPIT) trial were randomized to initiate antiretroviral therapy either early or late during TB treatment or after completion of TB treatment. Drug changes due to toxicity (defined as due to grade 3 or 4 adverse events) or virological failure (defined as viral load > 1000 copies/ml on two occasions, taken at least 4 weeks apart) were assessed in these patients.

Results—A total of 501 TB-HIV co-infected patients were followed for a mean of 16.0 (95% confidence interval (CI): 15.5 to 16.6) months after antiretroviral therapy (ART) initiation. The standard first-line ARV’s used were efavirenz, lamivudine and didanosine. Individual drug switches for toxicity occurred in 14 patients (incidence rate: 2.1 per 100 person-years; 95% CI: 1.1 to 3.5), and complete regimen changes due to virological failure in 25 patients (incidence rate: 3.7 per 100 person-years; CI: 2.4 to 5.5). The most common treatment limiting toxicities were neuropsychiatric effects (n=4; 0.8%), elevated transaminase levels and hyperlactatemia (n=2; 0.4%) and peripheral neuropathy (n=2; 0.4%). Complete regimen change due to treatment failure was more common in patients with CD4+ cell count < 500 cells/mm3 (p=0.001) at ART initiation and body mass index greater than 25 kg/m2 (p=0.01) at entry into the study.

Conclusion—Both drug switches and complete regimen change were uncommon in patients co-treated for TB-HIV with the chosen regimen. Patients with severe immunosuppression need to be monitored carefully, as they were most at risk for treatment failure requiring regimen change.

Introduction

There were an estimated 8.7 million cases of tuberculosis (TB) in 2011, approximately 1.1 million of which were co-infected with human immunodeficiency virus HIV [1]. Sub-

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Saharan Africa accounted for 80% of the global burden of TB–HIV co-infections [1]. Co-treatment of these diseases presents several management challenges. Treatment-limiting toxicity is an important concern when integrating TB-HIV treatment. Other concerns include drug interactions between rifampicin and some classes of antiretrovirals [2], immune reconstitution inflammatory syndrome (IRIS) and high pill burden [3, 4].

These clinical challenges potentially undermine the success of both HIV and TB control programs, contribute to the poor tolerability of combined antiretroviral therapy (ART) and TB therapy, and impact on treatment adherence. There is now evidence that initiating ART during TB therapy in co-infected patients significantly reduces mortality, and improves outcomes in both conditions [5–8]. However, these benefits need to be weighed against the risks of morbidity due to treatment interruptions, toxicity or treatment failure.

There are limited prospective data from randomized controlled trials available to inform clinical guidelines. In this paper we report the incidence, predictors of, and reasons for ART changes, in a cohort of TB-HIV co-infected patients enrolled in a randomized controlled trial designed to determine the optimal time to initiate ART in TB treatment.

Methods

Study Design and Participants

The Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPIT) trial was an open label, three-arm, randomized, controlled trial, which enrolled 642 patients between June 2005 and July 2008, to determine the optimal timing of ART initiation in TB-HIV co-infected patients. Details of the study design and procedures and the primary outcomes of the study have been described previously [5, 6]. In brief, TB-HIV co-infected patients, aged 18 years or older (screening CD4+ count < 500 cells/mm³), were enrolled at the CAPRISA cThekwini clinical research site, which adjoins the Prince Cyril Zulu Communicable Disease Centre (PCZCDC), in Durban, South Africa. HIV-infection was confirmed by two rapid HIV tests and pulmonary TB (PTB) was confirmed by acid fast bacilli smear positivity.

Study Procedures

Patients were randomized to initiate ART within 4 weeks of tuberculosis treatment initiation (early integrated treatment arm), within 4 weeks after completion of intensive phase of tuberculosis treatment (late integrated treatment arm), or within 4 weeks after tuberculosis therapy completion (sequential treatment arm). Patients were initiated on a once daily ART regimen consisting of efavirenz 600mg, lamivudine 300mg and enteric-coated didanosine 250mg (weight <60kg) or 400mg (weight ≥ 60kg). All first episode PTB was treated with a fixed–dose combination of rifampicin, isoniazid, ethambutol and pyrazinamide according to pre-treatment weight for 2 months (intensive phase), with subsequent fixed-dose combination of isoniazid and rifampicin for 4 months (continuation phase). Patients with re-treatment PTB received a 60-day intensive phase which included streptomycin, followed by a 100-day continuation phase, in accordance with the national policy. Patients were offered community- or clinic-based directly observed therapy. All patients received a standard package of care which included adherence counseling and cotrimoxazole prophylaxis. Additionally, female patients were required to use hormonal contraception while on efavirenz.

Follow-up visits for the monitoring of safety, clinical status and adherence to ART were scheduled monthly for 24 months. Laboratory investigations included baseline (at screening and enrolment) CD4+ cell count using a FACS flow cytometer (Becton Dickinson, Franklin Lakes NJ, USA), viral load by HIV RNA PCR (Roche Cobas Amplicor HIV-1 Monitor...
v1.5-lower limit of detection 400 copies/ml, full blood counts, urea, electrolytes, creatinine, liver function, Hepatitis B surface antigen tests and syphilis serology. These investigations were done at baseline and repeated every 6 months or earlier, if clinically indicated. ART adherence was assessed monthly using pharmacy pill counts. Pill counts were assessed based on the number of pills dispensed and physically returned. In addition we took into account lost doses and remaining doses reported on previously that may have been returned at a subsequent visit.

Adverse events were graded with the use of the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 1.0) [9]. A toxicity grading of 3 or 4 was used as indication for discontinuation or substitution of specific antiretroviral drugs, and referred to as drug switch due to toxicity. Drug switch could also occur as a result of contraindication or drug interaction.

Virolological failure, defined as a viral load >1000 copies/ml on two occasions, taken at least 4 weeks apart, resulted in discontinuation or complete regimen change of all first line ART drugs. Viral suppression or undetectable viral load was defined as a viral load of <400 copies/ml. Drug changes therefore referred to both individual drug switches, as a result of toxicity, and to complete regimen changes, as a result of virolological failure. The most commonly utilised (72%) second line regimen in patients requiring complete regimen change comprised, lopinavir/ritonavir, tenofovir and zidovudine.

Study Oversight
Ethical approval for the study was provided by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (E107/05), and the Medicines Control Council of South Africa (MCC Ref: 20060157).

Statistical analysis
This analysis was based on a 24 months post randomization follow-up time period to allow for the patients in the sequential treatment arm to have sufficient time on antiretroviral therapy to be comparable to the other two arms.

Time at risk was calculated from ART initiation to the date on which drugs were stopped, death, withdrawal or termination from the study. For patients who changed drugs more than once, only the first change was included in the incidence rate calculation. Confidence intervals (CI) for incidence and incidence rate ratios (IRR) assumed a Poisson distribution. Multivariate Cox proportional hazards regression models were used separately for drug switch and complete regimen change to assess the risk factors for regimen changes. Data published in 2010 [5] provided interim results following the September 2008 safety monitoring committee review. Results presented in 2011 were based on the complete set of trial data [6]. The data presented in this paper, in addition, cover the full 24-month follow-up period post randomization. All statistical tests were two sided. Fisher’s Exact test or Fisher-Freeman-Halton test was used for the analysis of categorical data. The T-test for independent samples, Wilcoxon two-sample, one way ANOVA or the Kruskal-Wallis tests were used for the analysis of continuous data. Statistical analysis was done using SAS (version 9.2; SAS Institute Inc., Cary, NC, USA).

Results
Of 1331 patients screened for eligibility, 642 were enrolled and randomized into the study, with 501 initiating ART; 198 (39.5%); 164 (76.3%); 139 (65.3%) in the early integrated, late integrated and sequential arms respectively (Figure 1). Patients were followed for an average of 17.6 (95% CI: 16.6 to 18.6); 16.8 (95% CI: 16.0 to 17.6) and 13.0 (95% CI: 12.3 to 13.7)
months after ART initiation, with a retention rate at 24 months post randomization of 76.6%, 71.2% and 71.3%, in the early integrated, late integrated and sequential arms respectively.

Baseline results

There were differences only for weight (p=0.01) and haemoglobin (p=0.001) across the three treatment arms, and CD4+ cell counts were lower in in patients who had drug changes (p=0.01) (Table 1). At baseline, the proportion of patients with Hepatitis B surface antigenemia, peripheral neuropathy and raised transaminases (>5 times the upper limit of normal) were similar across the three treatment arms (Table 1).

Incidence of complete regimen change and drug switch across the three treatment arms

ART changes occurred in 39/501 patients, with an incidence rate (IR) of 5.8 (95% CI: 4.1 to 8.0) per 100 person-years (py). One participant experienced two individual drug switches for different reasons. Among 14-501 (2.8%) patients, drug switches for toxicity occurred at a median time of 3.6 months (IQR: 2.5 to 6.9) post ART initiation, with an incidence rate of 2.1 (95% CI: 1.1 to 3.5). Complete regimen change occurred in 15/501 (5.0%) patients with an incidence rate of 3.7 (95% CI: 2.4 to 5.5) per 100 py. There was no significant difference in the incidence of individual drug switches or complete regimen changes between the three arms (p=0.23). There were no differences in median time to single drug switches (p=0.64) and complete regimen changes (p=0.86) across the three treatment arms. Incidence of complete regimen changes in the early integrated treatment arm was 2.3 per 100 py (95% CI: 0.9 to 4.8) compared to 3.9 per 100 py (95% CI: 1.8 to 7.4) in the late integrated treatment arm (IRR: 0.6, 95% CI: 0.2 to 1.8; p=0.37) and 5.9 per 100 py (95% CI: 2.7 to 11.1) in the sequential treatment arm (IRR: 0.4, 95% CI: 0.1 to 1.2; p=0.19) (Table 2). In patients with CD4+ cell counts <500 cells/μL, the incidence of complete regimen change was 5.5 (95% CI: 1.1 to 16.1), 12.9 (95% CI: 4.7 to 28.2) and 13.4 (95% CI: 2.8 to 39.3) per 100 py in the early integrated, late integrated and sequential treatment arms respectively (p=0.53). In patients with CD4+ count >500 cells/μL, the incidence of complete regimen change was 1.6 (95% CI: 0.4 to 4.2), 1.6 (95% CI: 0.3 to 4.8) and 4.6 (95% CI: 1.7 to 10.0) per 100 py in the early integrated, late integrated and sequential treatment arms, respectively (p=0.17).

Reasons for drug switches

The reasons for and time to individual drug switches from ART initiation are shown in Table 3. We found the most common treatment-limiting toxicities to be neuropsychiatric effects (n=4; 0.8%) elevated transaminases and hyperlactatemia (n=3; 0.6%) and peripheral neuropathy (n=2; 0.4%). Eleven of the 15 drug switches occurred within the first 6 months after ART initiation. Among the 14 patients with drug switches, five were on concurrent TB-HIV treatment. Five patients in each of the early and late treatments arms and one in the sequential treatment arm experienced ART treatment interruptions due to toxicity, but these toxicities did not lead to any drug switches.

Complete Regimen Change

The median time to complete regimen change from ART initiation was 9.9 (IQR: 6.4 to 13.0), 10.4 (IQR: 9.7 to 11.0), 9.5 (IQR: 8.1 to 10.9) months with no significant difference between the arms (p=0.64). Among the patients with complete regimen change none were on concurrent TB therapy at the time of regimen change. The median viral load before complete regimen change was 4.9 (IQR: 4.3 to 5.6) log copies/ml. Virologic suppression rates were high in all treatment arms after 18 months of follow-up [5, 6].
Adherence

The overall adherence at 24 months post ART initiation, based on pill count data, was similar across the 3 treatment arms (p=0.64). Among patients with drug changes, the adherence rates were 90.4%, 86.2% and 93.6% (p=0.58), whereas among patients without drug changes, the adherence rates were 95%, 96% and 97.4% in the early, late, and sequential treatment arms, respectively (p=0.48).

Risk factors associated with drug switches and complete regimen change in co-treated patients

Treatment arm was not associated with drug switches and complete regimen changes. Baseline CD4+ cell count < 50 cells/mm³ was significantly associated with complete regimen change (HR: 4.7; 95% CI: 1.6 to 14.0; p=0.005) compared to CD4+ cell count ≥50 cells/mm³. Additionally, patients with a BMI greater than 25 kg/m² were more likely to experience complete regimen change (HR: 3.3; 95% CI: 1.4–7.8; p=0.01) compared to patients with BMI 18.5–25 kg/m². (Table 4)

Discussion

We demonstrated similar incidence of ART drug switches irrespective of the timing of ART initiation relative to the start of TB treatment, providing evidence that potentiated drug toxicity may be of limited concern in TB-HIV co-treatment. Low rates of drug switching due to toxicity was observed in all three arms, with no significant difference in the incidence of drug switching between the treatment arms, although the number of drug switches was higher in the early and late integrated compared to the sequential treatment arm. The regimen chosen for this study provided a once-daily option at a time before the availability of tenofovir, to be taken with once daily TB treatment. Reports from two other randomised controlled trials also show similar rates of toxicity in patients who start ART early (within 2 weeks), or later (within 8 weeks), in the course of TB treatment. In the STRIDE study, 44% and 47% of patients experienced grade 3 and 4 adverse events, with 14/40 patients in the early group. and 7/101 patients in the late-ART group switching ART regimen for toxicity, respectively. Likewise, the CAMELIA study found similar incidence of drug-related adverse events; 2.93 (95% CI: 2.58 to 3.22) and 2.31 (95% CI: 2.31 to 3.63) events per 100 person months in the earlier and later ART groups respectively. The first line ARV treatment regimen used in the STRIDE and CAMELIA studies, included once daily efavirenz, emtricitabine and tenofovir and efavirenz lamivudine and stavudine taken twice daily, respectively.

