REVIEW

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Optimal Timing of Antiretroviral Therapy Initiation for HIV-Infected Adults With Newly Diagnosed Pulmonary Tuberculosis

A Systematic Review and Meta-analysis

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Background: Initiation of antiretroviral therapy (ART) during tuberculosis (TB) treatment remains challenging.

Purpose: To assess evidence from randomized, controlled trials of the timing of ART initiation in HIV-infected adults with newly diagnosed pulmonary TB.

Data Sources: PubMed, EMBASE, Cochrane Central Register of Controlled Trials, conference abstracts, and ClinicalTrials.gov (from January 1980 to May 2015).

Study Selection: Randomized, controlled trials evaluating early versus delayed ART initiation (1 to 4 weeks vs. 8 to 12 weeks after initiation of TB treatment) or deferred ART initiation (after the end of TB treatment).

Data Extraction: Three reviewers independently extracted data and assessed risk of bias. The main outcome measures were all-cause mortality and the TB-associated immune reconstitution inflammatory syndrome (TB-IRIS).

Data Synthesis: The 8 included trials (n = 4568) were conducted in Africa, Asia, and the United States and were generally at low risk of bias for the assessed domains. Overall, early ART reduced mortality compared with delayed ART (relative risk [RR], 0.81 [95% CI, 0.66 to 0.99]; I^2 = 0%). In a prespecified subgroup analysis, early ART reduced mortality compared with delayed ART among patients with baseline $CD4^+$ T-cell counts less than 0.050×10^9 cells/L (RR, 0.71 [CI, 0.54 to 0.93]; I^2 = 0%). However, a mortality benefit from early ART was not found among those with $CD4^+$ T-cell counts greater than 0.050×10^9 cells/L (RR, 1.05 [CI, 0.68 to 1.61]; I^2 = 56%). Early ART was associated with a higher incidence of TB-IRIS than delayed ART (RR, 2.31 [CI, 1.87 to 2.86]; I^2 = 19%).

Limitation: Few trials provided sufficient data for subgroup analysis.

Conclusion: Early ART in HIV-infected adults with newly diagnosed TB improves survival in those with $CD4^+$ T-cell counts less than 0.050×10^9 cells/L, although this is associated with a 2-fold higher frequency of TB-IRIS. In patients with $CD4^+$ T-cell counts greater than 0.050×10^9 cells/L, evidence is insufficient to support or refute a survival benefit conferred by early versus delayed ART initiation.

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The epidemiology and natural history of tuberculosis (TB) has been altered by HIV infection in resource-limited settings (1). HIV is the most potent risk factor for reactivation of latent TB and progression to active TB after primary exposure or reinfection (2). Without antiretroviral therapy (ART), the risk for death during TB treatment in HIV-infected adults ranges from 16% to 37% among those with $CD4^+$ T-cell counts greater than 0.350×10^9 cells/L (1, 3–10). Initiation of ART concomitantly with anti-TB drugs during treatment of drug-susceptible pulmonary TB remains challenging for many reasons, including patients' adherence to multiple antiretroviral and anti-TB drugs (11, 12), drug–drug interactions (for example, between rifampicin-based TB treatment and ART, including nevirapine or ritonavir-boosted protease inhibitors) (13–15), overlapping adverse effects of TB drugs and ART (14), and frequency of the TB-associated immune reconstitution inflammatory syndrome (TB-IRIS) (6–10).

The optimal timing of ART initiation in HIV-infected persons with newly diagnosed TB who have begun TB treatment requires further definition. Current World Health Organization (WHO) guidelines recommend that TB treatment be started first and followed by ART as soon as possible "within the first 8 weeks" of starting TB treatment and within the first 2 weeks for patients with profound immunosuppression ($CD4^+$ T-cell counts $<0.050 \times 10^9$ cells/L). These guidelines state that there is low-quality evidence for the optimal timing of ART initiation for HIV-infected patients with newly diagnosed TB who have $CD4^+$ T-cell counts greater than 0.350×10^9 cells/L.

Since publication of the WHO guidelines and various expert reviews (16, 17), further data have emerged, including a large, randomized trial conducted under programmatic settings within health services in sub-Saharan Africa (18). To provide an up-to-date summary of reliable evidence that could be used to inform the updating of international guidelines, we conducted a systematic review of trials evaluating the effectiveness and safety of early versus delayed or deferred ART initiation in HIV-infected adults with newly diagnosed pulmonary TB and various degrees of immunosuppression.

METHODS

The study background, rationale, and methods were specified in advance and documented in a study protocol registered in the PROSPERO database (CRD42012001884).

Data Sources and Searches

We searched the PubMed, EMBASE, and Cochrane Central Register of Controlled Trials databases from January 1980 to May 2015. We used keywords related to TB and HIV, and there were no language restrictions. Further, we searched abstracts from major HIV/AIDS or infectious diseases conferences (from 2008 onward), including the Conference on Retroviruses and Opportunistic Infections; the International AIDS Conference; the International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention; the International Conference on Antimicrobial Agents and Chemotherapy; and the Infectious Diseases Society of America Conference. In addition, we manually checked the reference lists of identified studies.

Study Selection

Three authors independently evaluated the eligibility of studies obtained from our literature search. Disagreements were resolved by discussion, and agreement was reached by consensus. We included only randomized, controlled trials that compared early initiation of ART (commenced 1 to 4 weeks after the start of TB treatment) with delayed initiation (commenced 8 to 12 weeks after the start of TB treatment) or deferred initiation (commenced at the end of 6 months of TB treatment) in HIV-infected adults with newly diagnosed pulmonary TB. The primary outcomes considered included all-cause mortality and TB-IRIS; secondary outcomes were HIV-1 RNA suppression rates (viral load <400 copies/mL), TB cure rates, grade 3 or 4 adverse events (excluding TB-IRIS events), and loss to follow-up.

Data Extraction and Quality Assessment

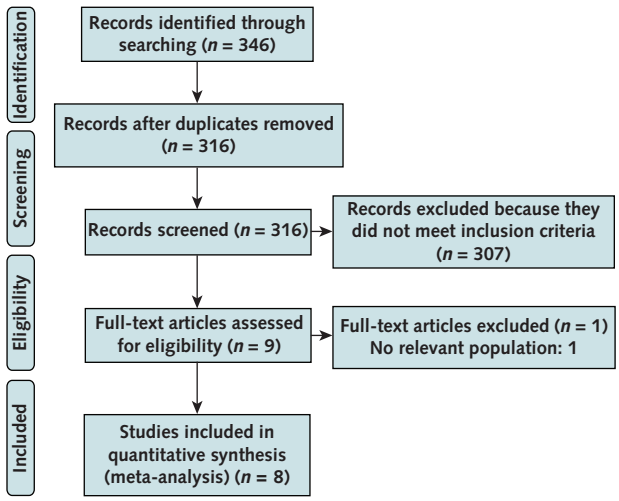
Three authors independently extracted and compared the data. For each included study, details on the design, population characteristics, intervention, and outcome measures were extracted and the risk of bias was evaluated. Discrepancies were resolved by reaching consensus through discussion. We used the Cochrane Collaboration's tool (19) for assessing the risk of bias of the individual studies and evaluated 6 domains: sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome data (whether the investigators reported completeness of outcome data, including attrition and exclusions from the analysis, and whether missing data were imputed using appropriate methods), selective outcome reporting (assessed by checking the published protocols and contacting authors), and other sources of bias. Risks of bias due to blinding of outcome assessors and incomplete outcome data were assessed for each study but not for each outcome. We reported each domain as having a low, unclear, or high risk of bias. The main outcome measures were all-cause mortality and TB-IRIS. We contacted authors of included studies for additional unpublished data to use in our planned subgroup analysis and risk-of-bias assessment.

