

Early initiation of antiretroviral therapy in HIV-infected adults and adolescents: a systematic review

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Objectives: The objective of this review was to update evidence on when to initiate antiretroviral therapy (ART) to inform revision of the 2013 WHO guidelines for ART in low and middle-income countries.

Design: A systematic review and meta-analysis.

Methods: We comprehensively searched the published literature and conferences for randomized controlled trials (RCTs) and cohorts. Outcomes were mortality, clinical progression, virologic failure, immunologic recover, and severe adverse events. We pooled data across studies and estimated summary effect sizes. We graded the quality of evidence from the literature for each outcome.

Results: We identified 24 studies; 3 were RCTs. Studies found reduced risk of mortality [1 RCT: hazard ratio 0.77, 95% confidence interval (CI) 0.34–1.76; 13 cohorts: relative risk (RR) 0.66, 95% CI 0.55–0.79], progression to AIDS or death (2 RCTs: RR 0.48, 95% CI 0.26–0.91; 9 cohorts: RR 0.70, 95% CI 0.40–1.24) and diagnosis of a non-AIDS-defining illness (1 RCT: RR 0.14, 95% CI 0.03–0.64; 1 cohort: RR 0.47, 95% CI 0.23–0.98), and an increased risk of grade 3/4 laboratory abnormalities in patients initiating ART at at least 350 cells/ μ l (1 RCT: RR 1.49, 95% CI 1.25–1.77). The quality of evidence was low or very low for clinical outcomes due to few events and imprecision, and high for adverse events.

Conclusions: Our findings contributed to the evidence base for the revised 2013 WHO guidelines on ART, which recommend initiating ART at CD4⁺ T-cell counts of 350–500 cells/ μ l, but not above 500 cells/ μ l compared to initiating it later when CD4⁺ T-cell counts fall below 350 cells/ μ l.

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Introduction

The optimal timing for initiating antiretroviral therapy (ART) in individuals infected with HIV-1 has not yet been resolved. The US Department of Health and Human Services [1] and the International Antiviral Society – USA [2] recommend starting ART as close to

diagnosis as possible. France [3] and Brazil [4] have recently announced plans to extend therapy to anyone who is infected regardless of clinical or immunologic stage, and several other countries recommend starting ART below a threshold of 500 CD4⁺ T-cells/ μ l [5]. On the contrary, the 2012 British HIV Association guidelines and the 2103 European AIDS Clinical Society (EACS)

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guidelines recommended starting ART in all patients with fewer than 350 CD4⁺ T-cells/ μ l [6,7], and EACS recommends considering initiation for those with between 350 and 500 CD4⁺ T-cells/ μ l unless one of the several clinical conditions is present [7].

The WHO, which has provided global ART guidelines since 2002 [8–11], has approached this question more cautiously, given its adoption of a public health approach to ART scale-up (a balance between implementing the best proven standard of care, and what is feasible on a large scale in resource-limited settings), the more limited healthcare infrastructure and availability of antiretroviral drugs in many countries, and the need to prioritize patients with the most advanced disease. In 2006, WHO recommended starting ART in adults and adolescents irrespective of clinical stage at a CD4⁺ T-cell count of below 200 cells/ μ l and to consider initiating treatment at CD4⁺ T-cell counts of between 200 and 350 cells/ μ l [10]. Additionally, the guidelines recommended starting ART if patients had less than 350 CD4⁺ T-cells/ μ l and were either pregnant or had tuberculosis [10]. The general threshold for initiating treatment was raised in the 2010 guidelines to 350 cells/ μ l, and there were also new recommendations to start therapy irrespective of CD4⁺ T-cell count among children below 2 years of age, patients with stage 3 or 4 disease, and patients with concurrent hepatitis B virus (HBV) infection requiring therapy [11]. This strong recommendation for initiating ART at CD4⁺ T-cell counts below 350 cells/ μ l was based on evidence from both clinical trials [12,13] and observational studies [14–17] showing that beginning ART at a threshold of 350 CD4⁺ T-cells/ μ l led to reductions in mortality, disease progression and serious adverse events, compared to starting it at CD4⁺ T-cell counts of less than 200 cells/ μ l. Subsequent to the 2010 guidelines, WHO assessed how effective early treatment is in preventing HIV transmission to uninfected sexual partners based on both a new trial [18] and observational studies [19], and expanded recommendations for early initiation of ART to also include infected persons in a serodiscordant partnership [20].

To update evidence and to inform revision of the 2013 WHO guidelines for use of antiretroviral drugs for the treatment and prevention of HIV infection in low and middle-income countries, we systematically reviewed the literature to estimate differences in risk of disease progression between patients with stage 1 or 2 disease whose baseline CD4⁺ T-cell count at ART initiation was at least 350 cells/ μ l, and, in particular, those with 350–499 cells/ μ l, and patients whose baseline CD4⁺ T-cell count was between 200 and 349 cells/ μ l.