Data on rates of adverse events and drug switches due to toxicity in patients receiving therapy for both HIV and tuberculosis are limited. Observational studies in TB-HIV co-treatment demonstrate conflicting rates of drug related adverse events, compared to evidence to the contrary from the three relatively large randomized controlled trials. A retrospective study from South Africa showed that the occurrence of serious adverse events was unrelated to the use of antiretroviral drugs in patients with TB. However, retrospective studies conducted in Thailand and India, among patients with CD4 < 100 cells/mm³, found drug-related adverse events occurred in 66% of co-treated patients in the first 2 months of TB treatment, and that concomitant use of ART and TB treatment was a predictor of adverse events (OR: 1.88) (12). Notably, in these two relatively small studies (< 150 patients), two thirds of all patients received a NVP-containing ART regimen, whereas almost all of our patients were initiated on an Efavir-based ART regimen.

Previous studies have shown that peripheral neuropathy (43%) and hepatotoxicity (5–10%) are the most common toxicities in patients receiving TB-HIV co-treatment (7, 13–15). The
most common cause of drug switching in our study was neuropsychiatric toxicity, most likely related to the use of an EFV-based first line regimen. Contrary to other studies, describing the increased risk of hepatotoxicity when ART is introduced during the intensive phase of TB therapy [15], there were no drug switch for treatment limiting hepatotoxicity among patients in the early integrated treatment arm. However, drug switch for hepatotoxicity was observed in the late integrated and sequential treatment arms. This may be as a result of patients having lower CD4+ cell counts due to delay in initiation of ART [15]. While studies that report an increased risk of hepatotoxicity in TB-HIV co-treatment cite baseline elevated transaminases and hepatitis B antigenemia as likely risk factors [16–25], the prevalence of both conditions was low in our study, which may account for the small number of drug switch from hepatotoxicity that were observed.

It is likely that the profile of toxicities presenting in this cohort is linked to our choice of first line ART regimen, which was chosen for its suitability to be co-administered with directly observed TB treatment and once daily dosing. The absence of clinically significant alteration of elavirenz plasma concentration when co-administered with rifampicin has been demonstrated [26, 27]. Elavirenz has also been shown to have a lower risk of hepatotoxicity than nevirapine [25]. Enteric coated didanosine (ddI-EC) has a lower risk of peripheral neuropathy and gastro-intestinal toxicities than stavudine and buffered ddI [14], the available NRTIs at the time of study conduct.

In addition, this study was conducted in ambulant, relatively clinically stable patients with TB disease mainly confined to the lungs. Although other nucleoside/nucleotide reverse transcriptase options, included in fixed-dose combinations, have now eclipsed didanosine-containing regimens as the first-line options, enteric-coated didanosine may still provide a useful alternative in patients unable to tolerate the alternative once-daily option [28].

Despite the additional pill burden when TB and ART therapy was co-administered in the early and late-integrated treatment arms, the adherence was similar across the three treatment arms. The incidence of ART complete regimen change from virological failure was low and did not differ by treatment arm, despite the addition of 3 ARVs to the 4-drug intensive phase of TB or to the 2 drug maintenance phase of TB therapy. Similar high rates of virological suppression were achieved and sustained, through to 18 months of follow-up after ART initiation across all study arms. These rates were similar to rates achieved at 48 and 50 weeks in the STRIDE and CAMELIA studies respectively [7, 8], and better than reports of virological suppression rates (76%) achieved in treatment programmes from sub-Saharan Africa at 12 months [29].

The higher incidence of complete regimen change in patients with CD4 <50 cells/mm³ observed in this study has also been reported in other TB and non-TB settings [30–33]. Several studies have shown that low CD4+ cell counts are a predictor for complete regimen change due to virological failure. [34–36]. The drug switches in patients with low CD4+ cell counts may not be directly associated with TB HIV co-treatment, but may instead be due to the presence of other co-morbidities in patients with advanced HIV disease.

Low BMI has been shown in previous studies to be associated with poor treatment outcomes and a potential predictor of treatment failure in resource constrained settings [34–36]. In contrast our study found higher BMI >25 kg/m² to be associated with a higher risk of complete regimen change, this may in part, be explained by findings from other studies which found sub-therapeutic drug levels [37] and BMI > 25 kg/m² to be an independent risk factor for virological failure [38].

The following study limitations need to be considered. We included ambulant patients with CD4+ cell count up to 500 cells mm³, higher than the CD4 threshold for ART in current
WHO and South African ART treatment guidelines. The inclusion of patients less advanced in the course of their HIV disease may have led to an under-estimation of the true effect of additive toxicity when co-treating TB-HIV. In this study, ART drug switches were triggered by grade 3 or 4 toxicities. However, grade 1 and 2 toxicities may affect adherence to therapy or patients’ quality of life. Interruptions to TB drug therapy are also not included in this analysis. Pill counts as a measure of adherence reported in this study, may have over-estimated the adherence reported.

Conclusion
Both drug switches and complete regimen changes were uncommon in patients co-treated for TB-HIV, using a didanosine, lamivudine and efavirenz first-line regimen. Manageable treatment-limiting toxicities occurred early, and affected a small percentage of the trial participants. The survival benefit from early initiation of ART in TB-HIV co-infected patients outweighed the concerns of treatment-limiting toxicities. Low CD4 count and higher BMI (≥25) at baseline increased the risk of treatment failure and complete regimen change, although the association with higher BMI may need further validation.

Patients with severe immunosuppression need to be monitored carefully, using viral load determinations, as they were most at risk for treatment failure requiring regimen change. The additional pill burden with combined TB-HIV treatment did not have a significant effect on adherence to ART in this study. These data further strengthen the available evidence of the benefits of integrating TB-HIV treatment and underline the continued usefulness of alternative once-daily regimens in such settings.

Acknowledgments
We thank the patients for their participation in this study, Mrs. Annelle Grobler for statistical support; Mr. Nanthu Samoudre for laboratory support; Dr. Aarush Singh and Dr. Muziru Xuma for additional clinical support; Fadie Burton for data management; Mrs. Cheryl Baxter for editorial assistance; and all other members of the SAVIT study team. CAPRISA was established as part of the Comprehensive International Program of Research on AIDS (CIPRA) grant # AI51794 from the US National Institutes of Health. The US President’s Emergency Plan for AIDS Relief (PEPFAR) funded the care of all the participants in the trial. The Global Fund to fight AIDS, Tuberculosis and Malaria funded the costs of the drugs used in the trial. The research infrastructure to conduct this trial, including the data management, laboratory and pharmacy cores was established through the CIPRA grant. Dr. K Naidoo, Dr. N Padayachy and Ms. Tanya Gigaba were supported by the Columbia University-Southern African Fogarty AIDS International Training and Research Program (AITRP) funded by the Fogarty International Center, National Institutes of Health (grant # D43TW00231).

Role of the funding sources
The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had access to data, commented on drafts, and approved the final report. The corresponding author had final responsibility for the decision to submit for publication.

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32. Khunprasit N, Chaiwarith R, Sirisanthana T, Supparatpinyo K. Incidence and risk factors of antiretroviral treatment failure in treatment-naive HIV-infected patients at Chiang Mai University Hospital, Thailand. AIDS Research and Therapy. 2011; 8:42. [PubMed: 22060823]


Figure 1.
SAPIT trial: Screening, randomization, and follow-up of study participants, demonstrating distribution of patients with drug switches due to toxicity and complete regimen change due to virological failure.

*1 patient experienced 2 individual drug switches due to toxicity for different reasons in the early integrated arm (9 drug switches and 16 ARV drug changes in total) but only the initial drug switch is illustrated in this figure and used in the incidence rate calculation.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early integrated treatment arm (N=190)</th>
<th>Late-integrated treatment arm (N=164)</th>
<th>Sequential treatment arm (N=139)</th>
<th>p-value</th>
<th>Participants without ART changes (N=62)</th>
<th>Participants with ART changes (N=39)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), years</td>
<td>34.6 (8.1)</td>
<td>35.1 (9.1)</td>
<td>34.8 (9.5)</td>
<td>0.86</td>
<td>149 (8.7)</td>
<td>35.1 (8.9)</td>
<td>0.81</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>90 (47.3)</td>
<td>79 (48.2)</td>
<td>86 (48.9)</td>
<td>0.79</td>
<td>211 (47.9)</td>
<td>164 (48.9)</td>
<td>0.30</td>
</tr>
<tr>
<td>WHO stage 3, n (%)</td>
<td>13 (6.7)</td>
<td>11 (6.7)</td>
<td>8 (5.8)</td>
<td>0.95</td>
<td>29 (6.5)</td>
<td>3 (1.7)</td>
<td>0.75</td>
</tr>
<tr>
<td>Past history of tuberculosis, n (%)</td>
<td>73 (36.9)</td>
<td>49 (29.9)</td>
<td>45 (30.9)</td>
<td>0.31</td>
<td>134 (33.4)</td>
<td>11 (28.2)</td>
<td>0.70</td>
</tr>
<tr>
<td>Median CD4+ (cells/mm³)</td>
<td>145.5 (73-267)</td>
<td>141 (57.5-247)</td>
<td>146 (74-269)</td>
<td>0.69</td>
<td>150 (82-253)</td>
<td>65 (27-215)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean log10 HIV RNA (SD, copies/ml)</td>
<td>5.0 (0.9)</td>
<td>5.0 (0.9)</td>
<td>5.0 (0.8)</td>
<td>0.98</td>
<td>5.0 (0.9)</td>
<td>5.2 (0.9)</td>
<td>0.27</td>
</tr>
<tr>
<td>Mean hemoglobin (SD), g/dl</td>
<td>10.6 (2.0)</td>
<td>11.5 (1.8)</td>
<td>12.0 (2.0)</td>
<td>&lt;0.001</td>
<td>11.3 (2.0)</td>
<td>11.3 (1.8)</td>
<td>0.87</td>
</tr>
<tr>
<td>Mean weight (SD), kg</td>
<td>59.6 (10.5)</td>
<td>61.7 (10.7)</td>
<td>62.9 (13.5)</td>
<td>0.01</td>
<td>61.0 (10.9)</td>
<td>62.2 (10.8)</td>
<td>0.51</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5 kg/m², n (%)</td>
<td>18 (9.5)</td>
<td>10 (6.1)</td>
<td>7 (5.1)</td>
<td>0.32</td>
<td>7 (7.9)</td>
<td>5 (13.5)</td>
<td>0.06</td>
</tr>
<tr>
<td>18.5-25 kg/m², n (%)</td>
<td>132 (68.7)</td>
<td>103 (64.0)</td>
<td>88 (64.2)</td>
<td>0.56</td>
<td>96 (66.5)</td>
<td>19 (68.7)</td>
<td>0.77</td>
</tr>
<tr>
<td>&gt;25 kg/m², n (%)</td>
<td>46 (24.4)</td>
<td>49 (29.9)</td>
<td>42 (30.7)</td>
<td>0.95</td>
<td>122 (28.5)</td>
<td>17 (43.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Past history of alcohol use, n (%)</td>
<td>0.81</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>199 (98.6)</td>
<td>138 (85.7)</td>
<td>110 (82.1)</td>
<td>0.37</td>
<td>374 (93.9)</td>
<td>37 (88.9)</td>
<td>0.44</td>
</tr>
<tr>
<td>Occasionally</td>
<td>23 (12.3)</td>
<td>16 (5.9)</td>
<td>17 (12.7)</td>
<td>0.54</td>
<td>54 (12.1)</td>
<td>2 (5.6)</td>
<td>0.06</td>
</tr>
<tr>
<td>Frequently</td>
<td>6 (3.2)</td>
<td>7 (4.4)</td>
<td>7 (5.2)</td>
<td>0.18</td>
<td>18 (4.4)</td>
<td>2 (5.6)</td>
<td>0.64</td>
</tr>
<tr>
<td>First line regimen, n (%)</td>
<td>195 (98.5)</td>
<td>162 (98.8)</td>
<td>134 (97.1)</td>
<td>0.59</td>
<td>455 (98.7)</td>
<td>36 (92.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>EFV, FTC, D4T</td>
<td>3 (1.5)</td>
<td>2 (1.2)</td>
<td>2 (1.4)</td>
<td>0.02</td>
<td>13 (2.8)</td>
<td>1 (2.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>NVP, FTC, D4T</td>
<td>6 (3.0)</td>
<td>6 (3.7)</td>
<td>6 (3.8)</td>
<td>0.08</td>
<td>18 (4.4)</td>
<td>2 (5.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>Presence of peripheral neuropathy before ART initiation, n (%)</td>
<td>6 (3.0)</td>
<td>6 (3.7)</td>
<td>6 (3.8)</td>
<td>0.08</td>
<td>18 (4.4)</td>
<td>2 (5.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hepatitis B surface antigen, n (%)</td>
<td>0.99</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>13 (9.4)</td>
<td>11 (7.3)</td>
<td>11 (8.5)</td>
<td>0.34</td>
<td>33 (6.4)</td>
<td>3 (8.3)</td>
<td>0.55</td>
</tr>
<tr>
<td>Negative</td>
<td>144 (90.6)</td>
<td>129 (92.7)</td>
<td>122 (91.7)</td>
<td>0.17</td>
<td>372 (93.6)</td>
<td>23 (91.7)</td>
<td>0.51</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>1 (0.3) (n=197)</td>
<td>6 (0.3) (n=164)</td>
<td>6 (0.3) (n=157)</td>
<td>0.57</td>
<td>106 (2.5) (n=459)</td>
<td>6 (1.3)</td>
<td>0.06</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>2 (1.2) (n=197)</td>
<td>2 (1.2) (n=164)</td>
<td>1 (0.7) (n=157)</td>
<td>0.57</td>
<td>106 (2.5) (n=459)</td>
<td>6 (1.3)</td>
<td>0.06</td>
</tr>
</tbody>
</table>
SD=standard deviation; IQR=Interquartile range; BMI=Body mass index; AST=aspartate transaminase; ALT=alanine transaminase

1 participant had missing CD4+ count in the sequential arm

At ARV initiation

6 participants in the early integrated treatment arm, 1 in the late integrated treatment arm and 2 in the sequential treatment arm had missing viral load

2 participants in the early integrated treatment arm, 2 in the late integrated treatment arm and 3 in the sequential treatment arm had hemoglobin

2 participants in the late integrated treatment arm do not have weight, missing data not included in percentage calculation

