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The effect of tuberculosis treatment on virologic and CD4 count response to combination antiretroviral therapy: a systematic review

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Abstract

Objectives—To determine the impact of tuberculosis (TB) treatment at the time of combination antiretroviral therapy (cART) initiation on virologic and CD4 count response to cART.

Methods—Systematic review and meta-analysis of studies reporting HIV RNA and CD4 count response, stratified by TB treatment status at cART initiation. Stratified random-effects and meta-regression analyses were used when possible.

Results—25 eligible cohort studies reported data on 49,578 (range 42-15,646) adults, of whom 8,826 (18%) were receiving TB treatment at cART initiation. 17 studies reported virologic response; 21 reported CD4 count response. The summarized random-effects relative risk (RR_{RE}) of virologic suppression in those receiving vs. not receiving TB treatment at different time points following cART initiation was 1.06 (0.86-1.29) at 1-4 months, 0.91 (0.83-1.00) at 6 months, 0.99 (0.94-1.05) at 11-12 months, and 0.99 (0.77-1.28) at 18-48 months. The overall RR_{RE} at 1-48 months was 0.97 (95% CI:0.92-1.03). Available data regarding the effect of TB treatment on virologic failure were heterogeneous and inconclusive (13 estimates). Differences in median CD4 count gain between those receiving vs. not receiving TB treatment ranged from -10 to 60 cells/μL (median 27) by 6 months (7 estimates) and -10 to 29 (median 6) by 11-12 months (5 estimates), though the heterogeneity of the response measures did not support meta-analysis.

Conclusions—Patients receiving TB treatment at cART initiation experience similar virologic suppression and CD4 count reconstitution as those not receiving TB treatment, reinforcing the

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need to start cART during TB treatment and allowing more confidence in clinical decision-making.

Keywords

HIV; tuberculosis; antiretroviral therapy; viral load; CD4 lymphocyte count; systematic review; adults

Introduction

Tuberculosis (TB) threatens the health of people living with HIV (PLWH). Globally in 2011, 13% of incident TB cases were co-infected with HIV and an estimated 0.4 million TB deaths occurred among PLWH [1]. Given the World Health Organization's 2010 recommendation that all PLWH with TB be initiated on combination antiretroviral therapy (cART), regardless of CD4 count [2], and the goal of 100% cART coverage of co-infected patients by 2015 [3], many individuals are initiating cART while concurrently on TB therapy. PLWH who are also being treated for TB may experience a differential response to cART due to drug-drug interactions [4, 5], an increased risk of drug toxicity [4, 5], immune reconstitution inflammatory syndrome [6], and the potential for lower adherence due to the high pill burden [5]. The effect of TB treatment and its associated potential challenges and complications regarding a patient's response to cART require careful evaluation.

We aimed to describe the impact of receiving TB treatment at the time of cART initiation on virologic and CD4 count response to cART among HIV-infected adults. In addition, we highlighted the various outcome measures used in the literature and make recommendations for some methodological standards that may ease future between-study comparisons.

Methods

Search strategy and selection criteria

To investigate the effect of TB treatment at time of cART initiation on virologic response and CD4 count response, we carried out a systematic and sensitive search using an *a priori* protocol developed according to PRISMA guidelines [7]. We searched PubMed and EMBASE, as well as abstract databases from the 2009 to 2012 Conferences on Retroviruses and Opportunistic Infections, International Union Against Tuberculosis and Lung Disease World Conferences on Lung Health, and International AIDS Society conferences. The search terms “HIV AND Tuberculosis AND (Viral Load OR CD4 lymphocyte count OR Mortality) AND Antiretroviral therapy” were used to identify relevant articles in PubMed and EMBASE. Searches were performed on January 29, 2013 and included original human subjects studies published since 1997 (the start of the cART era). Additional articles were identified from reference lists, reviews, and Web of Science citation lists.

H.M.S. and A.V.R. independently reviewed titles and abstracts of original studies retrieved by the search. H.M.S. reviewed full-text and references of selected articles. H.M.S. and M.R.P. independently abstracted study data from full reports; discrepancies were resolved by consensus among co-authors.

Studies were included if they reported HIV RNA and/or CD4 count response following cART initiation among antiretroviral treatment-naïve HIV-infected adults, stratified by TB treatment status at cART initiation. Studies with ≤5% antiretroviral-experienced patients or patients only previously exposed to a single intrapartum dose of nevirapine were also included. Studies of children <14 years of age were excluded. No additional exclusion criteria or language restrictions were imposed.