Methods

We included studies that compared clinical and laboratory outcomes in HIV-1-infected patients who began ART at

less than 350 CD4⁺ T-cells/ μ l with those who began therapy with at least 350 CD4⁺ T-cells/ μ l. We also examined studies in which ART was begun with at least 500 CD4⁺ T-cells/ μ l. We included data from both trials and cohort studies, but excluded data from structured treatment interruption studies, that is, studies in which ART was started but then stopped and subsequently restarted.

Search methods for identification of studies

Using Cochrane Collaboration methods, we formulated a comprehensive and exhaustive search strategy in an attempt to identify all relevant studies [21]. Databases searched included the Cochrane Central Register of Controlled Trials, Excerpta Medica Database (EMBASE), MEDLINE via PubMed and WHO's Global Index Medicus. The search strategy included Medical Subject Heading (MeSH) terms and a range of relevant keywords. The search period ranged from 1 January 1996 to 24 August 2012. The search strategy was iterative, in that references of included studies were searched to identify additional references. All languages were included. Additionally, we searched for potentially relevant abstracts presented at key scientific conferences (the Conference on Retroviruses and Opportunistic Infections, the International AIDS Conference, and International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention) held within the search period.

Selection of studies

We imported search results into bibliographic citation management software (EndNote X4, Thomson Reuters, New York, New York, USA) and excluded duplicate references. Reviewing only article titles, one author (T.H.) excluded all references that were clearly irrelevant. Two authors (G.W.R. and A.A.), working independently, then reviewed the titles, abstracts and descriptor terms of the remaining citations to identify potentially eligible reports. We obtained full text articles for all references identified as potentially meeting inclusion criteria. G.W.R. and A.A. reviewed these full text articles and applied the inclusion criteria to establish each study's eligibility or ineligibility. Our plan was to resolve any differences of opinion through discussion and, if necessary, a neutral third party arbiter, but we had no disagreements.

Data extraction and management

After identifying trials for inclusion, two authors (G.W.R. and A.A.) working independently examined and extracted data from each study. G.W.R. and A.A. separately entered these data into standardized data extraction forms and then compared extracted data. There were no disagreements.

Assessment of methodological quality

We used the Cochrane Collaboration tool [21] for assessing risk of bias in the included randomized controlled trials (RCTs). The Cochrane tool assesses

risk of bias in individual studies across six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential biases. We used the Newcastle-Ottawa Scale to assess quality and risk of bias in the nonrandomized studies [22]. This scale judges three general areas: selection of study groups, comparability of groups, and ascertainment of outcomes (in the case of cohort studies).

Statistical analysis and data synthesis

We used published estimated relative risks (RRs) if provided in study reports, but, when necessary, we calculated the RR for dichotomous outcomes and the 95% confidence interval (CI). We pooled data across studies and estimated summary effect sizes. We performed all meta-analyses in Review Manager 5.2 (Cochrane Collaboration, London, UK). Due to anticipated heterogeneity between study designs and populations, we modeled meta-analyses using a DerSimonian-Laird random-effects model. We present estimates of heterogeneity, determined by I^2 ; estimates of I^2 are interpreted as the percentage of variability in effect estimates due to heterogeneity rather than chance.

Sensitivity analysis

The observational literature for two major outcomes – mortality and clinical progression or mortality – includes a number of studies that report data from the same patient cohorts. To minimize the problem of overlap, we conducted a sensitivity analysis of studies with no or minimal overlap. Additionally, methods for dealing with lead-time bias in cohort studies have evolved since the earliest cohorts were reported [23,24]. For these two outcomes, we also examined the subgroup of studies that reported attempting to control for lead-time or frailty bias after removing those reporting data from the same cohorts.

Assessment of evidence quality (Grades of Recommendation Assessment, Development and Evaluation)

We graded the quality of evidence from the relevant literature for each outcome, as opposed to individual studies, using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) approach [25]. GRADE ranks the quality of evidence on four levels: high, moderate, low, and very low. Evidence from RCTs starts at high but can be downgraded based on study limitations, inconsistency of results, indirectness of evidence, imprecision (small numbers of events in the intervention and control groups), or reporting bias. Evidence from observational studies starts at low, but can be upgraded if the magnitude of treatment effect is very large, if there is a significant dose–response relationship or if all possible confounders would decrease the magnitude of an apparent treatment effect [25]. Evidence from observational studies can also be downgraded.