10 participants in the early integrated treatment arm, 3 in the late integrated treatment arm and 5 in the sequential treatment arm had missing past history of alcohol use

1 participant in the sequential arm had no regimen data

1 participant in the early integrated treatment arm, 14 in the late integrated treatment arm and 6 in the sequential treatment arm had missing hepatitis data
### Table 2

**Incidence rate of drug switches and complete regimen change across the 3 treatment arms**

<table>
<thead>
<tr>
<th>Drug change</th>
<th>Early Integrated treatment arm</th>
<th>Late Integrated treatment arm</th>
<th>Sequential treatment arm</th>
<th>Early vs late</th>
<th>Early vs sequential</th>
<th>Late vs sequential</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Person Years (n)</td>
<td>No. Of switches</td>
<td>Person Years (n)</td>
<td>No. Of switches</td>
<td>Person Years (n)</td>
<td>No. Of switches</td>
</tr>
<tr>
<td>Drug change</td>
<td>290.4 (198)</td>
<td>15</td>
<td>5.2(2.9-8.5)</td>
<td>275.0 (164)</td>
<td>11</td>
<td>4.8(2.4-8.8)</td>
</tr>
<tr>
<td>Drug switch</td>
<td>290.4 (198)</td>
<td>8</td>
<td>2.6(1.2-5.6)</td>
<td>275.0 (164)</td>
<td>2</td>
<td>0.9(0.1-5.2)</td>
</tr>
<tr>
<td>Complete regimen change</td>
<td>300.1 (198)</td>
<td>7</td>
<td>2.3(1.0-4.9)</td>
<td>276.6 (164)</td>
<td>9</td>
<td>3.9(1.5-9.7)</td>
</tr>
</tbody>
</table>

*combination of drug switches and complete regimen change*
Table 3

**Summary of ART changes**

<table>
<thead>
<tr>
<th>Drug switched and Reason for Switch</th>
<th>Early integrated treatment arm</th>
<th>Late integrated treatment arm</th>
<th>Sequential treatment arm</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Didanosine (ddI) N=5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplasticity</td>
<td>2 (0.9 and 1.0)</td>
<td>0</td>
<td>0</td>
<td>2 (0.9 and 1.0)</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>1 (1.2)</td>
<td>0</td>
<td>0</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Pancreatitis, hemoglobinopenia</td>
<td>0</td>
<td>1 (3.1)</td>
<td>0</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Acute viral Hepatitis</td>
<td>0</td>
<td>0</td>
<td>1 (3.2)</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>Efavirenz (EFV) N=5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td>3 (0.5, 2.5 and 3.6)</td>
<td>0</td>
<td>1 (5.6)</td>
<td>4 (0.5, 2.5, 3.6 and 5.6)</td>
</tr>
<tr>
<td>Bas</td>
<td>0</td>
<td>0</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Zidovudine (AZT) N=2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>0</td>
<td>1 (8.3)</td>
<td>0</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>1 (2.4)</td>
<td>0</td>
<td>0</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Nevirapine (NVP) N=2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>1 (8.9)</td>
<td>0</td>
<td>0</td>
<td>1 (8.9)</td>
</tr>
<tr>
<td>Rectal tuberculous</td>
<td>0</td>
<td>0</td>
<td>1 (5.3)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Didanosine (ddI) and Lamivudine(TC) N=1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe anaemia</td>
<td>1 (3.7)</td>
<td>0</td>
<td>0</td>
<td>1 (3.7)</td>
</tr>
</tbody>
</table>

**Changes in Second Line Drugs, Complete Regimen Change (CRC) N=25**

<table>
<thead>
<tr>
<th>EFV/3TC/ddT</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral failure</td>
<td>7 (5.9-0.9-1.0)</td>
<td>9 (10.4-0.7-1.0)</td>
<td>9 (9.5-0.8-1.0)</td>
<td>25 (10.2-0.1-1.1)</td>
</tr>
</tbody>
</table>

\(^{a}\)Median (IQR) for 25 that changed to second line due to virological failure
Table 4

Risk factors for drug switch and complete regimen change

<table>
<thead>
<tr>
<th>Variable</th>
<th>Drug switch for toxicity</th>
<th>Complete regimen change for virologic failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Randomization arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequential treatment arm</td>
<td>reference</td>
<td>1.4 (0.4-4.8)</td>
</tr>
<tr>
<td>Early integrated treatment arm</td>
<td>reference</td>
<td>0.4 (0.1-2.6)</td>
</tr>
<tr>
<td>Lat integrated treatment arm</td>
<td>reference</td>
<td>0.4 (0.1-2.6)</td>
</tr>
<tr>
<td>Sex</td>
<td>reference</td>
<td>1.6 (0.7-7.2)</td>
</tr>
<tr>
<td>Age (per 1 year increase)</td>
<td>reference</td>
<td>0.99 (0.9-1.1)</td>
</tr>
<tr>
<td>CD4+ cell count (cells/mm^3)^a</td>
<td>&lt;50</td>
<td>1.7 (0.3-4.4)</td>
</tr>
<tr>
<td>Body mass index (kg/m^2)</td>
<td>&lt;18.5</td>
<td>2.2 (0.5-10.0)</td>
</tr>
<tr>
<td></td>
<td>≥18.5</td>
<td>0.8 (0.2-2.9)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>reference</td>
<td>1.1 (0.3-8.5)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>reference</td>
<td>2.3 (0.5-10.9)</td>
</tr>
<tr>
<td>Negative</td>
<td>reference</td>
<td>2.3 (0.5-10.9)</td>
</tr>
</tbody>
</table>

^a At ARV initiation HR: Hazard ratio
Chapter 9 presents secondary analysis of SAPiT trial data assessing costs and cost-effectiveness of ART timing relative to TB treatment. This study demonstrated that ART initiation after the intensive phase of TB therapy was most cost-effective in patients with CD4 counts $\geq 50$ cells/mm$^3$, with important implications for policy makers and funders.

Chapter 10 is a review paper that explores expanding and adapting the lessons learned from the integration of TB and HIV to other non-communicable diseases (NCD) and describes the data needed for cost-effectiveness analyses. Cervical dysplasia and depression are used as case studies on how integration of NCDs with HIV care could be cost-effective.
CHAPTER 9
COST-EFFECTIVENESS OF INITIATING ANTIRETROVIRAL THERAPY AT DIFFERENT POINTS IN TB TREATMENT IN HIV-TB COINFECTED AMBULATORY PATIENTS IN SOUTH AFRICA.


PUBLISHED: Journal of Acquired Immune Deficiency Syndrome.
Cost-Effectiveness of Initiating Antiretroviral Therapy at Different Points in TB Treatment in HIV-TB Coinfected Ambulatory Patients in South Africa

Kogileleu Naidoo, MBChB,* Anneke C. Grobler, PhD,* Nicola Deghaye, MSc; Tarylee Reddy, MSc,* Sathanalakshmi Gengiah, MA,* Andrew Gray, MSc,* and Salim Abdool Karim, MBChB, PhD* as

Objective: Initiation of antiretroviral therapy (ART) during tuberculosis (TB) treatment improves survival in TB-HIV coinfected patients. In patients with CD4<sup>+</sup> counts <50 cells per cubic millimeter, there is a substantial clinical and survival benefit of early ART initiation. The purpose of this study was to assess the costs and cost-effectiveness of starting ART at various time points during TB treatment in patients with CD4<sup>+</sup> counts ≥50 cells per cubic millimeter.

Methods: In the SAPIT trial, 642 HIV-TB coinfected patients were randomized to 3 arms: receiving ART within 4 weeks of starting TB treatment (early treatment arm, Arm-1), after the intensive phase of TB treatment (late treatment arm, Arm-2), or after completing TB treatment (sequential arm, Arm-3). Direct healthcare costs were measured from a provider perspective using a micro-costing approach. The incremental cost per death averted was calculated using the trial outcomes.

Results: For patients with CD4<sup>+</sup> count ≥50 cells per cubic millimeter, median monthly variable costs per patient were US $116, US $113, and US $102 in Arm-1, Arm-2, and Arm-3, respectively. There were 12 deaths in 177 patients in Arm-1, 8 deaths in 180 patients in the Arm-2, and 19 deaths in 172 patients in Arm-3. Although the costs were lower in Arm-3, it had a substantially higher mortality rate. The incremental cost per death averted associated with moving from Arm-3 to Arm-2 was US $4199. There was no difference in mortality between Arm-1 and Arm-2, but Arm-1 was slightly more expensive.

Conclusions: Initiation of ART after the completion of the intensive phase of TB treatment is cost-effective for patients with CD4<sup>+</sup> counts ≥50 cells per cubic millimeter.

Key Words: tuberculosis, ART integration, cost-effectiveness, SAPIT trial

(J Acquir Immune Defic Syndr 2015;69:576-584)

INTRODUCTION

Tuberculosis (TB) is a leading cause of death among HIV-infected patients. In Africa, 46% of TB patients are HIV-positive, and in South Africa TB-HIV comorbidity is estimated at 73%.<sup>1</sup> Initiation of antiretroviral therapy (ART) during TB treatment improved survival in TB-HIV coinfected patients.<sup>2</sup> Although severely immunosuppressed patients (CD4<sup>+</sup> count <50 cells/mm<sup>3</sup>) have better survival with early initiation of ART, the timing of ART initiation during TB treatment in patients with higher CD4<sup>+</sup> counts is less clear.<sup>3,4</sup> Based partly on the Starting Antiretroviral Therapy at Three Points in TB (SAPIT) study,<sup>4</sup> the World Health Organisation<sup>5</sup> and South African guidelines<sup>6</sup> recommended in 2010 that TB-HIV coinfected patients receive ART within 8 weeks of commencing TB treatment. In 2012, both guidelines were updated recommending that all HIV-positive TB patients initiate ART immediately, irrespective of CD4<sup>+</sup> count.<sup>7,8</sup> Given the extent of the HIV epidemic in South Africa<sup>9</sup> and the large number of HIV-TB coinfected patients eligible for ART, the budgetary implications of these changes in ART treatment guidelines are far-reaching.

Information on the cost of starting HIV treatment during TB treatment is vital for budgeting in countries where scale-up of early ART and TB care is required because of large numbers of coinfected patients. Extensive research has been done on the cost and cost-effectiveness of ART, ART provision, monitoring strategies, and regimen choices in...
sub-Saharan Africa. However, no studies were found that examined the comparative costs or cost-effectiveness of different timing of ART initiation in TB therapy for coinfected patients.

Integration of HIV and TB services has the potential to save money through shared utilization of resources, such as monitoring and evaluation, avoidance of duplicate testing, medicine procurement, laboratory equipment, infrastructure and human resources. Starting ART during TB treatment could also increase cost, because ART is provided to many patients and may require additional resources such as infrastructure and staff training.

Effectiveness and cost are both important considerations when determining the value of starting ART during TB treatment, especially in resource-limited settings where efficient allocation of health care resources is necessary. Although cost analysis methodologies quantify resources used for health interventions, thus enabling budgeting and planning, they do not inform about the overall value of interventions in years of life saved. Cost-effectiveness analysis weighs up both the costs and effectiveness of starting ART during TB treatment. Given the important budgetary implications of changes in ART eligibility for high-burden countries, consideration of costs may be of benefit in guiding the timing of ART.

The purpose of this study is to assess the costs and cost-effectiveness of initiating ART with TB treatment (early treatment), at the end of the intensive phase of TB treatment (late treatment), or on completion of TB treatment (sequential treatment), for adult patients coinfected with TB and HIV with CD4 counts ≥50 cells per cubic millimeter.

METHODS

The SAPTT trial, conducted between 2005 and 2010, was a randomized, open-label controlled clinical trial in patients coinfected with TB and HIV with CD4+ counts <500 cells per cubic millimeter. The study design, ART and TB regimens, and eligibility criteria have been described elsewhere. Patients were randomized at a municipal TB outpatient clinic where TB treatment was provided. HIV treatment was provided at an outpatient research clinic collocated with the TB outpatient clinic but in a different area with a different clinical team. Patients were randomized to 3 arms: initiate ART within 4 weeks after the initiation of TB treatment (early treatment: Arm-1), within the first 4 weeks of the continuation phase of TB treatment (late treatment: Arm-2), or after the completion of TB therapy (sequential treatment: Arm-3). Each patient was followed for 18 months. Patient characteristics are described elsewhere.

All patients gave written informed consent. The trial was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (E07/03) and the South African Medicines Control Council (2006/0137).

Data Collection

Variable financial costs were estimated using a micro-costing approach from randomization onward. The costs included were ART and non-ART medication costs, laboratory test costs, radiographs, outpatient consultations, and hospitalization costs. Resource utilization was captured at the patient level. Table 1 summarizes unit costs in US dollars. The average exchange rate for December 15, 2009, was used (7.47 South African rands per US dollar, www.xe.com).

Calculation of Costs

The cost of voluntary counseling and testing, screening and baseline consultations, TB diagnostics, TB treatment, capital costs, fixed costs, and overhead costs were excluded as they were common to all patients and did not vary by study arm. The decision to exclude these costs was guided by principles provided by Drummond et al. Total cost in this study is thus an underestimate of the true cost. Excluding the costs of TB treatment was appropriate because there was no statistically significant difference in the length of TB treatment, type of treatment, and incidence of multidrug-resistant TB between arms.

Medication

Medication use, including start and stop dates, was documented in study records. ART doses were specified, and, for other medications, standard doses were assumed. Provincial ART tender prices (valid to December 2010) were used to cost ART. Private sector prices were used for ceftriaxone and isoniazid (Videx EC, Bristol-Meyers Squibb, Moreton, United Kingdom), because this was not available in the public sector. Public sector prices obtained from facility-level requisitions in February 2009 (where available) or private sector prices (obtained from the Mediscor PBM product database) were used for non-ART medications.