Data Synthesis and Analysis

We used a fixed-effect meta-analysis for combining data when it was reasonable to assume that studies were estimating the same underlying treatment effect. We assessed heterogeneity among trials by inspecting the forest plots, using the chi-square test for heterogeneity with a 10% level of statistical significance and the I^2 statistic to quantify the degree of heterogeneity (19, 20). When trials could not be combined for meta-analysis because of clinical heterogeneity (for example, a wide range of baseline $CD4^+$ T-cell counts) or statistical heterogeneity ($I^2 > 50\%$; that is, >50% of the variation is due to heterogeneity rather than chance [21]), we used narrative syntheses. The results of individual trials were displayed graphically to provide a succinct summary of evidence. Subgroup analyses were prespecified to explore the effects in participants with different baseline $CD4^+$ T-cell counts ($<0.050 \times 10^9$ cells/L vs. $>0.050 \times 10^9$ cells/L).

We used Stata, version 13 (StataCorp), and Review Manager, version 5.2 (Nordic Cochrane Centre), for the meta-analysis.

Figure 1. Summary of evidence search and selection.



Role of the Funding Source

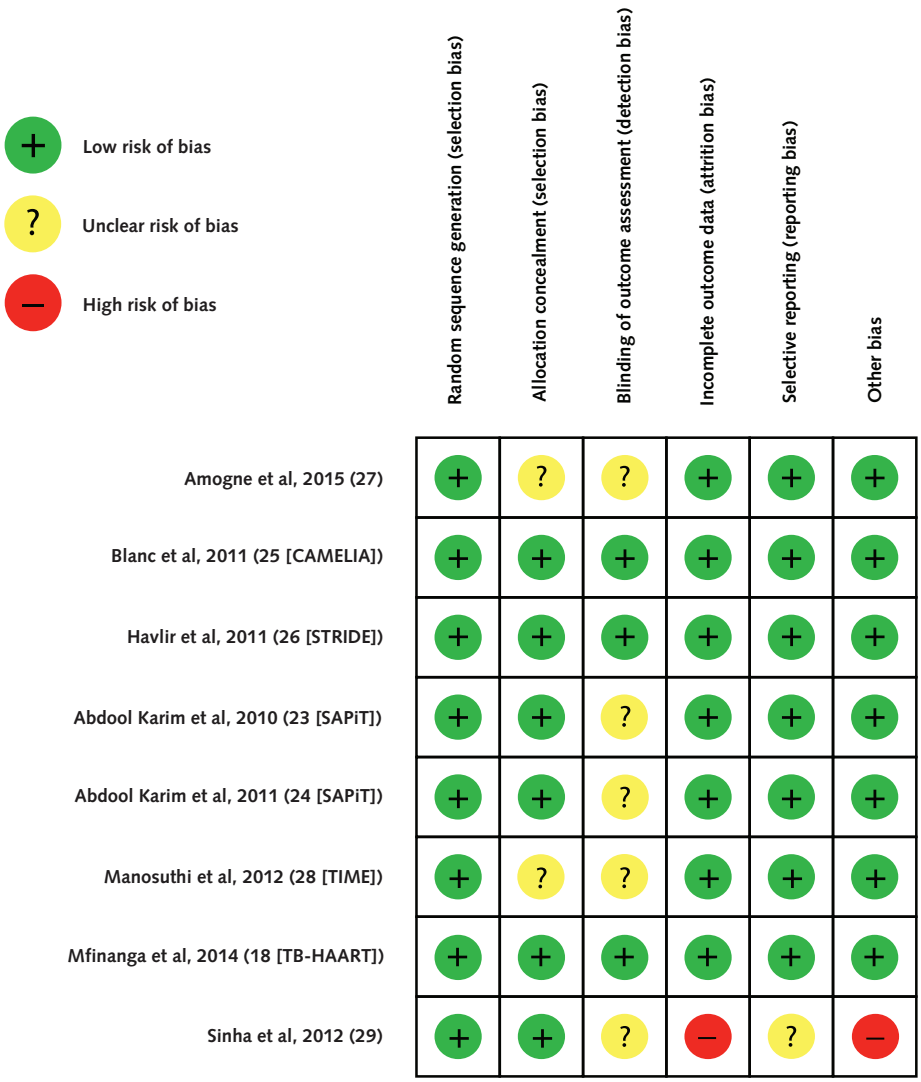
This study received no funding.

RESULTS

Study Characteristics

Figure 1 shows the process of study identification and selection. The literature search yielded 346 citations. After review of the title and abstract, we selected 9 full-text articles for critical reading. One trial (22) that recruited patients with tuberculous meningitis did not meet the inclusion criteria and was excluded. A total of 8 trials (18, 23–29), which included a total of 4568 participants with HIV and TB, met the inclusion criteria. The Appendix Table (available at www.annals.org) shows the characteristics of these trials. The trials were conducted in sub-Saharan Africa, Asia, and the United States between 2005 and 2013 and published between

Figure 2. Risk-of-bias assessment of included trials.



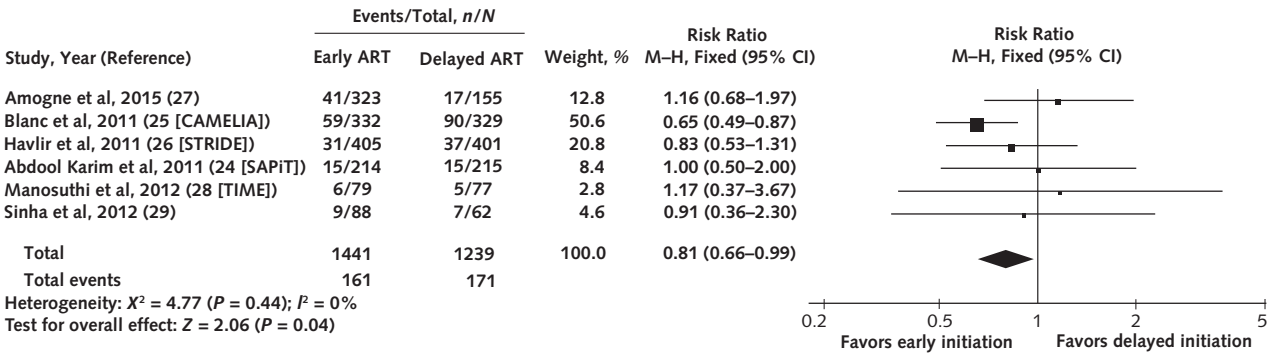
CAMELIA = Cambodian Early Versus Late Introduction of Antiretrovirals; SAPiT = Starting ART at Three Points in TB; STRIDE = Immediate Versus Deferred Start of Anti-HIV Therapy in HIV-Infected Adults Being Treated for Tuberculosis; TB-HAART = An Evaluation of the Impact of Early Initiation of HAART on TB Treatment Outcomes for TB Patients Co-infected With HIV; TIME = Appropriate Timing of HAART in Co-infected HIV/TB Patients.