Results

Our searches identified 1055 articles and meeting abstracts, of which 201 were duplicates and 816 not relevant. Of the remaining 38 articles and abstracts, we identified 24 studies that met our inclusion criteria (Fig. 1). Of these, 21 were observational studies [17,26–45], and three were RCTs [12,18,46] (Table 1). Studies were conducted in Africa [12,18], Asia [12,18], Australia [12,28,29], Europe [12,17,25–28,30–33,36,37,39–42], North America [12,17,18,26,27,31,32,35–38,41,44,45] and South America [12,18] and reported a variety of outcomes including mortality, progression to AIDS, progression to category B or C disease, CD4⁺ T-cell count increase, progression to AIDS or death, virologic suppression, virologic failure, virologic rebound, non-AIDS-defining cancer, serious non-AIDS events and non-opportunistic diagnoses, severe adverse events, and grade 3 or 4 laboratory abnormalities.

Mortality

One RCT [18] and 13 observational studies [17,29,31,32,35–37,40–45] reported a mortality outcome. All consistently found a decreased risk of death in persons who initiated ART at CD4⁺ T-cell counts with at least 350 cells/ μ l; four observational studies found statistically

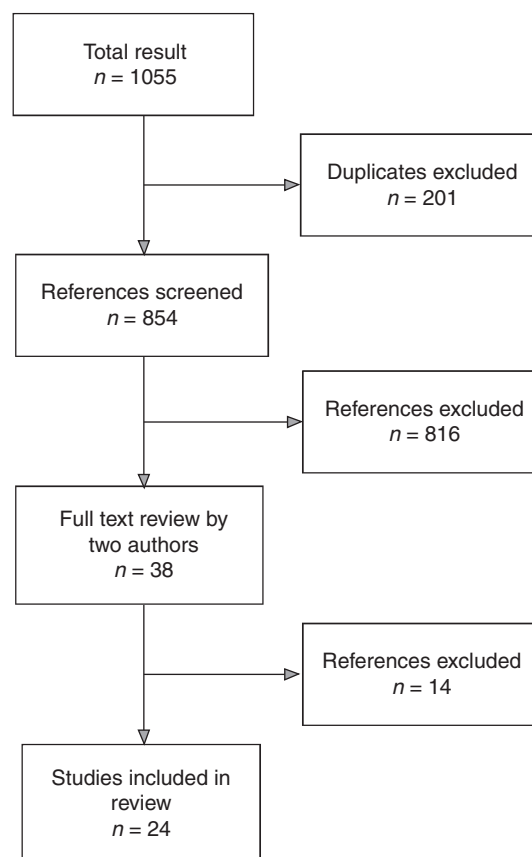


Fig. 1. Flow chart of articles identified, screened, assessed and included.

Table 1. Included studies.

Study and reference	Methods	Setting	Participants	Intervention	Outcomes
Ahdieh-Grant, 2003 [26]	Multicentre cohort study	United States of America	ART-naïve HIV-infected men initiating ART	Initiate ART with CD4 counts 350–499 cells/ μ l	AIDS
Althoff, 2010 [26]	Meta-analysis of 19 cohort studies	Canada and United States of America	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count \geq 350 cells/ μ l	Virologic suppression to <500 copies/mL within 24 months CD4 cell count increase of \geq 100 cells/ μ l within 24 months
CASCADE, 2003 [28]	Meta-analysis of 20 cohort studies	Australia, Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Switzerland, United Kingdom	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 counts 351–500 cells/ μ l	CD4 cell count increase of 50, 100, 150 or 200 cells/ μ l within 6 months
CASCADE, 2011 [29]	Meta-analysis of 23 cohort studies	Australia, Canada, Denmark, Estonia, France, Germany, Greece, Italy, Kenya, The Netherlands, Norway, Poland, Portugal, Russia, Rwanda, South Africa, Spain, Switzerland, Uganda, Ukraine, United Kingdom, Zambia, Zimbabwe	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 counts 350–499 cells/ μ l	AIDS-free survival at 2 or 4 years Death within 2 or 4 years
Cohen, 2011 [18]	Randomised controlled trial	Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, United States of America, Zimbabwe	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 counts 350–550 cells/ μ l	Death within 6 months AIDS-free survival within 6 months Severe adverse events Grade 3 or 4 laboratory abnormalities
Cozzi-Lepri, 2001 [30]	Multicentre cohort study	Italy	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count \geq 350 cells/ μ l	CD4 decrease to <200 cells/ mm^3 by 96 weeks Virologic failure
Egger, 2002 [31]	Meta-analysis of 13 cohort studies	Austria, Belgium, Canada, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Latvia, Lithuania, Luxembourg, The Netherlands, Norway, Poland, Portugal, Romania, Spain, Sweden, Switzerland, United Kingdom, United States of America	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count \geq 350 cells/ μ l	Death AIDS or death
Callant, 2011 [32]	Retrospective cohort study	United States of America	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count 350–500 cells/ μ l	Death
Garcia, 2004 [33]	Cohort study	Spain	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count 350–499 cells/ μ l	AIDS or death