Data extraction

The following information, if available, was abstracted from each article: first author surname; publication year; study dates; geographic location; study design; clinical setting; sample size; number receiving and not receiving TB treatment at cART initiation; if TB treatment was the main exposure of interest; types of TB included; culture confirmation of TB cases; TB site; timing of TB treatment in relation to cART initiation; length of follow-up; proportion antiretroviral-naïve; percentage male; mean or median participant age; criteria for cART initiation; cART regimen; baseline median CD4 count and HIV RNA; HIV RNA outcome measure(s); CD4 count outcomes measure(s); covariate adjustment; exclusion criteria; proportion lost-to-follow-up; and how each study handled loss-to-follow-up, mortality, and regimen switching. For this purposes of this review, we abstracted results as presented in the specific studies according to their individual methods and assumptions.

Statistical analysis

Reported effect estimates over any length of time were abstracted. If only count data of those who experienced an outcome, stratified by TB treatment status, were reported, a risk ratio (RR) and 95% confidence interval (CI) were calculated. If a study reported an outcome only graphically, outcome values were visually estimated [8]. Standard error estimates were inferred from reported CIs by [ln(upper limit) – ln(lower limit)]/3.92 [9]. As we aimed to quantify virologic suppression, if a study reported on patients who failed to suppress, this information was converted to obtain data on suppression. For CD4 counts, if 2 of 3 of the following measures were reported, we calculated the third measure: mean baseline CD4 count, mean change in CD4 count from baseline, mean absolute CD4 count. We were unable to calculate the missing measures if only median CD4 counts were reported.

For virologic suppression, summarized relative risks were calculated using random-effects summarization with unconditional variances and the method of moments estimated between-study variance (τ^2) [8]. As several studies reported estimates at multiple of time points, we used the estimate closest to the midpoint of each study's follow-up time to get an overall relative risk for virologic suppression. In addition, to examine short- and long-term virologic suppression, summary relative risks at 1-4 months, 6 months, 11-12 months and 18-48 months were calculated. The p-values for a standard chi-square homogeneity test statistic were used to assess overall consistency among the effect estimates across studies. τ^2 was used to calculate 95% population effects intervals [10] (where 95% of populations are estimated to have their means), opposite effects proportions [11] (proportion of populations likely to experience a relative risk below unity), and 95% prediction intervals [11] (95% of these intervals will cover the true value estimated by a future study). Stratified and random-

effects meta-regression analyses were used to calculate stratum-specific summary measures and 95% CIs, along with ratios of the stratum-specific RRs as described by Bassler [12].

Funnel plots of ln(virologic suppression relative risk) vs. the inverse-variance weight of studies were visually examined for asymmetry and statistically assessed using methods proposed by Begg [13] and Egger [14] and the trim-and-fill method [15]. STATA (version 12, Stata corporation, College Station, TX) was used for these analyses.

Results

Selected studies

990 unique abstracts were reviewed: 795 from PubMed, 143 from EMBASE, and 52 from conference proceedings (Fig. 1). Of these, 120 full-text articles were selected for review. In total, 18 articles [16-33] and five conference abstracts [34-38] were eligible. Five additional articles met our inclusion criteria: two from reference lists [39, 40] and three from Web of Science citation searches [41-43]. One included abstract [34] was subsequently published as a full article [44]; only data from the full article was included. Three eligible studies were excluded: one because some patients included in the TB treatment-exposed group had completed TB treatment just prior to cART initiation [36], and two because they included some early incident TB cases in their TB treatment-exposed group [20, 31]. Articles reporting on the same study population, but at differing time points following cART initiation, were retained [26, 27, 39]. Similarly, we retained both reports of a Tanzanian cohort [22, 42].

Study and population characteristics

The 25 final studies provided data on 49,578 PLWH, of which 8,826 (18%) were receiving TB treatment at cART initiation. Selected study and population characteristics are displayed in Table 1. All were cohort studies; four reported virologic response, eight reported CD4 count response, and 13 reported both outcomes. While the majority of studies was based in Sub-Saharan Africa, nine included Asian populations [17, 23, 26, 27, 29, 32, 33, 38, 39] and three were from Europe or North America [19, 21, 28]. Most publications assessed response to cART, regardless of regimen type, though some reported estimates specific to nevirapine- [18, 26, 27, 30, 39] or efavirenz-based [18, 22, 25, 29, 30, 42] cART (see Supplemental Digital Content 1, which provides study-specific details on cART regimens). Though included studies used a variety of cART regimens, nevirapine was often used in combination with stavudine and efavirenz was often used in combination with zidovudine and lamivudine. All studies used cART initiation as the time origin, except one which began at the commencement of cART education and adherence sessions, with most patients starting cART a month or two later [44]. Two studies included women previously exposed to a single intrapartum dose of nevirapine [18, 40], and one study included 3% antiretroviral-experienced patients [17].