Laboratory Tests

CD4+ count and viral load (VL) tests were recorded in patient files. Electronic results for safety laboratory tests were obtainable from February 2007 to the end of the study. Only 347 patients (285 with CD4+ count ≥50) had electronic laboratory data for the entire study period. This laboratory cost sample included a disproportionately low number of patients who did not initiate ART (12% in the sample, 22% overall) and a disproportionately high number who experienced immune reconstitution syndrome (IRIS) (18% in the sample, 33% overall). To overcome the problem of missing data, while addressing sources of potential bias, conditional mean imputation by category of patient was used to impute laboratory test costs for the remaining 296 patients.

The categories used in the imputation were defined by arm, presence of IRIS, ART initiation, and CD4 category (CD4+ counts <50 cells/mm³ or CD4+ counts ≥50 cells/mm³). Three outliers (with laboratory costs of greater than US $1339) were excluded from the process of imputation to reduce potential bias. These patients remained in the overall patient sample, as these laboratory costs did not seem to be erroneous. The cost calculated for each subgroup was then applied to all patients with these characteristics who did not have laboratory data recorded.
| TABLE 1. Unit Costs of Inputs and Resource Utilization by Treatment Arm |
|-----------------------------|-----------------------------|-----------------------------|
| **Unit Costs of Inputs, US$** | **Unit Cost** |
| ART | 47.17 |
| Cost of first-line ART regimen (per patient per month): didanosine, lamivudine, efavirenz | 47.17 |
| Laboratory tests (cost per test) | 8.51 |
| CD4<sup>+</sup> count | 8.51 |
| HIV VL | 40.16 |
| Chest radiograph | 11.93 |
| Liver function test | 39.41 |
| Full blood count | 6.47 |
| Urine and electrolytes | 19.53 |

**Visit costs**
- Average cost of unscheduled consultation: 23.68
- Cost per missed visit (cost of tracing)*: 8.16

**Hospitalizations**
- Cost per hospital day (level 2 hospital): 45.65

<table>
<thead>
<tr>
<th>Costs in Different Arms</th>
<th>Arm 1 (N = 214)</th>
<th>Arm 2 (N = 215)</th>
<th>Arm 3 (N = 213)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median monthly cost of second-line ART (for patients on second-line)</td>
<td>75.45</td>
<td>85.27</td>
<td>85.27</td>
</tr>
<tr>
<td>Outpatient visit costs</td>
<td>11.79</td>
<td>20.10</td>
<td>20.10</td>
</tr>
<tr>
<td>Average staff cost per ART consultation (clinician)</td>
<td>16.49</td>
<td>16.49</td>
<td>16.49</td>
</tr>
<tr>
<td>Average staff cost per ART consultation (professional nurse)*</td>
<td>13.93</td>
<td>14.01</td>
<td>14.01</td>
</tr>
<tr>
<td>Total cost of scheduled ART consultations over 18 mo</td>
<td>395.57</td>
<td>386.08</td>
<td>386.08</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>120.12</td>
<td>108.81</td>
<td>146.08</td>
</tr>
<tr>
<td>Average “other costs” per hospital admission*</td>
<td>47.22(1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resource Utilization</th>
<th>n (%)</th>
<th>n (%)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than 1 missed visit</td>
<td>29 (13.6)</td>
<td>41 (19.1)</td>
<td>47 (22.1)</td>
</tr>
<tr>
<td>More than 1 unscheduled consultation in the first 3 mo of TB treatment</td>
<td>57 (26.6)</td>
<td>13 (6.1)</td>
<td>4 (1.9)</td>
</tr>
<tr>
<td>Switched to second-line ART regimen</td>
<td>10 (4.7)</td>
<td>8 (3.7)</td>
<td>7 (3.3)</td>
</tr>
<tr>
<td>Did not initiate ART</td>
<td>15 (7.0)</td>
<td>52 (24.2)</td>
<td>77 (36.1)</td>
</tr>
<tr>
<td>Multidrug-resistant TB</td>
<td>13 (6.1)</td>
<td>8 (3.7)</td>
<td>9 (4.2)</td>
</tr>
<tr>
<td>Immune reconstitution syndrome</td>
<td>43 (20.1)</td>
<td>18 (8.4)</td>
<td>20 (9.4)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>52 (24.3)</td>
<td>43 (20.0)</td>
<td>62 (29.1)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>40 (18.7)</td>
<td>39 (14.0)</td>
<td>46 (21.6)</td>
</tr>
<tr>
<td>More than 5 d hospitalized</td>
<td>26 (12.2)</td>
<td>21 (9.8)</td>
<td>36 (16.9)</td>
</tr>
<tr>
<td>Total number (N)</td>
<td>689</td>
<td>519</td>
<td>624</td>
</tr>
<tr>
<td>Hospital days</td>
<td>2619</td>
<td>2636</td>
<td>2703</td>
</tr>
<tr>
<td>No. unscheduled consultations, median (IQR)</td>
<td>1 (1-3)</td>
<td>1 (1-3)</td>
<td>1 (1-3)</td>
</tr>
<tr>
<td>Time to ART regimen switch (mo), median (IQR)</td>
<td>8.5 (3.5-10.9)</td>
<td>11.8 (9.1-12.5)</td>
<td>8.2 (5.3-9.0)</td>
</tr>
<tr>
<td>Length of TB treatment (d), median (IQR)</td>
<td>204 (196-253)</td>
<td>202 (194-253)</td>
<td>198 (182-252)</td>
</tr>
<tr>
<td>No. CD4&lt;sup&gt;+&lt;/sup&gt; count tests, median (IQR)</td>
<td>5 (4-6)</td>
<td>6 (4-6)</td>
<td>5 (4-6)</td>
</tr>
<tr>
<td>No. VL tests, median (IQR)</td>
<td>4.5 (3-5)</td>
<td>5 (3-5)</td>
<td>4 (2-5)</td>
</tr>
<tr>
<td>Rate of hospitalization per 100 person years</td>
<td>18.2</td>
<td>15.5</td>
<td>23.0</td>
</tr>
</tbody>
</table>

All costs are in 2009 US dollars.

*Includes the cost of transportation to hospital, the CAPRISA staff cost of admission and follow-up while in hospital. Source of salary laboratory test prices: National Health Laboratory Services (2009).

*The staff cost includes the cost of all categories of staff that deal directly with the patient (reception, nursing staff, clinicians, and counselors). The cost of a visit is determined by the length of the visit and the salary of the type of staff member conducting the consultation.

*All professional nurses saw all stable patients for scheduled consultations from the eighth month of ART treatment onward. Clinicians saw patients at regular scheduled intervals, after CD4<sup>+</sup> count and VL tests.

IQR, interquartile range; VL, viral load; ART, antiretroviral treatment.
The 2009 public sector price (charged by the National Health Laboratory Service) was used for all laboratory tests. The costs of documented radiographs were included. To make the results of this analysis more generalizable to primary health care settings where ART and TB treatment is usually provided, all tertiary level laboratory tests were excluded from the calculation of laboratory test cost.

**Labor and Overhead Costs**

Outpatient consultations (number and type) were recorded in patient files. Interviews were conducted with a sample of staff to determine the time taken for the different types of clinical consultations. These time estimates were multiplied by the average hourly public sector salary per staff type to determine staff costs per consultation. The Department of Public Service and Administration 2009 salary data (with effect from April 1, 2009) was obtained from the KwaZulu-Natal Department of Health directly. Salaries included all benefits such as pension and leave. Where specific roles did not exist within the public sector, the CAPRISA salaries were used. The cost per different type of consultation was calculated.

**Hospital Costs**

Dates of hospital admission and discharge were recorded in patient files. Records were reviewed to determine resource use during hospitalization, including procedures performed, use of intravenous fluids and blood products, and level of hospital and ward admitted to. Data on medications prescribed and laboratory tests performed in hospital were incomplete and were not used, instead prices per inpatient day and procedures performed in a public sector hospital from the 2009 Uniform Patient Fee Schedule were used. These prices are flat fees charged to patients with medical insurance who use public sector hospitals and are calculated to cover the estimated cost of consumables (with the exception of some high-cost theatre and ward consumables), medication, hospital overheads, and cost of support and medical staff. The prices exclude discharge medication, medication not on the essential drug list, anaesthetic and laboratory tests. Blood products were charged at the South African National Blood Service rate to public sector patients (the SANDS State patient price list, 2009, www.sands.gov.za). Hospital costs include the cost of transportation to hospital and the cost of staff time spent referring patients. Several simplifying assumptions were made, for example, ward admitted to was inferred from information available, blood transfusions were assumed to have consisted of 2 units, costs of procedures and intravenous drugs were not included, and patients admitted to high care were assumed to have spent 50% of the stay in high care, the rest in a general ward. Assumptions made are expected to bias hospitalization costs downward. In the sensitivity analysis, the cost of procedures and intravenous drugs were included in hospitalization cost.

**Analysis**

Direct health care costs were measured from a provider perspective. Each resource used by each patient was multiplied by its unit cost and summed to determine the total cost per patient and per arm. The median cost per patient per month was calculated by dividing the total cost per patient by the number of months of follow-up. Discounting was not used, because the treatment spanned a short period and the timing of costs and benefits was similar across arms. To adjust for inflation, 2009 prices were used throughout.

The outcome measure was all-cause mortality at 18 months using Kaplan–Meier methods. A simple patient-level micro-costing model was developed in OpenOffice Calc (version 3.2) (Apache Software Foundation, Forest Hill, MD) to combine data and calculate total variable cost per patient and patient month. The incremental cost per death averted was calculated over 18 months, by calculating the ratio of incremental total variable cost to incremental number of deaths averted between arms. The 3 treatment options were compared based on total cost and number of deaths associated with the treatment option. Any dominated options (treatment options with higher cost and lower effectiveness than the next alternative) were eliminated. Fisher exact test was used with categorical data, and Wilcoxon 2-sample test or Kruskal-Wallis test with continuous data. Data were analysed in SAS (version 9.2) (SAS Institute, Cary, NC).

One-way sensitivity analysis was used to test the implications of lower ART, lower VL, and laboratory test costs and alternative costs per inpatient day on the cost per patient month. Scenario analysis was conducted to evaluate the impact of several key assumptions on the model. The cost of laboratory tests received particular attention because these were inflated due to the frequency and comprehensiveness of laboratory safety monitoring within a clinical trial setting.

Some data were missing in non-ART medications and in detailed hospitalization data (procedures, use of intravenous fluids, ward). Where duration and dosage information was missing, standard duration and dosage for the indication was assumed. Non-ART medication costs were small and, even if incorrectly estimated, would not impact overall results. Data used were from December 2009. A previous publication was based on earlier incomplete interim data.

**RESULTS**

The SAPIT trial enrolled 642 patients and demonstrated a 56% reduction in mortality [hazard ratio: 0.44, 95% confidence interval (CI): 0.25 to 0.79, P = 0.003] among patients initiating ART during TB treatment compared with after the completion of TB treatment. No difference in mortality was found between patients randomized to Arm-1 and Arm-2 (incidence rate ratio = 0.96, 95% CI: 0.44 to 2.10), except in patients with CD4 counts <50 cells per cubic millimeter. Mortality rates in patients with CD4 counts <50 cells per cubic millimeter were 5.6/100 person years (95% CI: 2.9 to 9.8) in Arm-1, 3.8/100 person years (95% CI: 1.7 to 7.6) in Arm-2, and 10.0/100 person years (95% CI: 6.4 to 15.7) in Arm-3. The mortality benefit was pronounced in patients with CD4 counts <50 cells per cubic millimeter, and cost-effectiveness arguments were not relevant in this subgroup. Consideration of cost-effectiveness is appropriate in choosing the optimal strategy for patients with CD4.
counts ≥50 cells per cubic millimeter. Although all results are for patients with CD4⁺ counts ≥50 cells per cubic millimeter, the subgroup analysis of costs per arm in patients with <50 cells per cubic millimeter is presented. Loss to follow-up was 8.9%, 11.6%, and 13.1% in the 3 treatment arms.

The median monthly variable cost per patient was US $116 (Arm-1), US $113 (Arm-2), and US $102 (Arm-3), $P < 0.001. Arm-1 and Arm-2 had similar costs and mortality. Although costs in Arm-3 were lowest, this arm had the highest mortality. Incremental cost per death averted in Arm-2 compared with Arm-3 was US $41899 (Fig. 1). Switching from sequential ART (ART offered at the end of TB treatment) to offering ART at the end of the intensive phase of TB treatment amounted to a cost of US $41899 per death avoided. Arm-1 has slightly higher mortality than Arm-2, whereas Arm-1 is also marginally more expensive. This means that Arm-1 is dominated by Arm-2, and Arm-2 is a better choice both in cost and mortality outcomes.

The costs of treating cotected patients comprise 4 components: drugs, laboratory testing, outpatient care, and hospitalization. Laboratory investigations, driven largely by research protocol safety requirements, contributed the largest proportion of variable cost in all 3 treatment arms (33.3% in Arm-1, 43.6% in Arm-2, and 10.7% in Arm-3). CD4⁺ count and VL tests contributed between 10.6% and 12.2% to total variable costs, depending on the arm. The number of CD4⁺ count and VL tests performed was higher in Arm-2 than in the other 2 arms. Spending on laboratory tests was significantly higher in Arm-2 than in Arm-1 ($P = 0.005). Baseline CD4⁺ count <50 cells per cubic millimeter and presence of HIV significantly increased spending on laboratory tests ($P < 0.01). Spending on laboratory testing was higher for patients who did not initiate ART due to abnormalities in safety laboratory results because these patients required repeated testing. The cost of ART was the second largest contributor to total variable costs in Arm-1 (32.4%) and Arm-2 (28.7%), although it contributed only 17.6% to total costs in Arm-3. Outpatient consultations made up between 18.3% and 19.7% of total costs across the arms. Hospitalization cost was the third largest cost in Arm-3 (Table 2).

The median cost of consultations was similar across arms. The only difference in length of consultations was for the ART initiation visit, which was longer in Arm-1.

Hospitlizations comprised 12.9%, 7.7%, and 22.4% of the total variable costs for Arms-1, 2, and -3, respectively. Both mean and median costs per patient hospitalized were highest in Arm-3. The median cost per patient hospitalized was US $564 in Arm-1, US $815 in Arm-2, and US $1295 in Arm-3. The mean cost of hospitalization per patient hospitalized (Table 3) was much higher: US $1603 in Arm-1, US $1086 in Arm-2, and US $2195 in Arm-3. The costs of hospitalization were more variable than other costs.