Grant, 2011 [46]	Randomised controlled trial	United States of America	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count ≥ 350 cells/ μ l with ABC/3TC or TDF/FTC-containing regimens	Virologic failure
Gras, 2007 [34]	Multicentre cohort study	The Netherlands	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count 350–500 cells/ μ l	CD4 cell count ≥ 800 cells/ μ l
HIV-CAUSAL, 2010 [35]	Meta-analysis of 12 cohort studies	France, The Netherlands, United Kingdom, United States of America	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count 350–499 cells/ μ l	Death
HIV-CAUSAL, 2011 [36]	Meta-analysis of 12 cohort studies	France, The Netherlands, United Kingdom, United States of America	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count 350–499 cells/ μ l	Death AIDS or death
Kitahata, 2009 [37]	Meta-analysis of 22 cohort studies	Canada and United States of America	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count 351–500 cells/ μ l	Death
Krishnan, 2011 [38]	Multicentre cohort study	United States of America	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count >350 cells/ μ l	Non-AIDS-defining malignancy
Merito, 2006 [39]	Multicentre cohort study	Italy	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count ≥ 350 cells/ μ l	AIDS or death
Opravil, 2002 [40]	Multicentre cohort study	Switzerland	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count >350 cells/ μ l	AIDS Death AIDS or death Progression to stage B/C disease
Palella, 2003 [41]	Cohort study	United States of America	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count 351–500 cells/ μ l	Death
Phillips, 2001 [42]	Meta-analysis of 3 cohort studies	Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Israel, Italy, The Netherlands, Norway, Poland, Portugal, Spain, Sweden, Switzerland, United Kingdom	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count ≥ 350 cells/ μ l	AIDS or death
Plettenberg, 2011 [43]	Multicentre cohort study	Germany	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count 350–499 cells/ μ l	AIDS Death CD4 cell count fall to <200 cells/ μ l

(continued)

Table 1 (continued)

Study and reference	Methods	Setting	Participants	Intervention	Outcomes
Strategies for Management of Antiretroviral Therapy (SMART), 2008 [12]	Randomised controlled trial	Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Denmark, Finland, France, Germany, Greece, Ireland, Israel, Italy, Japan, Morocco, New Zealand, Norway, Portugal, Russia, South Africa, Spain, Switzerland, United Kingdom, United States of America, Uruguay	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count ≥ 350 cells/ μ l	AIDS AIDS or death Serious non-AIDS events or non-opportunistic disease deaths
The Antiretroviral Therapy (ART) Cohort Collaboration, 2003 [44]	Meta analysis of 13 cohort studies	Austria, Belgium, Canada, Czech Republic, Denmark, Estonia, France, Germany, Hungary, Ireland, Israel, Italy, Latvia, Lithuania, Luxembourg, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Spain, Sweden, Switzerland, United Kingdom, United States of America	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count ≥ 350 cells/ μ l	AIDS or death within 6 months Death within 6 months
The Antiretroviral Therapy (ART) Cohort Collaboration, 2009 [45]	Meta-analysis of 13 cohort studies	Austria, Belgium, Canada, Czech Republic, Denmark, Estonia, France, Germany, Hungary, Ireland, Israel, Italy, Latvia, Lithuania, Luxembourg, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Spain, Sweden, Switzerland, United Kingdom, United States of America	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count ≥ 350 cells/ μ l	AIDS or death within 6 months Death within 6 months
When to Start Consortium, 2009 [17]	Meta-analysis of 18 cohort studies	Australia, Austria, Belgium, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Latvia, Lithuania, Luxembourg, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Spain, Sweden, Switzerland, United Kingdom, United States of America	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count ≥ 350 cells/ μ l	AIDS or death Death

ABC/3TC, abacavir/lamivudine; ART, antiretroviral therapy; TDF/FTC, tenofovir/emtricitabine.

significant decreases [29,35,37,40]. In one RCT, Cohen *et al.* [18] reported nonsignificantly lower risk of mortality (hazard ratio 0.77, 95% CI 0.34–1.76, $P = 0.27$) (Fig. 2). The 13 observational studies reported data from 58 cohorts. Of these 58 cohorts, data from 40 were reported in more than one study (Appendix 1, <http://links.lww.com/QAD/A491>). Two studies reported the results from single cohorts that did not appear in other studies [32,43]. We analyzed data from the two cohorts that were reported only once and then from those two cohorts in addition to data from two other large studies that reported large numbers of cohorts predominantly from North America ($n = 22$ cohorts) [37] and Europe ($n = 23$ cohorts) [29]. The two large studies had 17 517 and 9455 participants, respectively; 154 patients from the Southern Alberta Cohort appeared in both. The pooled RR of mortality from the two cohorts that were only reported in one publication each was 0.36 (95% CI 0.12–1.06) [27,38]. The pooled RR of mortality from these two cohorts and the largest, least overlapping studies was 0.55 (95% CI 0.44–0.70) [24,27,28,32] (Fig. 2). The pooled RR for overall mortality from all 13 studies (0.66, 95% CI 0.55–0.79), however, is more attenuated.