Seventeen studies examined TB treatment at cART initiation as the main exposure of interest [18, 19, 21, 23, 25-27, 29, 30, 32, 33, 35, 37-39, 43, 44]. The other eight studies examined TB treatment as a secondary exposure; five aimed to describe general cART

outcomes [16, 24, 28, 40, 41], and one each examined the primary exposures of timeliness of clinic attendance [17], β-defensin genomic copy number [22], and liver enzyme abnormalities [42]. The type of TB being treated varied across studies. Only one study had a subset of bacteriologically-confirmed TB cases [44], while others included both confirmed and probable TB cases. One study focused solely on pulmonary TB [32], and three excluded patients who developed incident TB from the reference group [18, 30, 35]. Sixteen studies reported detail on the duration of TB treatment at the time of cART initiation (see Table, Supplemental Digital Content 2, which provides study-specific information on the timing of TB treatment, if available).

Overall loss-to-follow-up was reported by 15 studies and ranged from 0% to 64% (median 10%, interquartile range 7% to 12%) (see Table, Supplemental Digital Content 3, which details methods utilized by studies to handle loss-to-follow-up and mortality). 5 studies limited their analysis to those who completed follow-up [16, 30, 35, 37, 44] and 3 studies considered those who discontinued cART for a variety of reasons and/or lacked follow-up laboratory data as treatment failures [21, 26, 27]. While most studies did not describe how they handled patients who switched cART regimens, one excluded patients who stopped or changed cART during follow-up [18], three explicitly retained patients who switched [24, 30, 40], and one did a sensitivity analysis considering those who discontinued stavudine as treatment failures [27].

All studies included both genders, with the proportion male ranging from 21% to 92% (median 45%). All patients were ≥14 years of age; mean patient age ranged from 31 to 41 years (median 36). Median baseline CD4 count ranged from 29 to 196 cells/μL (median 94), and baseline HIV RNA ranged from 4.9 to 5.8 log10 copies/mL (median 5.3). One study reported results stratified by baseline CD4 count [33].

Virologic suppression

There was heterogeneity in how each study quantified virologic response with respect to the reported effect measure, the cut-off used (50 or 400 copies/mL), and the timing of measurement (see Table, Supplemental Digital Content 4 for virologic measures as reported by each study). In total, 17 studies reported virologic suppression, either directly or as a measure that allowed conversion into virologic suppression. Times of reported virologic suppression ranged from 1 to 48 months following cART initiation, with some studies reporting multiple time points. While most studies had overall suppression proportions >75%, several observed relatively low suppression. The study with the shortest follow-up time (1 month) reported the lowest overall proportion suppressed (46%) [23]. Manosuthi et al. (2006, 2008, 2010) also reported low suppression among Thai patients: 69% at 6 months [39], 59% at 33 months [26] and 51% at 48 months [27]. Three other studies reported suppression rates between 64 and 70% [16, 21, 32]. However, three of these studies that reported low suppression rates considered those who discontinued cART or lacked follow-up laboratory data as treatment failures [21, 26, 27].

In total, 15 studies reported RRs for virologic suppression in those receiving vs. not receiving TB treatment at cART initiation (Fig. 2). Overall, the random-effects relative risk (RR_{RE}) for suppression was 0.97 (95% CI 0.92-1.03). When estimates were categorized

according to follow-up time, the RR_{RE} for suppression was 1.06 (0.86-1.29) at 1-4 months, 0.91 (0.83-1.00) at 6 months, 0.99 (0.94-1.05) at 11-12 months, and 0.99 (0.77-1.28) at 18-48 months after cART initiation (Table 2). In meta-regression analysis, a lower limit of detection of 50 or 400 copies/mL and type of cART regimen did not substantially influence the summary relative risks (see Table, Supplemental Digital Content 5 for meta-regression results).