Most hospital admissions (89.6%, 120/134) were to a general ward, 9.7% (13/134) were to high care, and 0.7% (1/134) to intensive care. 62.2% (84/134) were admitted to secondary-level hospitals. Procedures were recorded for 60.4% (81/134) of hospitalizations: these were procedures not requiring an operating theatre (54.5%, 54/99), radiological (20.2%, 20/99), minor surgical (20.2%, 20/99), and major surgical (5.1%, 5/99) procedures. The most common procedures performed were lumbar puncture, computed tomography scan, administration of intravenous fluids for rehydration, radiograph, and ultrasound. The median cost per procedure was US $20. General ward costs accounted for 78% of total hospital costs.

The costs in Arm-2 were similar to costs in Arm-1, and patient survival was similar. Patients in the late treatment arm had the lowest number of hospitalizations, serious adverse events, and IRIS, which are recognized cost drivers in the provision of TB and HIV services.

Over 18 months, Arm-1 was the most expensive (US $1882), followed by Arm-2 (US $1840) and Arm-3 (US $657, $P < 0.001). The lower cost in Arm-3 was driven by shorter duration of ART provision, which lowered the cost of ART. The median cost of ART in Arm-3 was less than half the cost of ART in Arm-1.

Sensitivity analyses showed that the median cost per patient was not affected by changes in several key assumptions and changes in key prices (Table 4). Although some scenarios resulted in much lower cost estimates, the trends between the arms remained similar. Costs per patient were most sensitive to changes in ART prices and costs of investigations. Changes in the price of VL testing made little difference. The difference in costs between Arm-1 and Arm-2 was small when ART prices were reduced, but both strategies were still more expensive than Arm-3. The magnitude of the cost differences between the strategies did

**TABLE 2. Percentage (and Total Spending) of Total Variable Cost Spent on Different Categories (Patients With CD4⁺ Count ≥50 Cells/mm³)**

<table>
<thead>
<tr>
<th></th>
<th>Arm-1 (US $)</th>
<th>Arm-2 (US $)</th>
<th>Arm-3 (US $)</th>
<th>Total (US $)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART</td>
<td>32.4 (109,224)</td>
<td>28.7 (80,452)</td>
<td>17.6 (48,425)</td>
<td>26.7 (238,098)</td>
</tr>
<tr>
<td>Other medication</td>
<td>0.4 (151)</td>
<td>0.6 (154)</td>
<td>0.6 (179)</td>
<td>0.5 (463)</td>
</tr>
<tr>
<td>All investigations</td>
<td>35.5 (119,496)</td>
<td>43.0 (120,577)</td>
<td>40.7 (111,808)</td>
<td>39.4 (351,837)</td>
</tr>
<tr>
<td>CD4⁺ count and VL</td>
<td>10.6 (35,731)</td>
<td>12.2 (34,115)</td>
<td>11.4 (31,207)</td>
<td>11.3 (101,054)</td>
</tr>
<tr>
<td>Safety laboratory tests</td>
<td>22.7 (76,453)</td>
<td>28.3 (79,538)</td>
<td>26.4 (73,953)</td>
<td>25.8 (229,945)</td>
</tr>
<tr>
<td>X-rays</td>
<td>2.2 (729)</td>
<td>2.5 (698)</td>
<td>2.4 (668)</td>
<td>2.3 (20,838)</td>
</tr>
<tr>
<td>Outpatient consultations</td>
<td>18.6 (62,527)</td>
<td>19.7 (55,374)</td>
<td>18.3 (50,418)</td>
<td>18.9 (168,319)</td>
</tr>
<tr>
<td>Hospitalization cost</td>
<td>12.9 (43,291)</td>
<td>7.7 (21,710)</td>
<td>22.4 (61,455)</td>
<td>14.2 (126,454)</td>
</tr>
</tbody>
</table>

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not change when the costs of laboratory testing were reduced. New ART tender prices have been negotiated since starting this study. The median cost per patient month was slightly lower when using these prices (Table 4).

**DISCUSSION**

The timing of ART initiation during TB care has implications for quality and cost of health service provision. In patients with CD4+ counts <50 cells per cubic millimeter, the survival benefit of starting ART early during TB treatment is clear and outweighs the higher cost. Starting ART during TB treatment results in substantial increases in survival at moderate cost. However, in patients with CD4+ counts ≥50 cells per cubic millimeter, the best time to initiate ART during TB treatment is less clear as survival was similar among patients initiated on ART in Arm-1 and Arm-2. Cost analysis could be used to decide between early and late initiation of ART during TB treatment in these patients.

In countries like South Africa where a cost-effectiveness threshold has not been established, GDP per capita is used to decide the cost-effectiveness of interventions. Interventions costing between one and three times the annual GDP per capita are considered cost-effective. The cost per death averted in moving from sequential to late integrated treatment was estimated at US $4199. This is below the annual GDP per capita in South Africa in 2009 (US $5758 at 2009 prices). Because the cost per death averted is lower than the annual GDP per capita, late integration of ART into TB treatment is cost-effective for South Africa.

Our cost analysis suggests that late initiation of ART during TB treatment (Arm-2) is the optimal strategy for patients with CD4+ ≥50 cells per cubic millimeter, especially in resource-constrained settings.

**Cost of the Various Options**

The largest driver of costs in all 3 arms was laboratory investigations, which were done routinely every 6 months and when toxicity was suspected. Some of the tests are done routinely in a care setting, and some were specific to the research setting. Safety tests were repeated until safety parameters returned to normal. These costs will be lower in routine settings, with less frequent testing. The differences in ART and investigations’ costs are likely to shrink because duration on ART increases and ART prices decrease over time.

The cost of hospitalization per patient hospitalized was lowest in Arm-1, higher in Arm-2, and much higher in Arm-3. Hospitalization contributed 22.4% of the total cost in Arm-3, because of the larger number of patients hospitalized and longer duration of hospital stays among patients in this group. Although outpatient costs in Arms 1 and 2 are higher, these arms reduce the burden on the hospital system and associated costs. The Department of Health should be expecting to spend approximately US $1086 per patient hospitalized, if a strategy of starting ART after the intensive phase of TB treatment was adopted.

The difference in cost between Arm-1 and Arm-2 is small, but, given the large numbers of TB-HIV coinfected patients in South Africa, the choice of late over early initiation of ART could lead to substantial savings.

Based on a coverage rate of 70% and an estimated 270,000 HIV-TB coinfected people in South Africa, an estimated difference in cost of US $3.11 per month between Arm-1 and Arm-2 equates to a total saving of more than US $7 million per annum in South Africa through selecting late integration of ART rather than early integration. This assumes that all patients had drug-susceptible pulmonary TB.

**Comparison of Costs to Other Settings**

The costs in this study were higher than in published reports from HIV-only treatment programs. This is due to inclusion of hospitalization costs in our analysis. Some differences are country-specific, as hospital and labor costs are relatively high in South Africa. Importantly, our cost estimates were in a clinical trial context, with more frequent visits (monthly) and laboratory monitoring and more staff time per patient than in routine care settings. We
| TABLE 3. Variable Cost Per Patient (Over 18 Months and Per Month) in 2009 US Dollars |
|----------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| All patients                     | Median | IQR      | Median | IQR      | Median | IQR      | P      | <0.001 | <0.001 | <0.001 | <0.001 |
| ART                              | 76.94   | 181.89   | 66.78  | 0.499    | 340.59 | 0.481    | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Other medications                | 3.20    | 3.68     | 0.78   | 4.13     | 5.61   | 0.12     | 0.612  |        |        |        |        |
| All investigations               | 691.76  | 686.74   | 756.85 | 446.851  | 671.35 | 300.858  | 0.179  |        |        |        |        |
| CD4 count and VL                 | 227.55  | 163.25   | 243.37 | 155.252  | 203.21 | 106.252  | 0.042  | 0.530  | 0.110  | 0.001 |
| Safety laboratory tests          | 346.07  | 395.522  | 515.08 | 255.558  | 481.54 | 216.550  | 0.484  |        |        |        |        |
| X-rays                           | 8.66    | 6.48     | 8.74   | 5.48     | 5.74   | 2.44     | 0.008  | 0.009  | 0.000  | 0.006 |
| Outpatient consultation          | 399.37  | 352.43   | 399.48 | 191.431  | 383.59 | 100.407  | <0.001 | 0.041  | 0.014  | <0.001 |
| Hospitalization (in patients who were hospitalized) | 578.20  | 263.11   | 643.70 | 297.1939 | 1057.59 | 348.2181 | 0.218  |        |        |        |        |
| Total variable cost per patient month | 1930.71 | 1752.21 | 1856.88 | 1830.20 | 1659.89 | 658.1834 | <0.001 | 0.003  | <0.001 | <0.001 | <0.001 |
| Patients with CD4 count ≥ 50 cells/mm³ | 742.88  | 699.889  | 655.48 | 293.698  | 209.79 | 0.481    | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| ART                              | 8.44    | 31.80    | 8.73   | 2.29     | 6.84   | 0.9      | 0.256  |        |        |        |        |
| Other medications                | 667.82  | 728.90   | 806.62 | 741.969  | 620.64 | 330.829  | <0.001 | 0.748  | 0.002  | <0.001 |
| CD4 count and VL                 | 271.89  | 203.252  | 251.89 | 203.252  | 154.54 | 57.252   | 0.002  | 0.840  | 0.004  | 0.001 |
| Safety laboratory tests          | 597.97  | 474.602  | 648.35 | 453.648  | 399.53 | 238.550  | <0.001 | 0.615  | 0.002  | <0.001 |
| X-rays                           | 47.66   | 36.40    | 35.74 | 36.40    | 35.74 | 24.48    | 0.026  | 0.060  | 0.369  | 0.031 |
| Outpatient consultation          | 439.57  | 399.465  | 401.61 | 339.445  | 322.14 | 81.397   | <0.001 | 0.092  | 0.005  | <0.001 |
| Hospitalization (in patients who were hospitalized) | 615.82  | 513.1347 | 594.52 | 231.1187 | 643.90 | 371.1239 | 0.825  |        |        |        |        |
| Total variable cost per patient month | 2128.45 | 1967.251 | 1965.25 | 1785.2254 | 1697.16 | 751.1930 | <0.001 | 0.025  | 0.008  | <0.001 |
| Patients with CD4 count < 50 cells/mm³ | 742.88  | 300.898  | 611.78 | 0.499    | 340.59 | 0.481    | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| ART                              | 3.49    | 3.30     | 3.30   | 0.13     | 4.25   | 0.12     | 0.390  |        |        |        |        |
| Other medications                | 686.94  | 614.741  | 758.06 | 738.859  | 773.81 | 350.840  | 0.014  | 0.005  | 0.385  | 0.026 |
| CD4 count and VL                 | 203.21  | 155.252  | 211.73 | 106.252  | 207.47 | 106.252  | 0.496  |        |        |        |        |
| Safety laboratory tests          | 436.07  | 382.448  | 597.04 | 181.519  | 490.37 | 205.550  | 0.049  | 0.035  | 0.173  | 0.059 |
| X-rays                           | 47.66   | 36.48    | 35.74 | 24.48    | 35.74 | 24.48    | 0.055  |        |        |        |        |
| Outpatient consultation          | 399.37  | 290.423  | 397.34 | 143.411  | 383.59 | 100.407  | 0.002  | 0.149  | 0.158  | <0.001 |
| Hospitalization (in patients who were hospitalized) | 563.97  | 240.1366 | 813.41 | 298.1309 | 1294.80 | 346.2318 | 0.126  |        |        |        |        |
| Total variable cost per patient month | 1882.14 | 1470.2366 | 1839.79 | 746.1987 | 1656.80 | 552.1812 | <0.001 | 0.014  | 0.005  | <0.001 |

Only the major components of median cost per patient month are shown in the table, for ease of scaling.

*This include the cost of CD4 count, VL testing, X-rays, and all other laboratory tests. It includes staff cost, the price paid for investigations, and consumables cost.

†This is the median consultation cost per patient for all scheduled TB and ART consultations attended and all unscheduled consultations. It includes staff cost and consumables cost.

IQR, interquartile range.

Bold values refer to totals.

ARTL, antiretroviral treatment; VL, viral load.

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endavored to provide enough detail on resource utilization and various cost scenarios in our sensitivity analysis to enable generalizability of our findings to other countries. Although the total cost estimate in this clinical trial is higher than in routine care settings, the relative difference in price between the 3 treatment strategies is likely to translate to other settings.

A recent study by the Clinton Health Access Initiative (CHAI) found that the total cost of treating HIV in South African facilities was US $882 per annum, considerably higher than the average for 4 other African countries, which was US $200 per annum.13 This equates to US $1025 for 18 months, lower than the cost estimated in this study. However, the CHAI study did not include hospital costs or TB-related costs, which were included in this analysis. The cost of providing HIV-treatment in the US President’s Emergency Plan for AIDS Relief-supported programs in 43 clinics in Botswana, Ethiopia, Nigeria, Uganda, and Vietnam was US $880 per annum, or US $1320 over 18 months. These estimates did not include costs of hospitalization and management of TB.14

Costing of a single ART clinic in Haiti concluded that cotreatment of TB and HIV involved a small increase in cost and physician time compared with treating HIV alone and suggested integration of TB and ART as a way to conserve physician time.15

Study Limitations

Our patient population was ambulant and relatively healthy. The costs might not be generalizable to populations with higher morbidity or patients with nonpulmonary TB.

The most important limitation is the short follow-up of 18 months. ART monthly costs decline after 12 months.30,31 The short duration of the study therefore likely inflated median monthly cost. Monthly ART costs are likely to be similar in all arms at later time points because all patients will be receiving ART, leading to the shrinkage of cost differences associated with ART provision between the arms.

The study was done at 1 site only, but the costs are generalizable to other outpatient sites. Average medication cost while hospitalized was used in calculations. This could have lead to underestimation of hospitalization costs if patients required atypical and expensive medications not included on the Essential Medicines List applicable in the public sector, these were not included.