In a separate sensitivity analysis, we analyzed only cohorts that reported attempting to control for lead-time bias [17,29,35–37,43]. Four of these six studies had significant overlaps in the cohorts that were included [17,29,35,36], specifically Concerted Action on Seroconversion to AIDS and Death in Europe (CASCADE) [29] and HIV Cohorts Analyzed Using Structured Approaches to Longitudinal data (HIV-CAUSAL) [36], in their most recent publications report data from the same five cohorts (Appendix 1, <http://links.lww.com/QAD/>

A491). Among the two that either did not have overlap or had minor overlap with other studies, the pooled RR of mortality was 0.58 (95% CI 0.43–0.77) [37,43]. We also calculated pooled RR combining data from CASCADE with these two studies and in a separate calculation HIV-CAUSAL with the two studies and found overlapping and significant pooled RRs (0.56, 95% CI 0.44–0.71 with CASCADE; and 0.66, 95% CI 0.50–0.87 with HIV-CAUSAL).

The quality of evidence from the RCT literature for mortality was low and downgraded due to very serious imprecision owing to the small number of events. The quality of the observational literature for the entire 13 studies was very low due to the substantial overlap in patients among the studies. However, the quality of the literature for the four mostly nonoverlapping studies [29,32,37,43] was moderate because of a large effect size.

HIV disease progression

One RCT, which compared patients initiating ART at above 350 CD4⁺ T-cells/ μ l to those deferring until their CD4⁺ T-cell counts were below 250 cells/ μ l, found a nonsignificantly lower risk of developing an AIDS-defining opportunistic infection among persons initiating early compared to deferred treatment ($p = 0.30$) [12] (Fig. 3). Four observational studies estimated the effect of early versus deferred ART initiation; three found decreased risk of progression to AIDS among the cohorts initiating ART at 350–499 CD4⁺ T-cells/ μ l [26], at least 350 CD4⁺ T-cells/ μ l [40], and 350–449 CD4⁺ T-cells/ μ l [42], though only one of these found a statistically significant effect [40]. The ART Cohort Collaboration, the largest of the four synthesized observational studies,

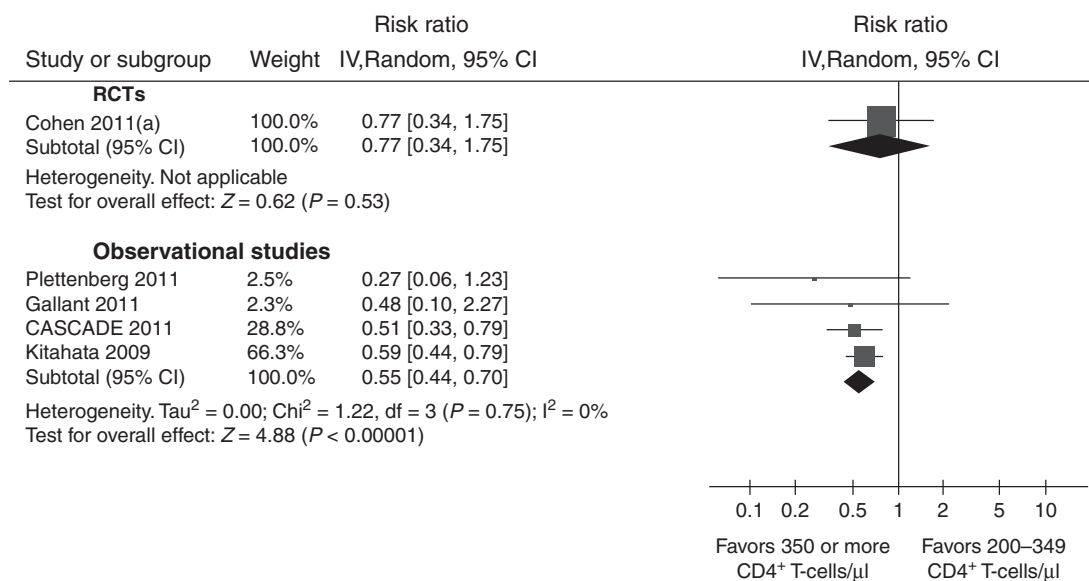


Fig. 2. Forest plots of mortality. CI, confidence interval; DF, degrees of freedom; IV, inverse variance; RCT, randomized controlled trial.