Additionally, 6 studies provided data on cART regimen-specific relative risks of virologic suppression (see Figure, Supplemental Digital Content 6 for forest plot). The three lowest RRs for TB treatment exposure all correspond to three follow-up time-points of the nevirapine-based cART arm of Boulle et al. (2008) [18].

The funnel plot of overall suppression relative risks did not appear asymmetrical due to publication bias or other factors, with Begg's and Egger's p-values for small study effects of 0.26 and 0.71, respectively (see Figure, Supplemental Digital Content 7, for the funnel plot).

Virologic failure

Measures of virologic failure were highly heterogeneous (Supplemental Digital Content 4), with studies measuring whether patients reached HIV RNA levels of >5000 copies/mL [17], failed to suppress <400 copies/mL [18], rebounded after being previously undetectable or never became undetectable [23, 25, 26], time to first value ≥400 [18], time to 2 consecutive values ≥5000 copies/mL [18], and time to first value >500 among those who initially suppressed [28]. Six of these studies did not find TB treatment to have a significant effect on virologic failure [17, 18, 23, 25, 26, 40]. Interestingly, Boulle et al. found an association between TB treatment and virologic failure among those on nevirapine-based cART, but not among patients on efavirenz-based cART in their 2008 study [18], but reported the opposite finding in their 2010 study [40]. The substantial heterogeneity among virologic failure outcome measures precluded a formal meta-analysis.

CD4 count response to cART

Methods for measuring and reporting CD4 count response were even more heterogeneous than those used for virologic response, due to measurements at different time points and use of a diversity of outcome measures. Eight studies reported mean or median change in CD4 count from baseline, five measured mean or median absolute CD4 count during follow-up, and three reported the difference in CD4 count gain from baseline in patients receiving vs. not receiving TB treatment at cART initiation (Table 3). In addition, some studies defined a specific measure of immunologic success [21, 24] or immunologic failure [24, 41], and two studies described the CD4 count recovery trajectory [24, 43] (see Table, Supplemental Digital Content 8 for detailed immunologic measures). Two studies limited reporting of CD4 count response to virologically suppressed patients [24, 40].

Overall, those receiving TB treatment at cART initiation tended to have lower baseline CD4 counts, greater increases in CD4 count from baseline, and lower absolute CD4 counts during follow-up. Median change in CD4 count from baseline after 6 months of cART (reported by 7 studies) ranged from 97 to 200 cells/μL (median 167) among TB treatment-exposed patients and from 89 to 177 cells/μL (median 138) among those not on TB treatment. At

11-12 months, median change in CD4 count from baseline (reported by 5 studies) ranged from 124 to 234 cells/μL (median 155) among TB treatment-exposed patients and from 104 to 205 cells/μL (median 165) among those not on TB treatment. This corresponds to a differential gain in CD4 count between patients receiving vs. not receiving TB treatment at cART initiation ranging from -10 to 60 more CD4 cells/μL (median 27) at 6 months and -10 to 29 more CD4 cells/μL (median 6) at 11-12 months. Heterogeneity among CD4 count response outcomes measures prevented formal meta-analysis.

Discussion

In this systematic review and meta-analysis of the effect of TB treatment on virologic and CD4 count response to cART, the first meta-analysis of this topic to our knowledge, we found that exposure to TB treatment at cART initiation does not impair virologic suppression or CD4 count gain. The effect on the risk of virologic failure could not be assessed. Our findings indicate that despite concerns about drug-drug interactions, toxicity, high pill burden, and IRIS, TB treatment does not appear to reduce the efficacy of cART in regards to virologic suppression and CD4 count response. The reported outcome measures were however highly heterogeneous, impeding sound between-study comparisons or meta-analytic summarization for outcome measures other than virologic suppression. While rigorous meta-analysis methods could not be applied for CD4 response, we did observe similar within-study effects of TB treatment, and the overall impression is that TB treatment exposure does not have a substantial impact on CD4 recovery.

Furthermore, time points reported by individual studies were also heterogeneous. The optimal time point for evaluating the effect of exposure to TB treatment on response to cART is unclear. Follow-up times shorter than 4 months may be too early to accurately describe response to cART, and follow-up times longer than two years may underestimate the impact of TB treatment at cART initiation, especially if patients who switch treatments or take second-line therapy are included in the analysis. For the sake of completeness, all reported outcome measures and follow-up times were retained in this review.