2011 and 2015. The mean age of the participants ranged from 32 to 38 years, and the percentage of men ranged from 48% to 84%. Five trials compared early ART with delayed ART (25–29). One trial compared early ART with deferred ART (18). Another trial, SAPiT (Starting ART at Three Points in TB) (23, 24), randomly assigned participants into 3 groups: early, delayed, or deferred ART initiation. Patients in all included trials were treated for TB with 6 months of standard short-course chemotherapy and 2 months of isoniazid, rifampicin, ethambutol, and pyrazinamide followed by 4 months of isoniazid and rifampicin. The ART regimens consisted of efavirenz with 2 nucleoside analogues.

Risk of Bias of Included Trials

The risk-of-bias assessments of the included trials are shown in Figure 2. Allocation sequence generation was adequate in all trials and allocation concealment was adequate in 6 trials and unclear in the remaining 2. All of the trials except for TB-HAART (An Evaluation of the Impact of Early Initiation of Highly Active Anti-Retroviral Therapy [HAART] on TB Treatment Outcomes for TB Patients Co-infected With HIV) (18) were open-label trials in which participants, investigators, and clinical staff were not blinded to treatment allocation. Three trials masked outcome assessors to treatment allocation, but the remaining trials did not state whether they did the same. In 1 trial (29), the rate of discontinuation was statistically significantly higher in the early ART initiation group than the delayed ART initiation group (12.5% vs. 1.6%; $P = 0.007$), which made the potential risk of bias from incomplete data high. No evidence of selective outcome reporting was

Figure 3. All-cause mortality comparing early versus delayed initiation of ART.



ART = antiretroviral therapy; CAMELIA = Cambodian Early Versus Late Introduction of Antiretrovirals; M-H = Mantel-Haenszel; SAPiT = Starting ART at Three Points in TB; STRIDE = Immediate Versus Deferred Start of Anti-HIV Therapy in HIV-Infected Adults Being Treated for Tuberculosis; TIME = Appropriate Timing of HAART in Co-infected HIV/TB Patients.

detected. Although the studies seemed to be free of other sources of bias, 1 trial (29) had unequal recruitment to trial groups (88 vs. 62 participants), which raised questions about the fidelity of the randomization process. No evidence of baseline imbalance was, however, detected in this trial (29).

Early Versus Delayed Initiation of ART

All-Cause Mortality

Overall, patients randomly assigned to early ART (11.2% [161 of 1441 patients]) had a lower all-cause mortality than those receiving delayed ART (13.8% [171 of 1239 patients]) at the end of follow-up (6 trials; relative risk [RR], 0.81 [95% CI, 0.66 to 0.99]; I^2 = 0%) (Figure 3). In a prespecified subgroup analysis, early ART reduced all-cause mortality among patients with baseline CD4$^+$ T-cell counts less than 0.050 × 10^9 cells/L (4 trials; RR, 0.71 [CI, 0.54 to 0.93]; I^2 = 0%) (Figure 4). But among those with CD4$^+$ T-cell counts greater than 0.050 × 10^9 cells/L, there was no evidence of reduced mortality with early ART (4 trials; RR, 1.05 [CI, 0.68 to 1.61]; I^2 = 56%) (Figure 4).

TB-IRIS

Among 1450 participants who received early ART, 253 (17.5%) developed TB-IRIS compared with 103 of 1239 (8.3%) in the delayed ART group (6 trials; RR, 2.31 [CI, 1.87 to 2.86]; I^2 = 19%) (Figure 5). As shown in Appendix Figure 1 (available www.annals.org), early ART was associated with a higher incidence of TB-IRIS than delayed ART for patients with CD4$^+$ T-cell counts

Figure 4. All-cause mortality comparing early versus delayed initiation of ART, stratified by baseline CD4$^+$ T-cell counts.

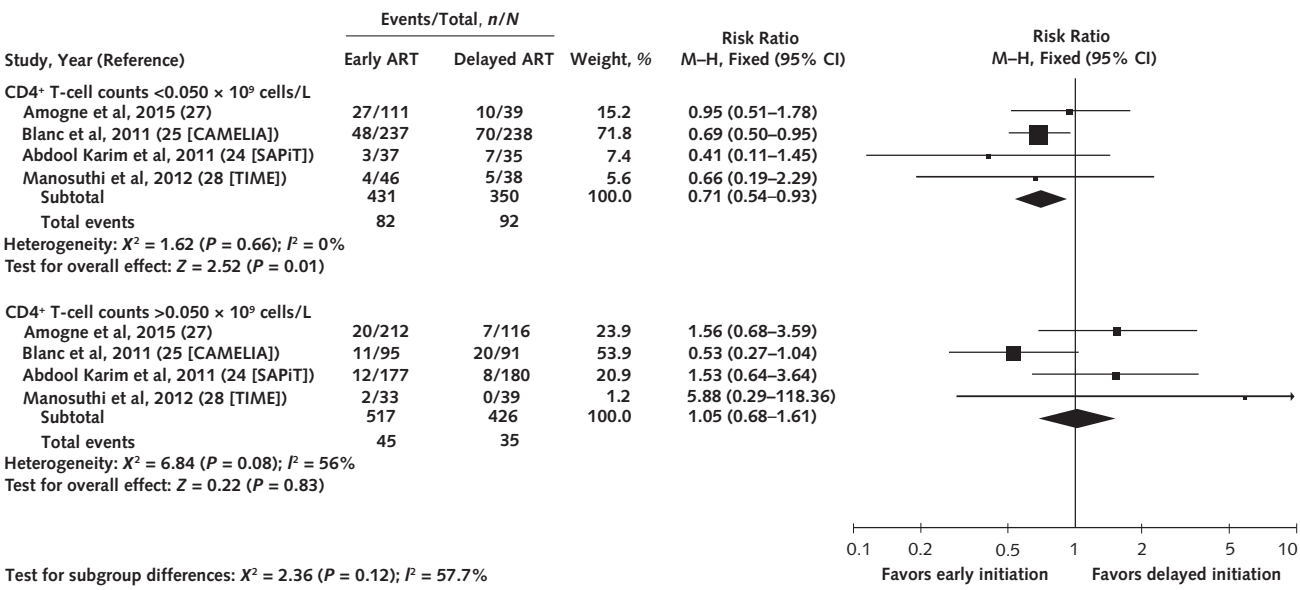


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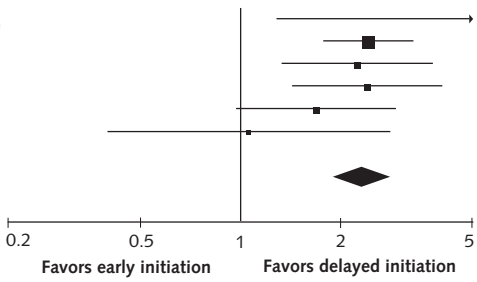
Figure 5. TB-IRIS comparing early versus delayed initiation of ART.