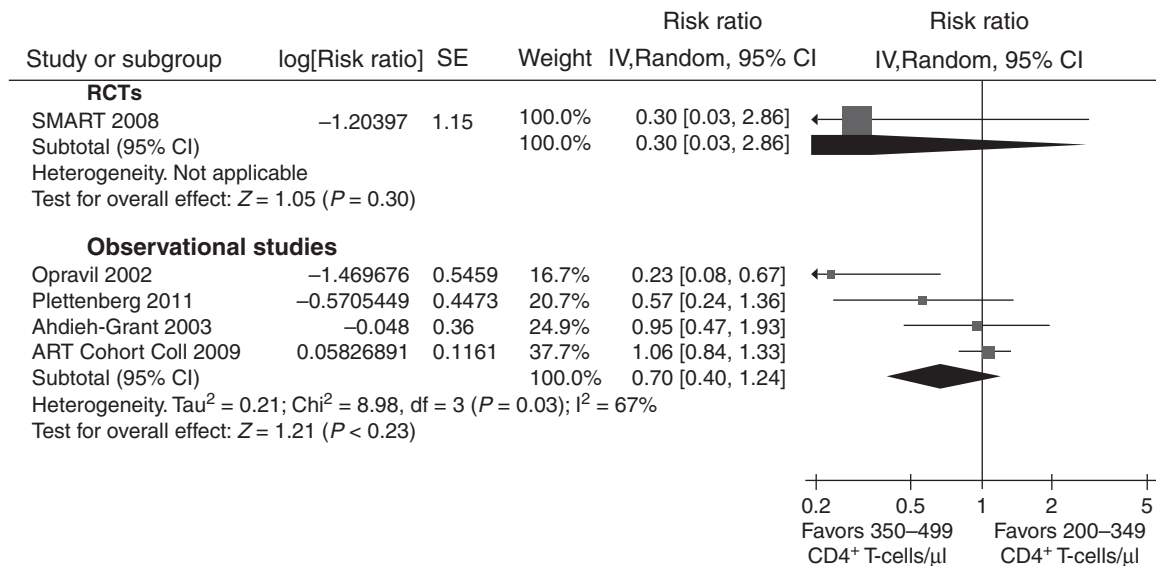


Fig. 3. Forest plots of AIDS progression. CI, confidence interval; DF, degrees of freedom; IV, inverse variance; RCT, randomized controlled trial; SE, standard error.

found no decreased risk of progression among patients beginning treatment at CD4^+ T-cell counts at least 350 cells/ μl compared to patients with deferred treatment [45]. The pooled RR across all four studies comparing early versus delayed treated patients on progression to AIDS was 0.70 (95% CI 0.40–1.24) (Fig. 3).

The quality of the RCT literature was rated as very low because of a very small number of events and indirectness due to the comparison between patients initiating ART at above 350 CD4^+ T-cells/ μl to those with less than 250 cells/ μl . The quality of the observational literature was similarly very poor due to inconsistency of findings across the four studies and potential imprecision in the estimates due to lack of adjustment in some of them.

HIV disease progression and/or mortality or AIDS-free survival

Two RCTs found a significantly lower risk of progression to AIDS or death among patients initiating ART treatment with at least 350 T-cells/ μl compared to less than 250 cells/ μl [12], and at 350–550 cells/ μl compared to less than 350 cells/ μl (RR 0.48, 95% CI 0.26–0.91) [12,18] (Fig. 4). Nine observational studies estimated the effect of early versus deferred ART initiation [17,29,31,33,36,39,40,42,44], and all nine found consistent decreased risk of progression to AIDS or death among the early treated cohorts. Four studies found statistically significant effects [17,29,40,44].

Compared to ART initiation at less than 350 CD4^+ T-cells/ μl , initiation of ART with at least 350 cells/ μl was found to marginally reduce the risk of progression to AIDS or death in a pooled analysis of two studies with unique patients (RR 0.71, 95% CI 0.47–1.05) (Fig. 4),

although this reduction of risk was not significant ($p = 0.08$) [29,33]. The nine studies reported data from 40 cohorts (Appendix 2, <http://links.lww.com/QAD/A491>). Of these 40 cohorts, 35 were reported in more than one study; three studies reported the results of single cohorts [33,39,40]. These three studies had a pooled RR of mortality or clinical progression of 0.48 (95% CI 0.25–0.92). We also examined how these estimates would change with the separate addition of the two large recently reported collaborations, CASCADE [29] and HIV-CAUSAL [36]. When data from CASCADE, which also contained results from the Italian Cohort of Antiretroviral-Naive Patients (ICONA) [39], and the Swiss HIV Cohort Study (SHCS) [40], were added to those from the Barcelona Hospital Clinic cohort [33], we found a pooled RR of 0.33 (95% CI 0.17–0.66). When we combined the results of HIV-CAUSAL [36], which contains results from SCHS but not ICONA, with ICONA [39] and the Barcelona Hospital Clinic cohort [33], we found a pooled RR of 0.72 (95% CI 0.60–0.87).