The exposure, TB treatment at cART initiation, captured both exposure to active TB disease and exposure to anti-tuberculosis drugs. This combined exposure is useful from a health systems perspective, particularly in low-resource countries, where active TB cannot always be confirmed, especially in PLWH. This is further highlighted by the fact that the included studies used a variety of methods for determining who had active TB and should receive treatment, and no studies were limited to bacteriologically-confirmed TB cases and only one study described this subset. Consequently, active TB could have been misclassified and some patients included in this meta-analysis may have received TB treatment even though they did not have TB.

Since being treated for active TB cannot be studied in a randomized controlled trial, all studies included in our review were observational. Consequently, there was much heterogeneity in the duration of TB treatment prior to cART initiation, with some patients on TB therapy for up to eight months and others beginning TB treatment and cART concurrently. While the timing of TB treatment in relation to cART initiation is an important

factor when evaluating mortality [45-49], it is unclear whether TB treatment timing would influence virologic or CD4 count response. Unfortunately, the included studies did not provide enough information on duration of TB treatment to systematically evaluate its effect on our results. Similarly, a lack of provided data on cART regimen switching during follow-up precluded a systematic evaluation of this factor.

This systematic review and meta-analysis may have been subject to some biases. First, virologic and immunologic response cannot be evaluated in those who have died or were lost-to-follow-up. Loss rates varied widely, ranging from 0% to 64% though most studies lost ≤12%, and studies handled loss-to-follow-up in a variety of ways, which may have influenced their results. Missing patients may systematically differ from those retained in the analysis. If response to cART among lost or deceased patients was differential by TB treatment status, than the results of these studies and our review could have been biased. Second, in 8 of 25 studies, TB treatment was not the primary exposure and covariates included in some multivariable models may differ from ideal confounder adjustment for this research question. Third, some bias may have been introduced by estimation methods used when a study did not directly report an outcome measure but provided the necessary data to calculate the desired effect measures [8, 9].

In conclusion, this recent comprehensive review of studies assessing the effect of TB treatment on response to cART indicates that TB treatment does not affect virologic suppression or CD4 count gain after cART initiation and we were unable to assess the effect on virologic failure. These findings will allow health care workers to be more confident in their clinical decision-making and in their communication to patients about the need to start cART during TB treatment. The heterogeneity in outcome measures posed a challenge to the interpretation and summarization of the virologic and CD4 count response to cART. Between-study comparisons could be greatly facilitated by methodological standardization of outcome measures and their time points in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

H.M.S. and A.V.R. devised and designed the study, developed the search strategy, established inclusion criteria, reviewed abstracts, and interpreted data. H.M.S. did all searches of published work, abstracted the study data, was responsible for the statistical analysis, created tables and figures, and drafted the report. M.R.P. double-abstracted the study data, discussed discrepancies and participated in revising the report. J.J.E. and S.N. helped design the analysis, provided expert clinical opinion, and participated in report revision.

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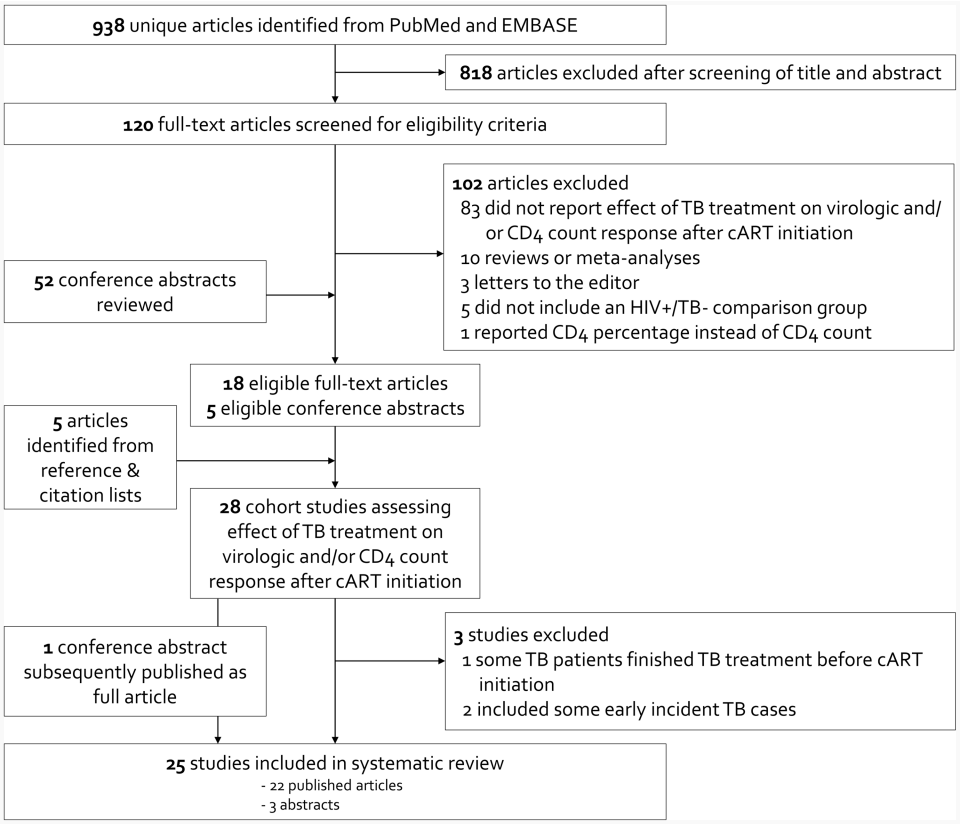

