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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

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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/mm³, showed no difference in incidence rate of AIDS or 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 < 50 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 randomised 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 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 Antiretrovirals (CAMELIA) 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 extra-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 OXTREC 023–04 trial, conducted in Vietnam among 253 HIV infected patients with mean baseline CD4 + T-cell counts of 41 cells/mm³

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; $p=5.50$). 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; $p=5.31$) 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 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 OXTREC 023–04 trial [27]. Overall the low rates of IRIS-associated mortality and IRIS-related hospitalizations 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 NNRTI's 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 (RDR) now recommends a dose increase of RGR to 800mg 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 empiric 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 <50 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 empiric 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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Figure 1.
Risks and benefits of early versus later antiretroviral therapy initiation in tuberculosis patients

Table 1
Comparison of recent randomized controlled trials evaluating co-initiation of antiretroviral therapy and anti-TB therapy

	SAPT	ACTG 5221	CAMELIA	OXTREC 023-04
Baseline characteristics:				
CD4+ T- cell cutoff (cells/mm ³)	500	250	200	< 200
TB status	known	known/suspected	known	Known TB meningitis
Early ART	Within 4 weeks of TB treatment initiation	Within 2 weeks of TB treatment initiation	Within 2 weeks of TB treatment initiation	Within 7 days of TB treatment initiation
Late ART	Within 8 weeks of TB treatment initiation	8–12 weeks of TB treatment initiation	Within 8 weeks of TB treatment initiation	After 8 weeks of TB treatment initiation
ART regimen	didanosine, lamivudine, efavirenz	emtricitabine, tenofovir, efavirenz	d4T, lamivudine, efavirenz	Zidovudine, lamivudine, efavirenz
Setting	South Africa	Africa, Asia, North America, South America	Cambodia	Vietnam
Mean age	34	34	35	28.5
Median CD4+ T- cell count	150	77	25	41
Median Viral load	5.21 log ₁₀	5.43 log ₁₀	5.64 log ₁₀	5.4 log ₁₀
Number enrolled	429	809	661	253
Median Follow up (months)	17.7	11	25	3

Outcomes:	Early (Event rate/100 p-y)	Late (Event rate/100 p-y)	IRR (95% CI), p value	Early (%)	Late (%)	95% CI for difference in prop. p value	Early (%)	Late (%)	Hazard Ratio (95% CI), p value	Early (%)	Late (%)	Hazard Ratio (95% CI), p value
Death												
All patients	5.7	6.0	0.96 (0.44–2.10), p=0.91	-	-	-	18	27	0.62 (0.44–0.86), P=006	59.8	55.6	1.12 (0.81–1.55) p=0.50
CD4+ count <50 cells/mm ³	6.3	16.3	0.39 (0.06–1.70), p=0.17	-	-	-	-	-	-	63.3	65.1	1.05 (0.68–1.61) P=0.84
CD4+ count >50 cells/mm ³	5.6	3.8	1.46 (0.55–4.10), p=0.41	-	-	-	-	-	-	49.0	41.5	*
AIDS defining illness/death												
All patients	6.9	7.8	0.89 (0.44–1.79), p=0.73	12.9	16.1	(–1.8–8.1) p=0.45	-	-	-	-	-	-
CD4+ count <50 cells/mm ³	8.5	26.3	0.32 (0.07–1.13), p=0.06	15.5	26.6	(1.5–20.5) p=0.02	-	-	-	-	-	-
CD4+ count >50 cells/mm ³	6.6	4.4	1.51 (0.61–3.95), p=0.34	11.5	10.3	(–6.7–4.3) p=0.67	-	-	-	-	-	-
IRIS												

Outcomes:	Early (Event rate/100 p- y)	Late (Event rate/100 p- y)	IRR (95% CI), p value	Early (%)	Late (%)	95% CI for difference in prop, p value	Early (%)	Late (%)	Hazard Ratio (95% CI), p value	Early (%)	Late (%)	Hazard Ratio (95% CI), p value
All patients	20.1	7.7	2.62 (1.48–4.82), p<0.001	10.6	4.7	p=0.002	IR 3.76 per 100 p-y	IR 1.53 per 100 p-y	2.51 (1.78–3.59), p<0.001	-	-	-
CD4+ count <50 cells/mm ³	46.8	9.9	4.71 (1.48–19.64), p=0.01	-	-	-	-	-	-	-	-	-
CD4+ count >50 cells/mm ³	15.8	7.2	2.18 (1.12–4.47), p=0.02	-	-	-	-	-	-	-	-	-

IRR—incidence rate ratio

* datafor all CD4 T cell count strata >50 cells/mm³ were combined but no IRR could be calculated as no person time of follow-up was provided

p-y – person years

IR Incidence rate