Study, Year (Reference)	Events/Total, *n*/*N* Early ART	Delayed ART	Weight, %	Risk Ratio M–H, Fixed (95% CI)
Amogne et al, 2015 (27)	22/332	0/155	0.6	21.08 (1.29–345.28)
Blanc et al, 2011 (25 [CAMELIA])	110/332	45/329	43.0	2.42 (1.77–3.31)
Havlir et al, 2011 (26 [STRIDE])	43/405	19/401	18.2	2.24 (1.33–3.78)
Abdool Karim et al, 2011 (24 [SAPiT])	43/214	18/215	17.1	2.40 (1.43–4.02)
Manosuthi et al, 2012 (28 [TIME])	26/79	15/77	14.4	1.69 (0.97–2.94)
Sinha et al, 2012 (29)	9/88	6/62	6.7	1.06 (0.40–2.82)
Total	1450	1239	100.0	2.31 (1.87–2.86)
Total events	253	103		

Heterogeneity: $X^2 = 6.20$ ($P = 0.29$); $I^2 = 19\%$
Test for overall effect: $Z = 7.71$ ($P < 0.001$)

ART = antiretroviral therapy; CAMELIA = Cambodian Early Versus Late Introduction of Antiretrovirals; M-H = Mantel-Haenszel; SAPiT = Starting ART at Three Points in TB; STRIDE = Immediate Versus Deferred Start of Anti-HIV Therapy in HIV-Infected Adults Being Treated for Tuberculosis; TB-IRIS = tuberculosis-associated immune reconstitution inflammatory syndrome; TIME = Appropriate Timing of HAART in Co-infected HIV/TB Patients.

less than 0.050×10^9 cells/L (4 trials; RR, 2.50 [CI, 1.84 to 3.40]; $I^2 = 19\%$) and greater than 0.050×10^9 cells/L (4 trials; RR, 2.21 [CI, 1.50 to 3.24]; $I^2 = 0\%$) (interaction $P = 0.62$).

Secondary Outcomes

Individual and pooled RRs for all secondary outcomes are provided in **Appendix Figure 2** (available www.annals.org). No statistically significant differences between participants receiving early or delayed ART with respect to viral suppression rates (4 trials; RR, 1.00 [CI, 0.98 to 1.03]; $I^2 = 0\%$), TB cure rates (3 trials; RR, 1.01 [CI, 0.92 to 1.07]; $I^2 = 0\%$), and grade 3 or 4 adverse events (5 trials; RR, 0.99 [CI, 0.92 to 1.07]; $I^2 = 0\%$) were found. In the early ART group, loss to follow-up was higher than in the delayed ART group (6 trials; RR, 1.60 [CI, 1.17 to 2.19]; $I^2 = 0\%$) (**Appendix Figure 2**).

Early Versus Deferred Initiation of ART

Two trials, TB-HAART (18) and SAPiT (23, 24), compared early ART with deferred ART but could not be combined for meta-analysis because of significant clinical heterogeneity in the study population. The TB-HAART trial (18) excluded patients with low $CD4^+$ T-cell counts; only participants with $CD4^+$ T-cell counts of 0.220×10^9 cells/L or more were included. The SAPiT trial (23, 24) included participants with $CD4^+$ T-cell counts less than 0.500×10^9 cells/L. The 2 trials found no statistically significant difference in all-cause mortality between the 2 treatment groups (**Appendix Figure 3**, available at www.annals.org). The incidence of TB-IRIS (RR, 5.35 [CI, 2.58 to 11.11]) was statistically significantly higher in early ART than deferred ART in SAPiT (23, 24), but there was no statistically significance difference in TB-HAART (18).

Delayed ART Versus Deferred ART

One trial (SAPiT [23, 24]) compared delayed ART with deferred ART and found that patients receiving delayed ART had lower all-cause mortality (RR, 0.55 [CI, 0.30 to 1.00]) and higher viral suppression rates (RR, 1.14 [CI, 1.00 to 1.29]) at the end of follow-up than those receiving deferred ART (**Appendix Figure 4**, available at www.annals.org). However, incidence of TB-IRIS (RR, 2.24 [CI, 1.00 to 5.04]) and grade 3 or 4 adverse events (RR, 1.49 [CI, 1.18 to 1.88]) were higher in patients receiving delayed ART than deferred ART (**Appendix Figure 4**). No statistically significant differences were found between the 2 treatment groups in terms of TB cure rate (RR, 1.12 [CI, 0.95 to 1.32]) and loss to follow-up (RR, 0.57 [CI, 0.29 to 1.12]) (**Appendix Figure 4**).

DISCUSSION

This systematic review of the effects of the timing of ART initiation in HIV-infected patients receiving TB treatment included 8 trials with 4568 randomly assigned participants. Across all $CD4^+$ T-cell count strata, patients commencing ART within 1 to 4 weeks versus 8 to 12 weeks after starting TB treatment had lower all-cause mortality, although this effect was not statistically significant. For the most immunosuppressed patients (baseline $CD4^+$ T-cell counts $<0.050 \times 10^9$ cells/L), we found a statistically significant decrease in all-cause mortality in those assigned to early ART initiation. Early ART initiation was associated with a sharp increase in the incidence of TB-IRIS compared with delayed initiation, regardless of $CD4^+$ T-cell count.

We found only 2 trials comparing early ART with deferred (after 6 months of TB treatment) ART. One of these trials (18) found no difference in all-cause mortality for patients with baseline $CD4^+$ T-cell counts greater than 0.220×10^9 cells/L if ART was delayed until after TB treatment had been completed at 6 months.

Although this meta-analysis strongly supports early ART initiation in adults with $CD4^+$ T-cell counts less than 0.050×10^9 cells/L, it also highlights the need for more nuanced data (for example, cohort analyses or subanalyses of existing trial data) on the role of early ART initiation in HIV-infected adults newly diagnosed with TB who have $CD4^+$ T-cell counts greater than

0.050×10^9 cells/L. Until such evidence becomes available to better define the $CD4^+$ T-cell count threshold for universal early ART, guidelines from the WHO and other groups should acknowledge this strong evidence for early ART among the most highly immunosuppressed patients with HIV and TB and the lack of definitive evidence for early versus delayed ART in those with $CD4^+$ T-cell counts greater than 0.050×10^9 cells/L.