Figure 1. Identification and selection of eligible studies

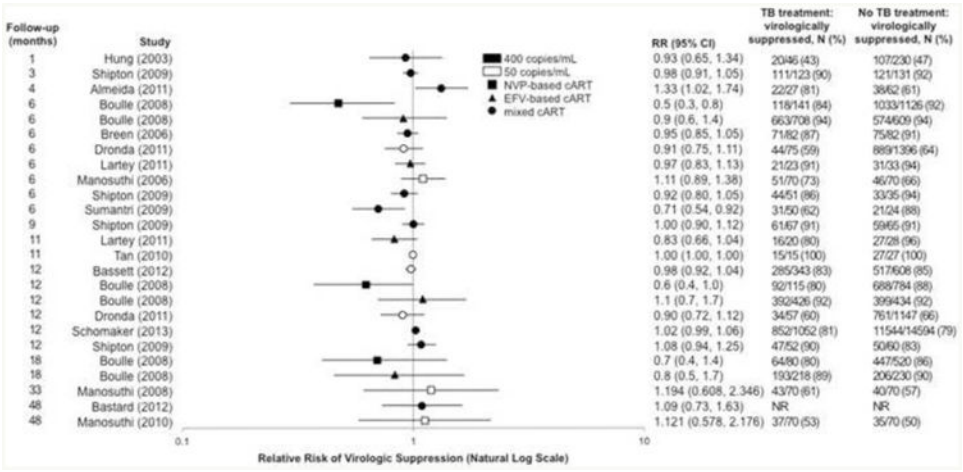

Figure 2.

Relative risk of virologic suppression in those receiving vs. not receiving tuberculosis treatment at cART initiation by length of follow-up time, as reported by 15 studies. Estimates were abstracted according to the precision and stratification used by the original authors. Estimates calculated using available data are reported to 2 decimal places. Abbreviations: cART, combination antiretroviral therapy; CI, confidence interval; EFV, efavirenz; NR, not reported; NVP, nevirapine; RR, relative risk.

Table 1

Characteristics of 25 studies reporting the effect of tuberculosis treatment on virologic and/or CD4 count response to combination antiretroviral therapy among HIV-infected adults