We also examined studies that reported attempting to control for lead-time bias in a separate sensitivity analysis. Of the three studies that reported this [29,36,39], there was substantial overlap among the cohorts reported in these studies. The pooled RR from the combined analysis for HIV-CAUSAL [36] and ICONA [39] was 0.73 (95% CI 0.60–0.88), whereas the RR reported from CASCADE [29] was 0.75 (95% 0.49–1.14).

The quality of the RCT literature for this outcome was low due to serious indirectness from few events and the indirect comparison made by the SMART study, noted above. Among the observational studies, eight of these nine studies reported adjusted estimates; as such,

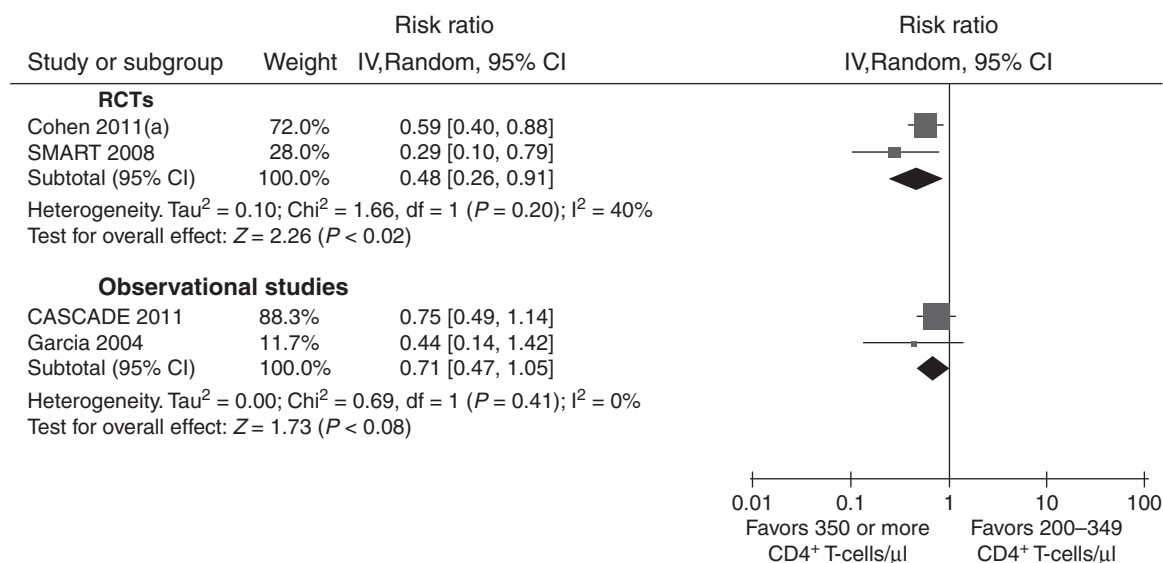


Fig. 4. Forest plots of AIDS progression or death. CI, confidence interval; DF, degrees of freedom; IV, inverse variance; RCT, randomized controlled trial.

the risk of bias from unadjusted estimates has been lessened. Additionally, these studies were consistent in their finding of treatment effect. However, the quality of the observational literature for this outcome is low due its observational status and the lack of strength.

Serious non-AIDS-defining illness and nonopportunity disease-related death

One RCT found a significantly lower risk of serious non-AIDS events and non-opportunistic disease-related deaths among ART-naïve patients beginning therapy at a CD4⁺ T-cell count of at least 350 cells/μl versus patients who delayed treatment until their CD4⁺ T-cell count had

fallen to 250 cells/μl or less (RR 0.14, 95% CI 0.03–0.64) [12] (Fig. 5). Similarly, one observational study found a significantly lower risk of non-AIDS-defining cancer diagnoses among patients treated early compared to patients who deferred treatment (RR 0.47, 95% CI 0.23–0.98) [38] (Fig. 5). The quality of the RCT literature was poor owing to serious imprecision because of the very small number of events and indirectness (the SMART trial subanalysis compared patients initiating ART at <250 CD4⁺ T-cells/μl to those initiating therapy at >350 cells/μl). Similarly, the quality of the observational literature was also poor due to serious imprecision owing to very few events.