Mortality benefit, although important, is not the only consideration in treating adults newly diagnosed with TB and HIV. Concurrent treatment of HIV and TB requires high adherence, multiple drugs for both infections (11, 12), consideration of clinically significant drug–drug interactions (especially between rifampin and nevirapine or ritonavir-boosted protease inhibitors, although these drugs may be used less commonly for first-line treatment because of emerging guidelines) (13–15), and assessment of the risk for transmission of untreated HIV. Our meta-analysis, although underpowered for many of these secondary outcomes, did not show any increase in grade 3 and 4 adverse events, TB cure rate, or HIV viral suppression. Early ART initiation doubled the risk for TB-IRIS, regardless of $CD4^+$ T-cell counts. These data highlight the need for further research aimed at prevention of TB-IRIS in settings where TB and HIV co-infection is highly endemic by rigorous controlled trials using anti-inflammatory agents, such as glucocorticosteroids or nonsteroidal anti-inflammatory drugs. Such trials are under way in high-burden settings, including South Africa (30).

Our analyses found that patients in the early ART group were more likely to be lost to follow-up than those receiving delayed ART. This finding possibly reflects the high morbidity (for example, the high incidence of TB-IRIS events) or mortality of this group of highly immunosuppressed patients who initiate ART early. Data from other cohorts in Africa show that mortality rates are clinically significantly higher among patients who are lost to follow-up because they are often less adherent to ART medication, are more immunosuppressed, and thus are more likely to die (31–33). Support for ART adherence and interventions to retain these patients at increased risk for dropping out are urgently needed.

Our search for reviews on the optimal timing of initiation of ART during TB treatment was updated in May 2015 and identified 2 published expert reviews (16, 17). Piggott and Karakousis (16) concluded that compelling evidence shows that ART should not be delayed pending the completion of TB treatment in adults co-infected with HIV and TB. Naidoo and colleagues (17) also concluded that trial data support earlier ART initiation in severely immunocompromised patients co-infected with HIV and TB. However, neither review was done systematically nor did the investigators provide reliable and precise estimates using meta-analysis.

Strengths of our review include a detailed search of several databases and other sources to identify eligible randomized, controlled trials, including one that was unpublished. We evaluated all included studies for risk of bias and applied rigorous methods to control for bias and the effects of chance during the review process. Our study also had limitations. On the basis of information available to us, we considered most included studies to be of low risk of bias; however, to the extent that evidence from trials is biased, such bias is mirrored in our analyses. Only 4 of the 6 trials that compared early ART with delayed ART provided sufficient data to analyze subgroups by baseline $CD4^+$ T-cell counts. Repeated attempts to contact relevant authors to obtain additional data needed for this analysis proved unsuccessful. Finally, although we used the end point of TB-IRIS as reported from individual trials, we acknowledge the possible challenges of adjudication of TB-IRIS events despite published case definitions from the International Network for the Study of HIV-associated IRIS (34).

Our data support existing clinical recommendations for patients with $CD4^+$ T-cell counts less than 0.050×10^9 cells/L but highlight the uncertainty around delaying ART for patients with $CD4^+$ T-cell counts between 0.050×10^9 cells/L and 0.220×10^9 cells/L. Further, our data support updating existing guidelines to possibly recommend deferring ART for patients with $CD4^+$ T-cell counts greater than 0.220×10^9 cells/L until after the intensive phase or the end of TB treatment. Additional analyses of clinical cohorts and existing trials are warranted to better define the $CD4^+$ T-cell count threshold (presumably between 0.050 and 0.220×10^9 cells/L) at which the mortality benefit of early ART begins to fade.

Early ART initiation in adults co-infected with HIV and TB who have $CD4^+$ T-cell counts less than 0.050×10^9 cells/L may be facilitated by the use of point-of-care testing tools for $CD4^+$ T-cell counts. In a setting in which these testing tools are not available, WHO staging of HIV (for example, stage 4) may serve as a guide. Because there are also clinical implications in terms of the risk for TB-IRIS, further research into interventions that could reduce the incidence or severity of TB-IRIS in this population would be useful in ensuring that the survival benefit is maintained.

In summary, early ART initiation in HIV-infected adults with newly diagnosed TB improves survival in those with $CD4^+$ T-cell counts less than 0.050×10^9 cells/L, although this is associated with a 2-fold increase in the frequency of TB-IRIS. In patients with $CD4^+$ T-cell counts between 0.050×10^9 cells/L and 0.220×10^9 cells/L, evidence is insufficient to support or refute a survival benefit. In addition, our review includes important recent trial findings that suggest that ART can be deferred until after the end of TB treatment in patients with $CD4^+$ T-cell counts greater than 0.220×10^9 cells/L. Clinical guidelines should be updated to consider this new evidence that supports a less rigid approach; emphasize such issues as clinical presentation; and call for additional analyses from existing cohorts, trials to inform the $CD4^+$ T-cell count threshold at which the survival benefit associated with early ART begins to attenuate, and cost-effectiveness data among patients

initiating ART at $CD4^+$ T-cell counts greater than 0.050×10^9 cells/L.

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Appendix Table. Characteristics of Included Trials