Publication year	Study	Geographic location	Sample size	TB treatment, N (%)	Main exposure is TB	Types of TB included[a]	Study design	cART regimen[b]	Naïve, %	Male, %	Mean age, years	Median baseline CD4 count, cells/μL	Median baseline HIV RNA, log_{10} copies/mL	Lost to follow-up[c], %	Outcomes reported
2003	Hung[23]	Taiwan	276	46 (17)	Yes	Definitive, probable, or possible TB and on TB treatment at cART initiation	P	All	100	92	33	73	5.4	7	Both
2004	Patel[29]	India	255	126 (49)	Yes	On TB treatment for definite or probable TB at cART initiation	P	EFV	100	73	37	101	NS	0	CD4
2006	Breen[19]	England	164	82 (50)	Yes	On TB treatment at cART initiation. TB diagnosed by culture, nucleic acid amplification, radiography, histology or clinical algorithm.	R	All	100	52	35	77	5.1	0	Both
2006	Manosuthi[39]	Thailand	140	70 (50)	Yes	Receiving rifampicin for active TB ≥1 month prior to cART enrollment	P	NVP	100	68	36	29	5.6	0	HIV RNA
2008	Boulle (a)[18][d]	South Africa	1935	209 (11)	Yes	Concurrent TB treatment at cART initiation and for ≥14 days post cART initiation. TB diagnosed by microscopy, culture or clinical algorithm.	P	NVP	100	21	31	110	5.0	6	Both
2008	Boulle (b)[18][d]	South Africa	2035	1074 (53)	Yes	Concurrent TB treatment at cART initiation and for ≥14 days post cART initiation. TB diagnosed by microscopy, culture or clinical algorithm.	P	EFV	100	40	33	78	5.2	6	Both
2008	Manosuthi[26]	Thailand	140	70 (50)	Yes	Receiving rifampicin for active TB ≥1 month prior to cART enrollment	P	NVP	100	68	36	29	5.6	10	Both
2008	Mussini[28]	Italy, Spain, England, Canada	624	168 (27)	No	TB as initial AIDS diagnosis prior to cART initiation	P	All	100	78	39	41	5.3	NS	HIV RNA
2008	Sumantri[32]	Indonesia	130	87 (67)	Yes	On TB treatment for pulmonary TB at cART initiation. TB was diagnosed via chest x-ray or microscopy.	P	All	100	80	32	156	NS	NS	Both
2009	Shipton[30]	Botswana	310	155 (50)	Yes	On TB treatment at cART initiation	R	All	100	40	36	79	5.8	64	Both
2010	Boulle[40]	South Africa	7323	2760 (38)	No	On TB treatment at cART initiation	P	All	100	32	33	101	5.1	10	Both
2010	Manosuthi[27]	Thailand	140	70 (50)	Yes	Receiving rifampicin for active TB ≥1 month prior to cART enrollment	P	NVP	100	68	36	31	5.6	11	Both
2010	Tan[38]	Malaysia	42	15 (36)	Yes	On TB treatment at cART initiation	P	All	100	NS	41	30	5.0	NS	Both
2010	Wanchu (a)[33][e]	India	104	52 (50)	Yes	Diagnosed with TB and started TB treatment 1 month prior to cART initiation. TB diagnosed by microscopy, radiography, clinical criteria or histology.	R	All	100	69	35	155	NS	NS	CD4
2010	Wanchu (b)[33][e]	India	130	65 (50)	Yes	Diagnosed with TB and started TB treatment 1 month prior to cART initiation. TB diagnosed by microscopy, radiography, clinical criteria or histology.	R	All	100	79	38	50	NS	NS	CD4
2011	Almeida[16]	Mozambique	89	27 (30)	No	Confirmed or suspected TB at cART initiation	P	All	100	45	NS	NS	NS	31	HIV RNA

Publication year	Study	Geographic location	Sample size	TB treatment, N (%)	Main exposure is TB	Types of TB included[a]	Study design	cART regimen[b]	Naïve, %	Male, %	Mean age, years	Median baseline CD4 count, cells/μL	Median baseline HIV RNA, log_{10} copies/mL	Lost to follow-up[c], %	Outcomes reported
2011	Auld[41]	Mozambique	2596	267 (10)	No	On TB treatment at cART initiation	R	All	100	38	34	153	NS	22	CD4
2011	Dronda[21]	Spain	1986	110 (6)	Yes	Definite or presumptive diagnosis of TB in the 6 months prior to cART initiation	P	All	100	76	38	196	5.0	7	Both
2011	Hermans[35]	Uganda	3797	570 (15)	Yes	On TB treatment at cART initiation	R	All	100	34	37	100	NS	NS	CD4
2011	Lartey[25]	Ghana	74	34 (46)	Yes	On TB treatment at cART initiation	P	EFV	100	49	NS	83	5.4	11	Both
2012	Bassett[44]	South Africa	951	343 (36)	Yes	Newly diagnosed by sputum culture at cART enrollment or previously diagnosed and currently on treatment	P	All	100	41	36	90	NS	7	Both
2012	Bastard[17]	Malawi, Kenya, Uganda, Cambodia	1580	305 (9)	No	On TB treatment at cART initiation	R	All	97	36	36	119	NS	NS	HIV RNA
2012	Hardwick (a)[22][f]	Ethiopia	649	365 (56)	No	On TB treatment at cART initiation	P	EFV	100	NS	NS	94	5.4	NS	CD4
2012	Hardwick (b)[22][f]	Tanzania	353	147 (42)	No	On TB treatment at cART initiation	P	EFV	100	NS	NS	99	5.8	NS	CD4
2012	Julg[24]	South Africa	442	187 (42)	No	Concurrent TB co-infection at cART initiation	R	All	100	39	35	95	NS	NS	CD4
2012	Mugusi[42]	Tanzania	473	220 (47)	No	Newly diagnosed at cART enrollment by smear microscopy, histology or clinical criteria	P	EFV	100	43	40	92	5.7	12	CD4
2012	Odo[37]	Nigeria	5338	290 (5)	Yes	On TB treatment at cART initiation	R	All	100	38	36	159	NS	NS	CD4
2013	Schomaker[43]	South Africa	15646	1052 (7)	Yes	On TB treatment for confirmed or probable TB at cART initiation	P	All	100	32	34	98	4.9	NS	Both