The small number of patients with IRIS in the laboratory sample may have led to inaccurate estimates of laboratory costs for these patients. Although laboratory costs were the biggest cost driver, a major limitation of our study is that these results are not readily generalizable to a clinical care setting as most of the laboratory tests were research-related safety assessments.

New technologies have been adopted in South Africa for TB diagnosis and resistance testing since this clinical trial. The introduction of the Xpert MTB/RIF will alter the costs estimates.

**CONCLUSIONS**

Current WHO recommendations call for initiating ART in all TB-HIV coinfected patients irrespective of CD4 count.
As more coinfected patients initiate ART, data on the cost-effectiveness of initiating ART during TB treatment becomes important. This study provides health system utilization and cost data associated with starting ART during TB treatment with implications for health policy makers and funders.

The SAPI, CAMELLIA, and ACTIG trials have shown that starting ART during TB treatment saves lives, and this analysis shows that starting ART during TB treatment is cost-effective. Late initiation of ART during TB and HIV treatment for patients with CD4+ counts ≥ 50 cells per cubic millimeter is the most cost-effective. Cost-effectiveness is only one consideration in starting ART in HIV-TB coinfected patients. The efficacy of the intervention and practical challenges of implementation of integrated services, especially in resource-limited settings, should also be considered.

In sub-Saharan Africa, where public sector hospitals are overburdened, the reduction of the burden on a struggling hospital system by starting ART during TB treatment needs to be emphasized.

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CHAPTER 10

HIV, TUBERCULOSIS, AND NON-COMMUNICABLE DISEASES: WHAT IS KNOWN ABOUT THE COSTS, EFFECTS, AND COST-EFFECTIVENESS OF INTEGRATED CARE?


PUBLISHED: Journal of Acquired Immune Deficiency Syndrome.
HIV, Tuberculosis, and Noncommunicable Diseases: What Is Known About the Costs, Effects, and Cost-effectiveness of Integrated Care?

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Abstract: Unprecedented investments in health systems in low- and middle-income countries (LMICs) have resulted in more than 8 million individuals on antiretroviral therapy. Such individuals experience dramatically increased survival but are increasingly at risk of developing common noncommunicable diseases (NCDs). Integrating clinical care for HIV, other infectious diseases, and NCDs could make health services more effective and provide greater value. Cost-effectiveness analysis is a method to evaluate the clinical benefits and costs associated with different health care interventions and offers guidance for prioritization of investments and scale-up, especially as resources are increasingly constrained. We first examine tuberculosis and HIV as 1 example of integrated care already successfully implemented in several LMICs; we then review the published literature regarding cervical cancer and depression as 2 examples of NCDs for which integrating care with HIV services could offer excellent value. Direct evidence of the benefits of integrated services generally remains scarce; however, data suggest that improved effectiveness and reduced costs may be attained by integrating additional services with existing HIV clinical care. Further investigation into clinical outcomes and costs of care for NCDs among people living with HIV in LMICs will help to prioritize specific health care services by contributing to an understanding of the affordability and implementation of an integrated approach.

Key Words: HIV/AIDS, noncommunicable diseases, cost-effectiveness, integrated care, tuberculosis

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INTRODUCTION

The number of people living with HIV (PLWHIV) with access to effective and life-saving antiretroviral therapy (ART) has grown rapidly in low- and middle-income countries (LMICs) over the past decade. Life expectancy has increased, and the burden of opportunistic infections has decreased. Data from the United States and Europe demonstrate the increasing burden of noncommunicable diseases (NCDs) among PLWHIV in the era of ART. A similar trend is anticipated in LMICs, where NCDs are already on the rise among the general population (see Table A1, Supplemental Appendix, http://links.lww.com/QAI/A545). With earlier age of onset and higher mortality compared with higher-income countries, PLWHIV in LMICs thus represent a population in whom preventive, screening, and therapeutic strategies for NCDs could offer substantial health benefits.

Existing HIV infrastructure offers an opportunity to address NCDs and their risk factors. To date, integration strategies have focused primarily on tuberculosis (TB), sexually transmitted infections, malaria prevention, and reproductive health, with some accompanying evaluations of cost-effectiveness. To determine the potential value of integrating clinical care for HIV and NCDs, it is critical to first assess the effectiveness of such integrated interventions. Additional questions then follow: Is the integrated approach cost-effective compared with the current nonintegrated care? Is it affordable? How can it best be implemented in a specific setting? Health economics offers useful methodologies to answer these questions and prioritize efforts. Here, we provide an overview of these methodologies and the data needed for such analyses.

Search Strategy and Selection Criteria

We searched the databases of PubMed and Ovid for studies published in English before January 30, 2014.
We used the search terms: “HIV,” “tuberculosis,” and “noncommunicable diseases” as the first set of terms, with “cost-effectiveness,” “costs,” “integration,” and “Africa” in subsequent searches. We also searched for specific NCDs such as “cervical cancer,” “depression,” and “hypertension.” We then used the bibliographies of relevant articles to expand the list of eligible articles.

**COST-EFFECTIVENESS ANALYSIS**

Cost-effectiveness analysis (CEA) and mathematical modeling provide guidance for strategic prioritization of resources by projecting clinical outcomes from specific strategies and examining the comparative value of different strategies. CEA evaluates both effectiveness (eg, in years of life saved) and costs to calculate an incremental cost-effectiveness ratio (ICER; or Δ costs/Δ effectiveness) that quantifies the value of different strategies of care. Guided by recommendations from World Health Organization CHOosing Interventions that are Cost-Effective (WHO-CHOICE),70 a strategy is often considered “cost-effective” if its ICER is less than 3 times the country-specific per capita gross domestic product and “very cost-effective” if its ICER is less than the per capita gross domestic product. Such analyses can inform policy and allocation of resources for HIV guidelines and care.11-51

**Data Needed**

For which specific NCDs will integration with HIV services have the greatest impact? As discussed by Petersen et al52 in this supplement, leveraging multi-regional research and programmatic HIV cohorts in LMICs can identify the prevalence and incidence of specific NCDs, including their risk factors and attributable mortality.53-57 The competing risks of different NCDs and HIV infection must be understood to prioritize an expansion of care services for PLHIV.70,79

The value of integration depends on the accuracy and availability of screening and prevention strategies, successful linkage to treatment for those who are eligible, and the effectiveness of the treatment. Necessary data include diagnostic test performance (eg, sensitivity, specificity) in settings with different disease prevalence (eg, yielding different positive and negative predictive values), and the risks associated with screening methods.58 Easily administered, low-cost tests that yield results rapidly—particularly point-of-care diagnostic tests—could be used in integrating NCD screening into HIV care.55 Access to treatment and risk factor modification after screening and diagnosis will also affect the value of integrating services.49 Treatment outcomes include effectiveness, relapse, the frequency and severity of treatment-associated adverse events, and quality of life,65 using either quality-adjusted life years or disability-adjusted life years.

Costs are a major consideration, especially where resources are most limited.59 and include direct medical costs (eg, diagnostic tests, preventive strategies, treatments) and costs for infrastructure, personnel, training, and monitoring and evaluation activities.60-61 Adding costs of NCD screening and treatment to already overstretched health services must be weighed against the burden inflicted by NCDs, including the direct costs associated with management of advanced disease and indirect costs such as time costs (eg, lost wages) for those affected.66 Additionally, integrating NCD services with existing HIV infrastructure could decrease overall costs by taking advantage of efficiencies of scope.

**Outcomes of Interest**

CEA can use modeling methods to project clinical outcomes and comparative value of interventions for NCD prevention, screening, and management. Although clinical trials largely define outcomes at early time points, models can estimate the clinical impact of interventions in the short and long term. CEA also quantifies the value of one strategy compared with another by projecting the additional clinical benefits attained for resources used.

A related methodology, budget impact analysis (BIA), assesses the costs of a program in specific settings. BIA focuses on program affordability from the perspective of stakeholders, such as ministries of health, nongovernmental organizations, or other payers. These analyses also account for the direct per capita costs of a program and the number of patients treated in a given program over a specified budget period.67 Thus, although a strategy may be cost-effective when measured against an external threshold of willingness to pay,60,66,67 BIA assesses the actual resources needed to implement that strategy in a specific setting.

**CASE STUDIES**

Integrating clinical services offers an opportunity to improve overall health among PLHIV but also has the potential to undermine HIV care. Further investigation will determine whether outcomes will improve or suffer. After a systematic review of the literature, we describe TB/HIV as 1 example of existing integrated services and discuss data needed to assess its cost-effectiveness. We then examine cervical cancer and depression as 2 case examples of the potential for integrated NCD/HIV care.

**TB/HIV Integrated Services**

**TB: Epidemiology, Quality of Life, and Mortality**

TB in PLHIV offers a prime opportunity to assess the impact and cost-effectiveness of an integrated approach to care compared with distinct treatment sites. Approximately 1.1 million of the 33.3 million PLHIV in the world were diagnosed with active TB in 2012 alone.70 PLHIV who have TB experience a substantially decreased quality of life29 and increased stigma, both of which improve with treatment.52 TB remains the leading cause of death among PLHIV; almost 25% of those with HIV and TB worldwide will die from TB.74

**TB/HIV: Screening and Treatment Outcomes**

Early detection and treatment of TB are critical to reducing TB mortality and transmission among PLHIV.75-80 Active TB screening results in timely, accurate TB diagnoses for which effective treatment exists.79-81 However, separate clinical sites for TB and HIV can result in reduced TB or HIV
case finding and poor (62%) or delayed (32%) linkage to care, and low rates of ART initiation (13%-62%). Integration of TB/HIV services can address these shortcomings. In Guatemala, TB/HIV integration improved initiation of TB treatment (23% vs. 94%, pre-vs. post-integration) and decreased mortality at 50 weeks (72% vs. 27%). In Uganda, integration resulted in modest gains; more patients completed TB treatment (62% vs. 68%, pre-vs. post-) and fewer experienced death or treatment default (33% vs. 25%).

Integrated TB/HIV care could lead to improvements not only in TB but also in HIV outcomes. In the Democratic Republic of Congo, 46% of TB patients preferred HIV counseling/testing by TB nurses rather than referral to a free-standing HIV voluntary counseling/testing site (25%) or a separate, on-site clinic (9%). In a Ugandan study, patients were more likely to initiate ART at some point during TB treatment (78% vs. 94%), especially during the earlier intensive treatment phase (23% vs. 60%). In an integrated South African site, time to ART initiation decreased from 147 days to 75 days, and patients were 1.6 times more likely to start ART.

**TB/HIV: Costs**

Although the direct costs of TB and HIV care have been reported, the detailed costs and tradeoffs of integrated TB/HIV care are not well described. In addition to diagnostic tests and medications, costs include infrastructure, personnel, and training. Integrated TB/HIV care could reduce overall resource utilization by relying on efficiencies of scope to increase the value of existing infrastructure and personnel.

**Cost-effectiveness of TB/HIV Integration**

Several studies have examined the cost-effectiveness of specific aspects of integrated TB/HIV care. Integrating routine HIV testing into TB treatment clinics in India is “very cost-effective” when compared with selective screening and is likely to be even more cost-effective in settings with higher HIV prevalence because more people are likely to be diagnosed with HIV and linked to care. Integrating TB screening methods (e.g., Xpert MTB/RIF or urine LAM) when initiating ART for PLHIV can be cost-effective in South Africa as compared with symptom screening and sputum smear or sputum culture. Point-of-care tests that improve linkage to care could outweigh limitations in test characteristics, such as reduced sensitivity or specificity, when compared with a laboratory-based test. Isoniazid preventive therapy among PLHIV offers another example of how integrating an aspect of TB prevention into HIV services can be cost-effective.

**OPPORTUNITIES TO INTEGRATE HIV AND NCD CARE: USING A COST-EFFECTIVENESS APPROACH**

In terms of value, data are limited but promising regarding the impact on NCD outcomes of integrating HIV care into primary care. Screening for NCDs and their risk factors, as well as associated treatments, fall along a wide spec- trum regarding continuity of care and costs (see Table A3, Supplemental Appendix, http://links.lww.com/QAI/A545). Interventions are more costly if they require intensive training or the use of new technologies or if they occur at frequent intervals among large numbers of people. Cervical cancer and depression are 2 examples of NCDs that merit further evaluation regarding the potential value of integration.

**CERVICAL CANCER/HIV INTEGRATED SERVICES**

**Cervical Cancer: Epidemiology**

As further described by Adenmorowo et al in this supplement, invasive cervical cancer (ICC) will likely be a major cause of mortality as women living with HIV gain increased access to ART in sub-Saharan Africa (SSA). The incidence of ICC in SSA is the highest in the world; age-standardized incidence rates in the general population range from 28 to 42.7 cases per 100,000 women. HIV-infected women are at even greater risk for ICC, which often occurs at younger ages and presents at more advanced stages when treatment is less likely to be successful. Furthermore, ART may not reduce cervical cancer risk, and life-long screening is needed.

**Cervical Cancer: Screening and Treatment Outcomes**

ICC often manifests with precursor cervical lesions evident with screening and amenable to treatment. Multiple screening methods have demonstrated accuracy in LMICs with the ability to incorporate mobile technologies and well-trained nonphysician clinicians to extend services. Likewise, when precancerous lesions are identified, multiple treatment options demonstrate excellent efficacy in LMICs. Operational aspects of screening and treatment for ICC and its precursor lesions have been demonstrated in Zambia, with more than 65,000 women screened in the first 5 years of a large program and more than 110,000 women screened over the past 8 years.

Although screening is available and accurate, only 6.4%-20.2% of African women receive even 1 screening test in their lifetimes. Loss to follow-up after initial diagnosis is high, and treatment opportunities are missed. Integrating ICC screening and treatment with HIV services could offer improved uptake of screening and treatment outcomes.