Trial Name	Trial Design	Trial Period	Trial Location	Participants	Early vs. Late Start of ART After TB Treatment Initiation	Randomly Assigned Participants (Early vs. Late ART), *n*	Male, %	Mean Age, *y*	Median Follow-up, *mo*	$CD4^+$ T-Cell Count $<0.050 \times 10^9$ cells/L, %	TB Regimen	ART Regimen	Funding Source
Early vs. delayed initiation of ART													
Blanc et al, 2011 (25) [CAMELIA]	Open-label, randomized, controlled	2006-2009	Cambodia	HIV-infected adults with no previous exposure to antiretroviral drugs who had a $CD4^+$ T-cell count of $<0.200 \times 10^9$ cells/L and had received a new diagnosis of TB as confirmed by any clinical sample that was smear-positive for acid-fast bacilli	2 wk vs. 8 wk	661 (332 vs. 329)	64.3	35.0	12.0	71.9	2HRZE/4HR	d4T + 3TC + EFV	French National Agency for Research on AIDS and Viral Hepatitis and the National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS
Havlir et al, 2011 (26) [STRIDE]	Open-label, randomized, controlled	2006-2009	Africa, South America, United States, Asia	Patients 13 y of age or older with HIV-1 infection with a $CD4^+$ T-cell count of 0.250×10^9 cells/L who had not previously received ART and had confirmed or probable TB	2 wk vs. 8-12 wk	806 (405 vs. 401)	62.0	34.0	25.0	35.4	2HRZE/4HR	EFV + TDF/FTC	Division of AIDS at the National Institute of Allergy and Infectious Diseases, Gilead Sciences, and Merck Pharmaceuticals
Abdool Karim et al, (24) 2011 [SAPiT]*	Open-label, randomized, controlled	2005-2008	South Africa	Patients with both pulmonary TB and HIV infection 18 y of age or older who had a $CD4^+$ T-cell count of $<0.500 \times 10^9$ cells/L at screening and were started on a standard TB treatment regimen	4 wk vs. 12 wk	429 (214 vs. 215)	48.7	34.4	17.7	16.9	2HRZE/4HR	ddI + 3TC + EFV	U.S. President's Emergency Plan for AIDS Relief; the Centre for the AIDS Programme of Research in South Africa (CAPRISA); the Global Fund to Fight AIDS, Tuberculosis, and Malaria; and the National Institutes of Health Comprehensive International Program of Research on AIDS
Amogne et al, 2015 (27)	Open-label, randomized, controlled	2008-2011	Ethiopia	HIV-infected patients who were ≥18 y, had a $CD4^+$ T-cell count of $<0.200 \times 10^9$ cells/L, and were ambulatory with suspected or confirmed new TB diagnosis	1-4 wk vs. 8 wk	478 (323 vs. 155)	50.6	35.3	11.2	31.4	2HRZE/4HR	d4T/ZDV/ TDF + 3TC + EFV	Swedish International Development Cooperation Agency Department for Research Cooperation (SIDA/SAREC) and European & Developing Countries Clinical Trials Partnership (EDCTP)
Manosuthi et al, 2012 (28) [TIME]	Open-label, randomized, controlled	2009-2011	Thailand	HIV-infected patients who were 18-65 y of age; had a $CD4^+$ T-cell count of $<0.350 \times 10^9$ cells/L; and had a diagnosis of active TB by clinical features, positive acid-fast staining, and/or positive culture for *Mycobacterium tuberculosis*	4 wk vs. 12 wk	156 (79 vs. 77)	77.6	38.0	12.0	42.6	2HRZE/4HR	TDF + 3TC + EFV	The Thailand Research Fund and the Department of Disease Control, Ministry of Public Health, Thailand
Sinha et al, 2012 (29)	Open-label, randomized, controlled	NR	India	All antiretroviral-naive HIV-positive patients with active TB presenting aged over 18 y who had not started TB treatment	4 wk vs. 8-12 wk	150 (88 vs. 62)	84.0	34.8	12.0	NR	2HRZE/4HR	d4T/ZDV + 3TC/EFV	National AIDS Control Organization (NACO), Ministry of Health & Family Welfare, Government of India, New Delhi, India

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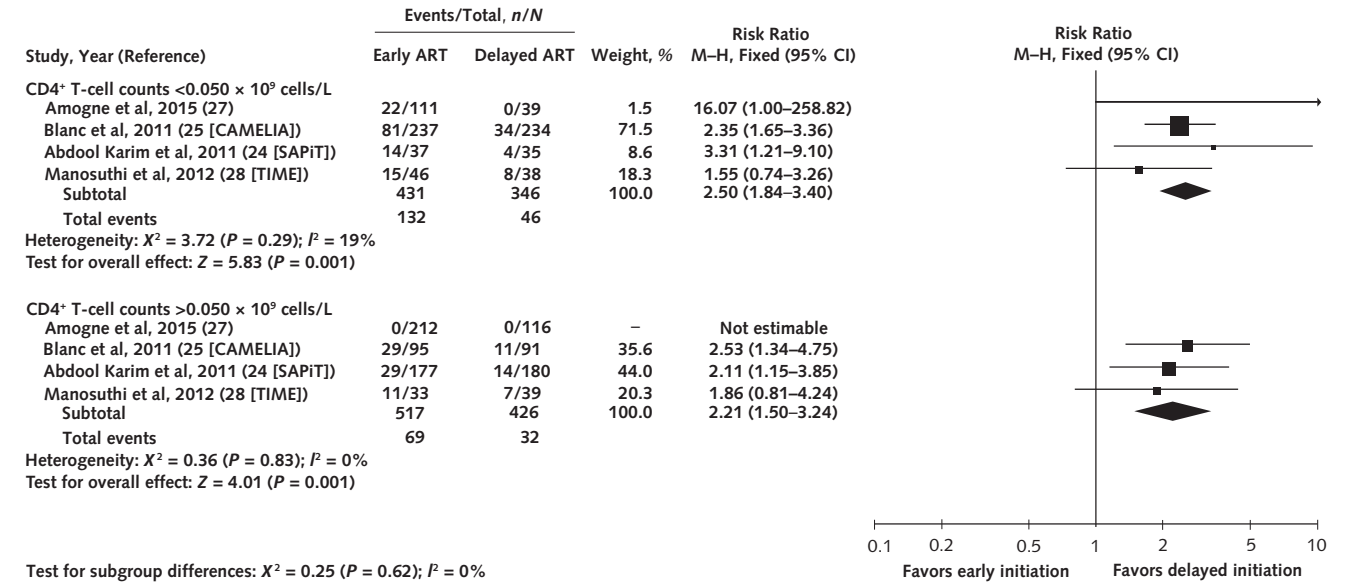
Appendix Table–Continued

Trial Name	Trial Design	Trial Period	Trial Location	Participants	Early vs. Late Start of ART After TB Treatment Initiation	Randomly Assigned Participants (Early vs. Late ART), *n*	Male, %	Mean Age, *y*	Median Follow-up, *mo*	$CD4^+$ T-Cell Count $<0.050 \times 10^9$ cells/L, %	TB Regimen	ART Regimen	Funding Source
Early vs. deferred initiation of ART													
Abdool Karim et al, 2010 (23) [SAPiT]*	Open-label, randomized, controlled	2005-2008	South Africa	Patients with both pulmonary TB and HIV infection 18 y of age or older who had a $CD4^+$ T-cell count of $<0.500 \times 10^9$ cells/L at screening and were started on a standard TB treatment regimen	4 wk vs. 6 mo	427 (214 vs. 213)	52.1	33.9	12.1	NR	2HRZE/4HR	ddI + 3TC + EFV	U.S. President's Emergency Plan for AIDS Relief for the care of patients; the Global Fund to Fight AIDS, Tuberculosis and Malaria
Mfinanga et al, 2014 (18) [TB-HAART]	Double-blind, randomized, placebo-controlled	2008-2013	South Africa, Uganda, Zambia, Tanzania	Participants at least 18 y of age and HIV-positive who were smear- and culture-positive for TB with $CD4^+$ T-cell counts of $>0.220 \times 10^9$ cells/L and no previous TB treatment in the preceding 2 y	2 wk vs. 6 mo	1675 (834 vs. 841)	60	32.0	24.0	NA	2HRZE/4HR	ZDV + 3TC + EFV	United States Agency for International Development (USAID), Zambia Ministry of Health, Tanzania Commission for Science and Technology, World Health Organization Special Programme for Research and Training in Tropical Diseases (WHO-TDR)
Delayed vs. deferred initiation of ART													
Abdool Karim et al, 2010 (23) [SAPiT]*	Open-label, randomized, controlled	2005-2008	South Africa	Patients with both pulmonary TB and HIV infection 18 y of age or older who had a $CD4^+$ T-cell count of $<0.500 \times 10^9$ cells/L at screening and were started on a standard TB treatment regimen	4 wk vs. 6 mo	427 (214 vs. 213)	52.1	33.9	12.1	NR	2HRZE/4HR	ddI + 3TC + EFV	U.S. President's Emergency Plan for AIDS Relief for the care of patients; the Global Fund to Fight AIDS, Tuberculosis and Malaria