Abbreviations: EFV, Efavirenz-based cART; HIV, human immunodeficiency virus; NS, not specified; NVP, Nevirapine-based cART; P, prospective study; R, retrospective study; TB, tuberculosis.

[a] See Table, Supplemental Digital Content 2 for further information on the timing of TB treatment in relation to cART initiation from each study, if available

[b] See Table, Supplemental Digital Content 1 for detailed information on cART regimens from each study, if available

[c] See Table, Supplemental Digital Content 3 for detailed information on methods used by each study to handle mortality and loss-to-follow-up, if available

[d] (a) Nevirapine-based cART; (b) Efavirenz-based cART

[e] (a) patients with baseline CD4 counts of 100-200 cells/μL; (b) patients with baseline CD4 counts <100 cells/μL

[f] (a) a cohort from Ethiopia; (b) a cohort from Tanzania

Table 2

Meta-analysis results for the effect of TB treatment on virologic suppression after combination antiretroviral therapy initiation, by length of follow-up time

Length of follow-up time	1-4 months	6 months	11-12 months	18-48 months	1-48 months
No. of estimates	3	8	7	5	13
Homogeneity p-value	0.088	0.064	0.134	0.718	0.060
Estimate of between-study variance (τ^2)	0.019	0.008	0.002	0.000	0.003
RR_{RE} (95% CI)	1.06 (0.86, 1.29)	0.91 (0.83, 1.00)	0.99 (0.94, 1.05)	0.99 (0.77, 1.28)	0.97 (0.92, 1.03)
95% population effects interval	(0.81, 1.38)	(0.76, 1.09)	(0.91, 1.08)	Undefined[a]	(0.87, 1.08)
Opposite effects proportion	34.9%	14.9%	41.1%	Undefined[a]	29.6%
95% prediction interval	(0.70, 1.58)	(0.73, 1.14)	(0.88, 1.12)	(0.74, 1.33)	(0.84, 1.12)

Abbreviations: CI, confidence interval; RRre, random-effects summary relative risk; TB, tuberculosis

[a] Undefined because $\tau^2 = 0.000$

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Table 3

Types of outcome measures used by 21 studies to quantify CD4 count response to cART

Measure of CD4 count response	Number of studies reporting this measure	Length of follow-up used in reporting this measure (months)
Immunologic success		
Change in CD4 count from baseline[a]	8	1; 3; 6; 9; 11; 12
Absolute CD4 count at a specific follow-up time[b]	5	3; 6; 9; 11; 48
Difference in the increase in CD4 count from baseline[c]	3	6; 18; 22
Increase of ≥50 cells/μL from baseline	1	6
Increase of ≥100 cells/μL from baseline	1	12
Absolute CD4 count >200 cells/μL	1	12
Absolute CD4 count >500 cells/μL	1	30
Rate of CD4 count increase from baseline (cells/month)	1	30
Difference in CD4 count recovery slope (cells/6 months)	1	6; 48
Median on treatment peak CD4 count	1	53
Median change between baseline and on treatment peak CD4 count	1	53
Immunologic failure		
CD4 count decline from baseline, CD4 count <100 cells/μL, or 50% decline from peak CD4 count after ≥6 months of cART	1	36
Rate of immunologic failure	1	36
Absolute CD4 count <500 cells/μL	1	30

Abbreviations: cART, combination antiretroviral therapy

[a] An additional 2 studies provided data that enabled the calculation of this measure.

[b] An additional 3 studies provided data that enabled the calculation of this measure.

[c] An additional 10 studies provided data that enabled the calculation of this measure.