**Cervical Cancer: Costs**

Studies have reported on the costs of reagents, technologies, and infrastructure for cervical cancer screening programs in LMICs, including cytology (2.0-4.4 per specimen), human papillomavirus DNA testing ($7.9-8.6 per test), and visual inspection with acetic acid (~$5 per test). Costs for staff, training, and quality assurance of procedures have not been reported, and the efficiencies of scope attained with integration of services have not yet been established.
Cost-effectiveness of Cervical Cancer and HIV Integration

Although extensive literature exists on the cost-effectiveness of screening interventions to reduce ICC among the general population in LMICs67–71 and among PLHIV in high-income settings,72 cost-effectiveness literature is limited regarding ICC in PLHIV in LMICs. A study from Brazil suggests that a 2-tiered screening approach (ie, annual human papillomavirus screening followed by cytology, if positive) is very cost-effective in HIV-infected women68; integrating such an approach into routine HIV care could further increase its value if outcomes are maintained and uptake improved. An analysis in SSA suggests that only 262 HIV-infected women receiving ART would need to be screened to prevent 1 cervical cancer death.73 Integration with HIV services and the utilization of existing infrastructure have the potential to facilitate scale-up and decrease barriers to access.112,116

DEPRESSION/HIV INTEGRATED SERVICES

Depression: Epidemiology and Quality of Life

Depression is highly prevalent among PLHIV in SSA, requiring repeated screening and longitudinal treatment, as described by Chibanda et al116 in this supplement. Up to 40% of PLHIV attending ART clinics in LMICs suffer from depression,117–119 and specific subgroups, such as women, are at particularly high risk.120

Depression can negatively impact adherence to ART, leading to worse HIV outcomes.121–123 In a meta-analysis from SSA, ART adherence was 55% lower in patients with depression symptoms.124 Women with HIV who reported symptoms of depression also experienced accelerated disease progression and higher mortality.125 Depression among PLHIV has been correlated with reduced quality of life in the United States,126 and early evidence suggests the same in SSA.127

Depression: Screening and Treatment Outcomes

Simple screening strategies for depression are feasible in LMICs and in HIV-infected populations, offering an opportunity for integration.119,128 Short surveys have been validated in HIV-uninfected populations,128 as have longer surveys129 and visual scales.130 Incorporating screening for substance use, especially alcohol use, could offer particular benefit, given its comorbidity with both HIV and depression.130,131 Integration of depression screening with HIV care could improve case detection and management.132

Treatment options for depression exist in LMICs. Medications, cognitive behavioral therapy, and interpersonal therapy have all been studied in PLHIV in LMICs.133–135 Further study is needed on the accessibility and sustainability of these interventions, the quantification of their impact on quality of life and life expectancy, and their integration into routine HIV care.136

Depression: Costs

Costs of screening for and treating depression include personnel, training, therapy, and associated medications, which could offset other medical costs from utilization of health services and improve economic outcomes in treated patients.137,138 If successful diagnosis and treatment of depression increased ART adherence or retention in care, then costly second-line ART regimens could be deferred or avoided. However, the scale of such benefit is unclear.

Cost-effectiveness of Depression/HIV Integration

In high-income country general populations, CEA has demonstrated that integrating depression screening and treatment with primary care can be cost-effective.139,140 Decreased overall costs of care can be achieved by integrating care for HIV, mental health, and substance use in the United States; longer follow-up for such interventions will provide more data about the sustainability of such an approach.139 This question, to our knowledge, has not yet been studied in LMICs.

TRADEOFFS AND CHALLENGES ASSOCIATED WITH IMPLEMENTATION OF INTEGRATED SERVICES

The optimal implementation of integrated strategies in specific settings remains to be determined,139 and integrated care could have unintended consequences. Wait times increased from 91 to 127 minutes in a Zambian clinic because of staff and patient flow problems after integration of HIV services with primary health care.141 Longer wait times could increase loss to follow-up or exacerbate stigma.142–144 and TB transmissions could even be increased.142,145 Staff training and program quality might be less effective or more costly when multiple interventions are provided together.142 Developing quality indicators for NCD and HIV outcomes will assist in programmatic feedback and assessment of these potential tradeoffs.120,123,150

The benefits of introducing integrated services and new technologies can be realized only if accompanied by initiatives that strengthen health systems, as emphasized by the Gene Xpert experience in South Africa.146 Any value of integrating NCDs or TB with HIV clinical care will only be achieved if health systems are capable of providing high-quality clinical care consistently and rapidly.

Integration of NCD/HIV services could build on innovative approaches from a diversity of tools and experiences. The expanded use of mobile health (mHealth) suggests that information technologies can improve effectiveness and decrease costs for integrated care.146,147,148 Analyses of primary health clinics in LMICs, which face similar challenges in terms of a management of diverse comorbidities, can offer guidance regarding NCD care for PLHIV.149 NCD screening and treatment could be included in decentralized public health clinics, mobile clinics, community-based campaigns, or home-based care, which may offer additional opportunities for accessing those absent from clinics and allow for increased coverage by integrated services.148,149 Although integration and expansion of NCD care within HIV services can be implemented more easily in settings with more
established health care infrastructures, integration may offer even more clinical benefits in the most resource-limited settings where NCD services are not yet routinely available. Barriers to access and methods to facilitate scale-up need investigation in specific clinical settings.

RESEARCH AND TRAINING AGENDAS

To assess the value of different strategies for screening, prevention, and management of NCDs among PLHIV in LMICs, innovative research at the intersection of NCDs and HIV in LMICs, screening and treatment outcomes, effects of NCDs on quality of life in PLHIV, and the costs associated with managing these comorbidities. The specific assessment of integrated services and the implementation of best practices are also critical.

Clinical training of health care workers for NCD screening and treatment is necessary, as is further training of students and health professionals in epidemiology and implementation science. As new programmatic initiatives are developed for NCDs in LMICs, formal training in costing methodology, CEA, and BIA will offer opportunities for capacity building to assist policymakers at local, regional, and national levels.

SUMMARY AND CONCLUSIONS

The remarkable success of ART scale-up in LMICs has established an infrastructure for providing longitudinal medical care to millions of people. PLHIV are living longer and healthier lives but are now at risk for morbidity and mortality from NCDs. The clinical impact and costs of different strategies for NCD prevention, management, and diagnosis in PLHIV is beginning to be quantified. Implementation science can inform the adaptation and expansion of lessons learned from HIV and TB-HIV integrated care to NCDs. Optimal strategies will vary by country, setting, and the underlying burden of different NCDs. Cost-effectiveness and BIA, in addition to observational studies and randomized clinical trials, are complementary tools to assess the value of screening for and treatment of NCDs and can inform health policy in an era marked by very effective HIV therapy, a growing NCD burden, and increasingly limited resources.

TABLE 1. Research Agenda on the Cost-effectiveness and Implementation of Integration of NCD Management With HIV Care for People in LMICs

| To assess the cost-effectiveness of NCD management for PLHIV in LMICs, collect data on: |
| Epidemiology: to determine prevalence, incidence, and attributable mortality by demographics and region |
| Quality of life to examine the impact of comorbid NCD diagnoses and their treatment |
| Screening: to evaluate the test characteristics, yield, and outcomes |
| Treatment: to assess the availability and outcomes of NCD management strategies |
| Costs: to quantify the resource use of screening, treatment, and management of NCD clinical outcomes |

To investigate optimal strategies for integration of expanded screening and treatment of NCDs in PLHIV, collect data on:

Outcomes: to measure clinical and economic outcomes with both distinct and integrated care

Time points to determine short-term and long-term outcomes, including linkage to and retention in care

To use existing clinical and research platforms, extend research training in LMICs in the following fields:

Clinical epidemiology
Implementation science
CEA
Mathematical modeling

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11.1 Discussion

11.1.1 Impact of ART timing in TB therapy on mortality

Despite the availability of safe and effective treatment for each of TB and HIV individually, co-treating these diseases presents several clinical challenges. The purpose of this doctoral research was to evaluate the clinical and programmatic challenges in integrating TB and HIV care in order to guide policy and programmatic implementation.

The Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPIT) trial showed a 56% reduction in mortality when ART was integrated with TB treatment, compared to when ART initiation was deferred to after TB treatment completion (57, 58). This study further described unexpectedly high mortality long after cessation of TB therapy in co-infected patients not initiated on ART. Findings from this study were rapidly incorporated into local and global policy guidelines, creating an impetus for the integration of TB and HIV care.

Further analysis of study data showed no difference in incidence rate of AIDS or death when comparing ART initiation among patients randomised to the early arm versus late arm (58). However, among patients with CD4 cell counts <50 cell/mm³, the incidence rate of AIDS or death was significantly lower in those receiving early vs delayed ART initiation in TB therapy. Similar findings were published from two other randomised clinical trials (60, 62), the AIDS Clinical Trials Group (ACTG) Study 5221 (STRIDE) (62), and the Cambodian Early versus Late Introduction of Antiretrovirals (CAMELIA) study (60).

A model, which was created in Rwanda, to predict the impact of different ART initiation strategies in TB patients on 2-year survival rates, concurs with findings of reduced mortality and improved retention in care among individuals with low CD4 cell counts that initiate ART early (46). A recently published systematic review and meta-analysis of eight randomised controlled clinical trials (n = 4568) (1, 145), conducted in the United States, Africa, Asia, that investigated optimal timing of ART in TB patients, concluded that early ART reduced mortality compared with delayed ART (relative risk [RR], 0.81). In patients with baseline CD4 cell count <50 cells/mm³, early ART decreased mortality compared with delayed ART (RR, 0.71) (145). The mortality benefit from early ART was however not found among those with CD4 cell count >50 cells/mm³, (RR, 1.05) (Figure 7) (145).
Data from these studies provide clear evidence on the optimal timing of ART initiation in patients with HIV associated pulmonary TB. They demonstrate that TB-HIV co-infected patients with advanced immunosuppression defined as CD4 cell count <50 cells/mm$^3$, benefit from initiating ART within 2 weeks of TB treatment initiation (57, 58, 60, 62). Among patients with higher CD4 cell counts defined as CD4 cell count >50 cells/mm$^3$, however, the incidence of AIDS and/or death were similar irrespective of initiation of ART early or later during TB treatment. An evaluation of other co-morbid clinical conditions may be warranted when determining the optimal timing of ART initiation in TB-HIV co-infected patients with higher CD4 cell counts.

11.1.2 TB-HIV Integration and Immune Reconstitution Inflammatory Syndrome

11.1.2.1 Paradoxical TB IRIS

TB Immune reconstitution inflammatory syndrome (IRIS), a paradoxical clinical deterioration in patients on effective TB treatment, remains the major hurdle to antiretroviral therapy (ART) initiation during tuberculosis treatment (70, 74, 86). Published reports of high incidence rates of IRIS from diverse settings has been one of the most important and often cited reason for delays in initiation of ART in patients receiving TB treatment (70, 73, 74, 84, 86, 90, 91, 146). In a review of 40 retrospective, cohort observational and randomised studies, pooled incidence of paradoxical TB-IRIS was 18%, (range from 4% to above 50%) (74). IRIS risk varied by study design, geographic location and whether inpatients or outpatients were studied (70, 73, 74, 84, 86, 90, 91, 146). Furthermore, higher risk of paradoxical TB IRIS was associated with ART initiation proximal to tuberculosis treatment initiation, and among patients with baseline CD4 cell counts <50 cells/mm$^3$ (58, 60, 62, 85, 87, 89, 147, 148). Data from RCTs including the SAPIT, CAMELIA, and STRIDE studies also provide some insights into the frequency of IRIS relative to ART timing (77, 149, 150).
In the SAPiT trial, we found IRIS incidence rates of 20.1 and 7.7 cases per 100 person-years in the early and late groups (incidence-rate ratio (IRR): 2.62; 95% CI, 1.48 to 4.82; p<0.001), respectively. Furthermore, patients with CD4 cell count <50 cells/mm³ had approximately five times higher incidence rates of IRIS in the earlier compared to later-ART group (p = 0.01). In addition, there was 2-fold higher paradoxical TB IRIS rates in patients with baseline CD4 cell count ≥ 50 cells/mm³ randomised to earlier ART, compared patients randomised to later ART (77).

The CAMELIA trial reported 36% (110/308) versus 16% (45/289) IRIS events in the early and late-ART groups, (2.61; 95% CI: 1.84–3.70 ; p<0.001) (62, 149); while the STRIDE study (60, 150) found a two-fold higher IRIS rates in the immediate compared to late ART groups,(10.4% vs 4.7% p=0.002), respectively. Like in the SAPIT trial, the STRIDE trial showed a higher risk of TB-IRIS with early ART in patients with baseline CD4 cell count <50 cells/mm³ (18.8% early vs 4.3% later) (60, 150). However, there was no difference in IRIS risk with earlier ART timing in patients with CD4 cell count ≥ 50 cells/mm³, (5.7% early vs 5.0% later) (60, 150). Cumulative TB-IRIS incidence rates reported in the Thai TIME trial, was 32.9 in the 4 week and 19.4% in the 12 week arms (RR: 2.03) (63). All four RCTs investigating ART timing in TB therapy confirm previous published findings from observational studies: earlier ART increases TB-IRIS risk; provides the evidence that quantifies IRIS risk (two- to threefold higher risk with ART initiation at 2 weeks vs. 8–12 weeks of TB therapy) and gives evidence for heightened risk in patients with CD4 cell counts <50 cells/mm³ (58, 60, 62, 63). The systematic review and meta-analysis published by Uthman et al, also showed higher incidence of TB-IRIS associated with early ART compared to delayed ART (RR, 2.31) (145).

The finding of low IRIS-associated mortality in the SAPiT trial, was not unique. Despite heterogeneity in baseline characteristics and setting, mortality from IRIS was low overall in all three RCT’s (58, 60, 62). IRIS-associated deaths reported in the CAMELIA (n=6) (60, 149), TIME (n=1) (63) and SAPiT (n=2) (77) studies occurred in patients randomised to earlier-ART initiation. Although the STRIDE study (62, 150), reported no IRIS associated deaths, the Torok et al TB Meningitis trial showed extremely high mortality rates from intracranial IRIS reported in both study arms (67). Overall the low rates of IRIS-associated mortality demonstrated in all these different studies denotes that scale-up of TB-HIV integration can be done without fear of worsening IRIS associated morbidity and mortality or of increasing resources needed for management of paradoxical TB IRIS.