2HRZE = 2 mo of isoniazid (600 mg), rifampicin (450 mg), pyrazinamide (1500 mg), ethambutol (1200 mg); 3TC = lamivudine; 4HR = 4 mo of isoniazid (600 mg) and rifampicin (450 mg); ART = antiretroviral therapy; CAMELIA = Cambodian Early Versus Late Introduction of Antiretrovirals; d4T = stavudine; ddI = didanosine; EFV = efavirenz; FTC = emtricitabine; NA = not applicable; NR = not reported; SAPiT = Starting ART at Three Points in TB; STRIDE = Immediate Versus Deferred Start of Anti-HIV Therapy in HIV-Infected Adults Being Treated for Tuberculosis; TB = tuberculosis; TB-HAART = An Evaluation of the Impact of Early Initiation of HAART on TB Treatment Outcomes for TB Patients Co-infected With HIV; TDF = tenofovir; TIME = Appropriate Timing of HAART in Co-infected HIV/TB Patients; ZDV = zidovudine.

* 1 trial (SAPiT) randomly assigned participants into 3 groups: early ART initiation, delayed ART, and deferred.

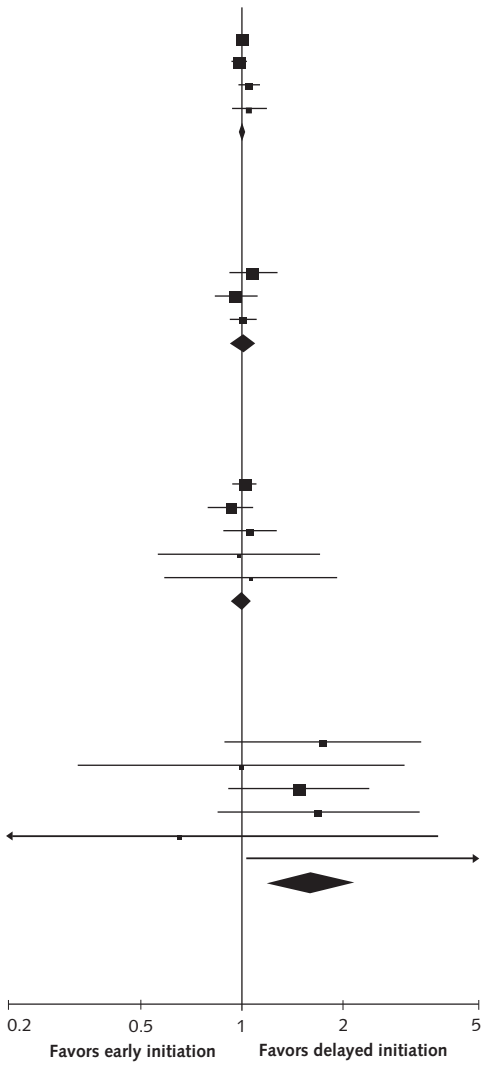
Appendix Figure 1. TB-IRIS comparing early versus delayed initiation of ART, stratified by baseline $CD4^+$ T-cell count.



ART = antiretroviral therapy; CAMELIA = Cambodian Early Versus Late Introduction of Antiretrovirals; M-H = Mantel-Haenszel; SAPiT = Starting ART at Three Points in TB; STRIDE = Immediate Versus Deferred Start of Anti-HIV Therapy in HIV-Infected Adults Being Treated for Tuberculosis; TB-IRIS = tuberculosis-associated immune reconstitution inflammatory syndrome; TIME = Appropriate Timing of HAART in Co-infected HIV/TB Patients.

Appendix Figure 2. Secondary outcomes comparing early versus delayed initiation of ART.

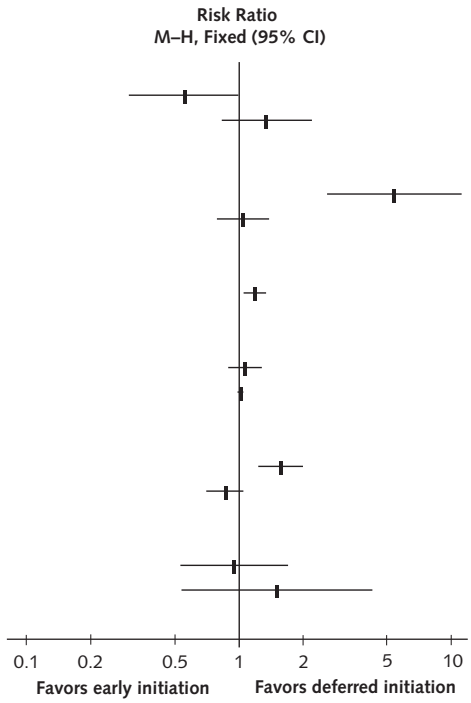
Study, Year (Reference)	Events/Total, *n*/*N* Early ART	Events/Total, *n*/*N* Delayed ART	Weight, %	Risk Ratio M–H, Fixed (95% CI)
Viral suppression rates				
Blanc et al, 2011 (25 [CAMELIA])	320/332	317/329	39.0	1.00 (0.97–1.03)
Havlir et al, 2011 (26 [STRIDE])	293/331	301/332	36.8	0.98 (0.93–1.03)
Abdool Karim et al, 2011 (24 [SAPiT])	147/159	130/147	16.5	1.05 (0.97–1.13)
Sinha et al, 2012 (29)	80/88	54/62	7.8	1.04 (0.93–1.17)
Subtotal	910	870	100.0	1.00 (0.98–1.03)
Total events	840	802		
Heterogeneity: $X^2 = 2.73$ ($P = 0.44$); $I^2 = 0\%$				
Test for overall effect: $Z = 0.17$ ($P = 0.86$)				
Tuberculosis cure rates				
Blanc et al, 2011 (25 [CAMELIA])	154/320	146/325	42.1	1.07 (0.91–1.26)
Abdool Karim et al, 2011 (24 [SAPiT])	131/214	138/215	40.0	0.95 (0.82–1.10)
Sinha et al, 2012 (29)	71/76	54/58	17.8	1.00 (0.92–1.10)
Subtotal	610	598	100.0	1.01 (0.92–1.11)
Total events	356	338		
Heterogeneity: $X^2 = 1.12$ ($P = 0.57$); $I^2 = 0\%$				
Test for overall effect: $Z = 0.25$ ($P = 0.80$)				
Grade 3 to 4 adverse events				
Blanc et al, 2011 (25 [CAMELIA])	251/332	245/329	42.5	1.02 (0.93–1.11)
Havlir et al, 2011 (26 [STRIDE])	177/405	190/401	33.0	0.92 (0.79–1.07)
Abdool Karim et al, 2011 (24 [SAPiT])	112/214	107/215	18.4	1.05 (0.87–1.27)
Manosuthi et al, 2012 (28 [TIME])	19/79	19/77	3.3	0.97 (0.56–1.69)
Sinha et al, 2012 (29)	21/88	14/62	2.8	1.06 (0.58–1.91)
Subtotal	1118	1084	100.0	0.99 (0.92–1.07)
Total events	580	575		
Heterogeneity: $X^2 = 1.60$ ($P = 0.81$); $I^2 = 0\%$				
Test for overall effect: $Z = 0.23$ ($P = 0.82$)				
Loss to follow-up				
Amogne et al, 2015 (27)	36/323	10/155	22.2	1.73 (0.88–3.39)
Blanc et al, 2011 (25 [CAMELIA])	6/332	6/329	9.9	0.99 (0.32–3.04)
Havlir et al, 2011 (26 [STRIDE])	37/405	25/401	41.3	1.47 (0.90–2.39)
Abdool Karim et al, 2011 (24 [SAPiT])	20/214	12/215	19.7	1.67 (0.84–3.34)
Manosuthi et al, 2012 (28 [TIME])	2/79	3/77	5.0	0.65 (0.11–3.78)
Sinha et al, 2012 (29)	11/88	1/62	1.9	7.75 (1.03–58.49)
Subtotal	1441	1239	100.0	1.60 (1.17–2.19)
Total events	112	57		
Heterogeneity: $X^2 = 4.23$ ($P = 0.52$); $I^2 = 0\%$				
Test for overall effect: $Z = 2.92$ ($P = 0.003$)				



ART = antiretroviral therapy; CAMELIA = Cambodian Early Versus Late Introduction of Antiretrovirals; M-H = Mantel-Haenszel; SAPiT = Starting ART at Three Points in TB; STRIDE = Immediate Versus Deferred Start of Anti-HIV Therapy in HIV-Infected Adults Being Treated for Tuberculosis; TIME = Appropriate Timing of HAART in Co-infected HIV/TB Patients.

Appendix Figure 3. Outcomes comparing early versus deferred initiation of ART.

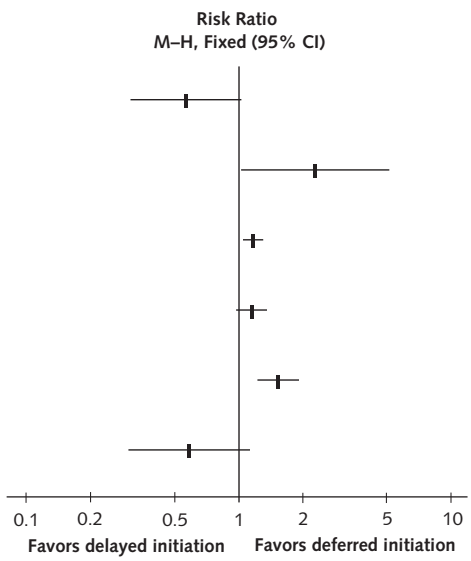
Study, Year (Reference)	Events/Total, *n/N*		Risk Ratio
	Early ART	Deferred ART	M–H, Fixed (95% CI)
All-cause mortality			
Abdool Karim et al, 2010 (23 [SAPiT])	15/214	27/213	0.55 (0.30–1.01)
Mfinanga et al, 2014 (18 [TB-HAART])	36/834	27/841	1.34 (0.82–2.19)
TB-IRIS			
Abdool Karim et al, 2010 (23 [SAPiT])	43/214	8/213	5.35 (2.58–11.11)
Mfinanga et al, 2014 (18 [TB-HAART])	87/834	84/841	1.04 (0.79–1.39)
Viral suppression rates			
Abdool Karim et al, 2010 (23 [SAPiT])	147/159	70/90	1.19 (1.06–1.34)
Tuberculosis cure rates			
Abdool Karim et al, 2010 (23 [SAPiT])	131/214	98/171	1.07 (0.90–1.26)
Mfinanga et al, 2014 (18 [TB-HAART])	619/649	636/675	1.01 (0.99–1.04)
Grade 3 to 4 adverse events			
Abdool Karim et al, 2010 (23 [SAPiT])	112/214	71/213	1.57 (1.25–1.97)
Mfinanga et al, 2014 (18 [TB-HAART])	149/834	174/841	0.86 (0.71–1.05)
Loss to follow-up			
Abdool Karim et al, 2010 (23 [SAPiT])	20/214	21/213	0.95 (0.53–1.70)
Mfinanga et al, 2014 (18 [TB-HAART])	9/834	6/841	1.51 (0.54–4.23)



ART = antiretroviral therapy; M-H = Mantel-Haenszel; SAPiT = Starting Antiretroviral Therapy at Three Points in Tuberculosis; TB-HAART = An Evaluation of the Impact of Early Initiation of HAART on TB Treatment Outcomes for TB Patients Co-infected With HIV; TB-IRIS = tuberculosis-associated immune reconstitution inflammatory syndrome.

Appendix Figure 4. Outcomes comparing delayed versus deferred initiation of ART.

Study, Year (Reference)	Events/Total, *n/N*		Risk Ratio
	Delayed ART	Deferred ART	M–H, Fixed (95% CI)
All-cause mortality			
Abdool Karim et al, 2010 (23 [SAPiT])	15/215	27/213	0.55 (0.30–1.00)
TB-IRIS			
Abdool Karim et al, 2010 (23 [SAPiT])	18/214	8/213	2.24 (1.00–5.04)
Viral suppression rates			
Abdool Karim et al, 2010 (23 [SAPiT])	130/147	70/90	1.14 (1.00–1.29)
Tuberculosis cure rates			
Abdool Karim et al, 2010 (23 [SAPiT])	138/215	98/171	1.12 (0.95–1.32)
Grade 3 to 4 adverse events			
Abdool Karim et al, 2010 (23 [SAPiT])	107/215	71/213	1.49 (1.18–1.88)
Loss to follow-up			
Abdool Karim et al, 2010 (23 [SAPiT])	12/215	21/213	0.57 (0.29–1.12)



ART = antiretroviral therapy; M-H = Mantel-Haenszel; SAPiT = Starting Antiretroviral Therapy at Three Points in Tuberculosis; TB-IRIS = tuberculosis-associated immune reconstitution inflammatory syndrome.