The overall incidence rates of paradoxical TB IRIS in published RCT’s were not as high as previous reports (60, 62, 63, 67, 77, 149, 150). As patients with advanced immunosuppression are at highest risk of developing paradoxical TB IRIS, the balance of improved survival when initiating ART earlier
during TB treatment outweighs the increased IRIS risk. A diagnostic marker suitable for routine clinical and laboratory settings that will enable efficient IRIS diagnosis and further management, is needed.

11.1.2.2 Unmasking TB

We found alarmingly high TB incidence rates (11.5/100 py) among HIV infected patients in the first 3 months post ART initiation, while incident TB identified during 4-24 months of follow-up post ART initiation, was not as high (3.2/100 py), p <0.001. TB incidence rates remained consistently high irrespective of a baseline CD4 cell count of < 50 or > 200 cells/mm³ (57, 58, 77). In another published report from South Africa, unmasking TB accounted for more than one third of all TB cases that presented during the first 4 months of ART (93). The relative contribution of unmasking TB IRIS to the high rates of incident TB is largely unknown due to diagnostic complexities. Unlike paradoxical tuberculosis-associated IRIS, the understanding of unmasking TB IRIS is less clear. High rates of tuberculosis are diagnosed in ART programmes in resource-limited settings, due to varied reasons. TB may present as a result of ongoing immune deficiency, due to previously missed diagnosis, flare-up of active subclinical disease due to restoration of ART-induced TB immune responses.

The data we present demonstrates an inverse relationship between TB incidence and time on ART, demonstrating highest rates of TB due to “unmasked” infection in the first three months post ART initiation, highlighting the need for close monitoring for TB in this period. Additionally, this data is in keeping with published reports that demonstrate continued high incidence rates of new TB infections even at 24 months post ART initiation. These reports show that despite the decline of TB incidence with time on ART, ART-accessing patients remain at heightened risk for TB, at rates far higher than in the general HIV uninfected population (151).

Other publications report a far more considerable time dependant decrease in TB incidence among patients on ART (152-161), reporting highest TB incidence rates during the first 3 months of ART (96), with a reduction in all forms of TB from 5.77/100 to 2.23/100 py (162) during the first year of follow-up. Differences in background risk of TB infection, is a likely contributor to varying TB incidence rates among patients on ART in other settings. Published meta-analysis data from a developed country show that among patients accessing ART, TB incidence rates were estimated at 3 per 1000 py; which is approximately 10 fold lower than the TB incidence rates we found (96). Moreover, recently published TB incidence rates estimates TB incidence rates of 7.43 per 1,000 person years over a 10-year period among patients receiving HIV Treatment in Nigeria (163). Findings similar to ours, emerged from an urban informal settlement in Cape Town, which has a background TB notification rate of >1000/100 000 population and HIV sero-prevalence of 28%. Here, TB incidence reduced from 22.1 after approximately three years of ART, to 4.5/100 py (164, 165). A meta-analysis of 9 studies evaluating ART associated TB risk reduction found that most studies (n = 6), showed ART-associated risk
reduction of > 70% (IQR: 54% to 92%), irrespective of setting or background TB burden (42, 99, 166-170). TB rates during ART appear to be dependent on the duration that patients spend at low CD4 cell counts. This is further complicated by the high risk for nosocomial TB infection due to care in congregate settings with poor infection TB control practices, which is typical of most ART programmes in sub-Saharan Africa (171).

11.1.3 TB-HIV Integration and Impact on Additive Drug Toxicity

Our study shows that the risk of treatment limiting additive drug toxicity was low with TB-HIV co-treatment. Overall, we found low rates of drug switching from toxicity in all three arms, and no significant difference in the incidence rate of drug switches secondary to toxicity between the treatment arms (57, 58). Concerns that treating TB and HIV simultaneously will worsen rates of additive toxicity and undermine TB and HIV treatment outcomes was also assessed in the CAMELIA (60), and STRIDE studies (62). The trials all demonstrated similar rates of drug toxicity irrespective of treatment group assignment.

The most common drug toxicities warranting drug change in our study were neuropsychiatric side-effects (n=4), hyperlactatemia and elevated transaminase levels (n= 3) and, peripheral neuropathy (n=2). These occurred mainly in the first six months (11/15 events) post ART initiation, and was most likely due to our choice of first line ART regimen (172). It is important to note that these findings may not be generalizable to a sicker population, or to those taking a different background ART or TB regimen, as this study was conducted in ambulant, patients with pulmonary TB.

11.1.4 Costs and Cost-Effectiveness of ART timing in TB treatment

GDP per capita is the benchmark used to select cost-effectiveness of interventions in countries such as South Africa, where a cost-effectiveness threshold remains to be established. An intervention is considered cost-effective if it costs between one and three times annual GDP per capita. Until now, there was a lack of objective evidence as to whether integration of services will contribute to increased or decreased costs to the healthcare provider. On one hand, integration of HIV and TB services could potentially save money through shared use of resources, which includes: monitoring and evaluation systems, medicine supply chain management, laboratory equipment, shared human resources and infrastructure (48, 173, 174). However, TB-HIV co-treatment could also increase costs, as ART is provided to larger numbers of patients and more resources may be required, such as clinical infrastructure, systems to manage complications of co-treatment and additional staff and staff training (48).

Timing of ART initiation during TB treatment has repercussions for cost and quality of health service delivery. In patients with CD4 cell counts <50 cells/mm³, the mortality benefit of starting ART early
during TB treatment is well-defined (58, 62) and far outweighs any implications of higher cost. However, in patients with CD4 cell counts ≥50 cells/mm³, the best time to initiate ART during TB treatment is less well-defined as survival was similar among patients initiating ART within one month or after 2 months of TB treatment start. In the context of this unclear survival benefit with earlier ART initiation in TB therapy, questions of cost-effectiveness, and affordability became important considerations for health funders and planners. Increased costs of care with early integrated ART are linked to more frequent hospitalisation, more numerous diagnostic investigations for IRIS and drug toxicity, compared to late integrated care.

In assessing the costs and cost-effectiveness of initiating ART at three points in TB treatment in patients with CD4 cell counts ≥50 cells/mm³, late initiation of ART during TB treatment (Arm-2) was shown to be the most cost-effective strategy for patients with CD4 cell counts ≥50 cells/mm³ (175). Mortality and costs was similar in Arm-1 and Arm-2. Arm-3, while having the highest mortality, also showed the lowest costs. The 2009 annual GDP per capita in South Africa was $5758. We found the cost per death averted in moving from sequential to late integrated treatment was $4199 per annum, an amount below the 2009 prices, consequently supporting ART integration at the end of the intensive phase of TB treatment, for South Africa. Arm-1, while marginally more expensive, has slightly higher mortality than Arm-2, indicating that Arm-2 is the better choice both in terms of both mortality outcomes and cost (175).

Laboratory testing, hospitalization, outpatient care and drugs make up the four key cost components that need to be considered when treating TB and HIV co-infected patients. Laboratory investigations accounted for the biggest contributor of costs in all three arms, (10.7% in Arm-3, 43.0% in Arm-2 and 35.5% in Arm-1). While spending on laboratory tests was lower in Arm-1 than in Arm-2 (p=0.005), these costs will likely be lower in routine settings adopting a managed care approach and less frequent testing. The cost of ART contributed sizeably to total variable costs in Arm-1 (32.4%) and Arm-2 (28.7%). It is worth noting however, that costs of routine and safety laboratory investigations and costs of drugs used to treat complications are likely to shrink as duration on ART increases, a reduction in ART prices due largely to use of generic fixed drug combinations (175).

Hospitalization, while accounting for a significant amount of Arm-3 costs, was more variable than other costs. Arm-3 had higher hospitalization costs, due to there being more patients hospitalized and longer hospital stays among the sick patients in this group. With the wide-scale adoption of the late integrated strategy for co-infected patients in endemic settings, it is worth noting that health planners should expect to spend approximately $1086 per patient hospitalized.
Patient survival and costs in Arm-1 and Arm-2 were similar (175). Patients in the late integrated treatment arm did however experience fewest serious adverse events, IRIS events and hospitalizations, which are all associated with significant costs especially in the provision of TB and HIV services. Notwithstanding the small differences in cost between Arms-1 and-2, given the magnitude of the TB-HIV co-infection epidemic in sub-Saharan Africa, the choice of late initiation of ART in TB could lead to substantive savings.

The costs in this study were higher when compared to published data from programs offering HIV care and treatment services only (141, 176). The higher costs in this analysis can be attributed to the clinical trial context which typically has more frequent monthly visits, frequent and intensive laboratory monitoring, higher patient to staff ratio and longer staff time allocated per patient compared to routine care settings. Furthermore, the inclusion of hospitalization costs, and the relatively high labour costs in South Africa, also account for higher costs in this analysis (177). Despite these factors, the relative differences in the costs of implementing these three treatment strategies is likely to be similar in other settings. Interestingly, the Clinton Health Access Initiative (CHAI) published findings that compared the total cost of treating HIV in South African health facilities with four other African countries, and found that costs in South Africa was $682 per annum, compared to an average of $200 per annum the other countries (139). Hospital and TB-related costs were not presented in this study’s analyses. Data reporting costs of providing HIV-treatment within PEPFAR-supported programs in other low and middle income countries also show average costs of $880 per annum. Costing analysis conducted at a single ART clinic in Haiti suggested that TB-HIV integration was a strategy to safeguard clinician time, concluding that integration involved small cost and time increases when compared to treating HIV alone (178, 179). These studies while estimating lower per annum costs in HIV treatment provision, do not account for hospital costs, or TB-related costs which were included in this analysis (139, 141).

In summary, it is estimated that South Africa could save more than $7 million per annum by implementing the strategy of late integration of ART rather than the early integration strategy in patients with CD4 cell counts ≥50 cells/mm³. To derive this we assume coverage of 70% of the projected burden of HIV-TB co-infected patients, and that all patients had drug susceptible pulmonary TB, if the cost difference between Arm-1 and Arm-2 is estimated at $3.11 per month (175).

11.2 Limitations

The SAPIT trial included only ambulant patients with sputum smear positive TB, therefore the results presented here may not be directly generalizable to all forms and severity levels of TB, e.g. smear negative TB, extra-pulmonary TB etc. Furthermore, while there were no significant differences in patient retention across the study arms, it may be likely that as a result of more patients being retained in the early integrated treatment arm, endpoint ascertainment of mortality, IRIS, and drug toxicity was
greater here than in the other 2 arms. Although CD4 cell count was a strong predictor of mortality and of IRIS risk, it is important to note that CD4 cell count testing is not always available in many settings. Furthermore the use of CD4 count to determine eligibility for ART in TB HIV co-infected patients has recently been removed from WHO guidelines. Therefore, decisions regarding ART timing in patients need to be tempered by clinical judgment of disease severity together with an assessment of existing capacity to diagnose and manage these clinical complexities. The use of retrospectively collected data within the CAT program, limited access to diagnostic microbiologic and radiologic services compounded by missing data elements of routinely collected data, may have led to an underestimation of unmasking-TB, and unmasking TB-IRIS in this setting.

11.3 Conclusion

The overall aim of this study was to assess the impact of ART initiation in TB-HIV co-infected patients with respect to mortality; unmasking TB; TB associated immune reconstitution inflammatory syndrome, drug tolerability and additive toxicity, and costs and cost effectiveness of co-treatment. Notwithstanding the limitations of these studies, the following outcomes and conclusions can be drawn from this series of studies:

a. Mortality: Initiation of ART in TB treatment in TB-HIV co-infected patients resulted in a 56% survival benefit. This benefit was more profound in patients with a CD4 counts < 50 cells/mm³

b. Unmasking TB following ART initiation: High rates of newly diagnosed TB was found in HIV infected patients in the first three months post ART initiation, irrespective of a baseline CD4 cell count of < 50 or > 200 cells/mm³

c. IRIS incidence, severity and outcomes: Initiation of ART early during TB treatment resulted in significantly higher IRIS rates, longer time to resolution, and more severe cases of IRIS requiring hospitalization.

d. Costs and cost effectiveness of integration: The most cost-effective strategy for patients with CD4 cell counts ≥50cells/mm³ is the late initiation of ART during TB treatment

e. Additive drug toxicity and tolerability with TB-HIV integration: Additive drug toxicity from co-administration of TB and HIV drugs is of limited concern in TB-HIV co-treatment
Tuberculosis is the most common cause of death in HIV infected individuals. The evidence demonstrates that initiation of ART during TB treatment improves survival in TB-HIV co-infected patients. While TB-HIV co-infected patients with severe immunosuppression have a five-fold risk of IRIS with early ART initiation in TB therapy, the clear survival benefit outweighs this risk. In stable ambulant patients with CD4 cell counts ≥ 50 cells/mm³, deferring ART to 8 weeks after tuberculosis treatment initiation may be a recommended strategy since with this approach IRIS incidence is lower, IRIS events are less severe, and the risk of AIDS or mortality is not increased. The survival benefit from early initiation of ART in TB-HIV co-infected patients outweighed the concerns of overlapping drug toxicities. We found relatively low rates of drug switches and complete regimen changes from virologic failure among co-treated patients. Manageable toxicities occurred early, affecting small numbers of trial participants. The burden of the dual epidemics of TB and HIV is most severe in sub-Saharan Africa, a region with constrained budgets dedicated for health, infrastructure, human resources, and poor practices in TB infection control. The programmatic burden of sustaining the costs associated with integrated care in this environment has been addressed through the demonstration that late integrated treatment has substantial cost reduction over early integrated therapy in stable patients with CD4 counts ≥ 50 cells/mm³.

Findings from the work presented here has been incorporated into local and international guidelines and has been used to inform TB-HIV integration policy aimed at improved patient outcomes and public health benefit, especially in TB and HIV endemic settings. However, it is important to acknowledge that several operational and implementation challenges need to be overcome in order to translate the evidence from these clinical trials into public health benefit within diverse operational settings.
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