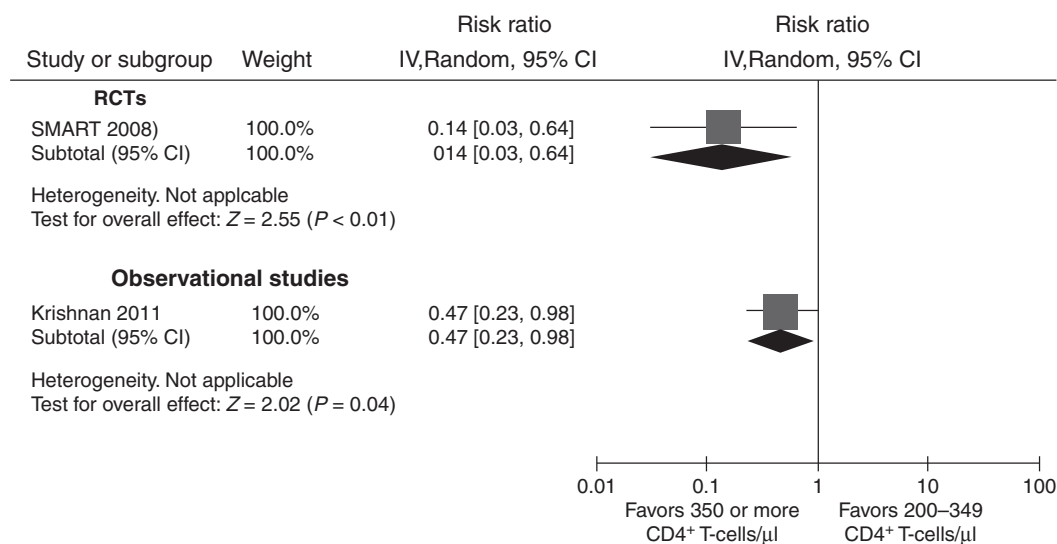


Fig. 5. Forest plot of serious non-AIDS-defining illness and non-opportunistic disease-related death. CI, confidence interval; IV, inverse variance; RCT, randomized controlled trial.

Virologic failure

One RCT conducted in the United States found a nonsignificantly higher risk of virologic failure among patients initiating two different ART treatment regimens at CD4⁺ T-cell counts of at least 350 cells/ μ l compared to patients who deferred treatment until CD4⁺ T-cell counts were 250 cells/ μ l or less (abacavir/lamivudine-containing regimen: RR 1.54, 95% CI 0.92–2.56; tenofovir/emtricitabine-containing regimen: RR 1.30, 95% CI 0.77–2.20) [46] (Fig. 6). Two observational studies estimated the likelihood of viral suppression among patients initiating ART with at least 350 CD4⁺ T-cells/ μ l versus those deferring [27,42], and one observational study estimated the risk of virologic failure among patients beginning therapy at at least 350 cells/ μ l versus deferred cohort patients [30]. In the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) meta-analysis of 19 North American cohorts, initiating ART at a CD4⁺ T-cell count level of above 350 cells/ μ l was associated with a borderline significantly decreased adjusted hazard of achieving viral suppression [adjusted hazard ratio (aHR) 0.94, 95% CI 0.89–1.00] [27]. Conversely, in a meta-analysis of three large European cohorts, Phillips *et al.* [42] found that the adjusted hazard of achieving viral suppression below 500 copies/ μ l at 32 weeks of follow-up was no more or less likely among patients who began therapy at 200–349 CD4⁺ T-cells/ μ l than those who began at at least 350 CD4⁺ T-cells/ μ l (aHR 1.08, 95% CI 0.98–1.21). The pooled effect of early treatment on viral suppression among observational studies was not significant (RR 1.00, 95% CI 0.87–1.14) (Fig. 6). Similarly, the large Italian registry study ICONA found that there

was no difference in the adjusted relative hazard (aRH) of virologic failure through 96 weeks of follow-up for those who began ART at CD4⁺ T-cell counts of between 201 and 350 cells/ μ l compared to those with counts above 350 cells/ μ l (aRH 1.0, 95% CI 0.79–1.29) [30]. The quality of the RCT literature related to this outcome was rated poor because of serious imprecision owing to very few events. The quality of the observational literature for this outcome was also very poor because of the observational study design and overlap of study populations.

Immunologic recovery

Specific outcomes used to determine immune recovery in this literature included CD4⁺ T-cell count reaching at least 800 cells/ μ l after ART initiation and CD4⁺ T-cell count increases (at least 50, 100, 150, and 200 cells/ μ l). One observational study estimated the effect of early versus deferred treatment on CD4⁺ T-cell count reaching 800 more cells/ μ l after starting ART [34], and found that, compared to patients who began ART at between 200 and 350 CD4⁺ T-cells/ μ l, those who began ART at 350–500 CD4⁺ T-cells/ μ l had an aHR 2.84 times higher (95% CI 2.45–3.28). Conversely the NA-ACCORD study found no relationship between a CD4⁺ T-cell count increase of at least 100 cells/ μ l after 24 months of therapy between those who began ART at less than 350 CD4⁺ T-cells/ μ l and those who began at at least 350 cells/ μ l (aHR 1.05, 95% CI 0.98–1.12) [27]. Similarly, the large European and Australian registry study CASCADE found no difference in the adjusted odds of having a CD4⁺ T-cell count rise of at least 100 cells/ μ l among those who initiated ART at between

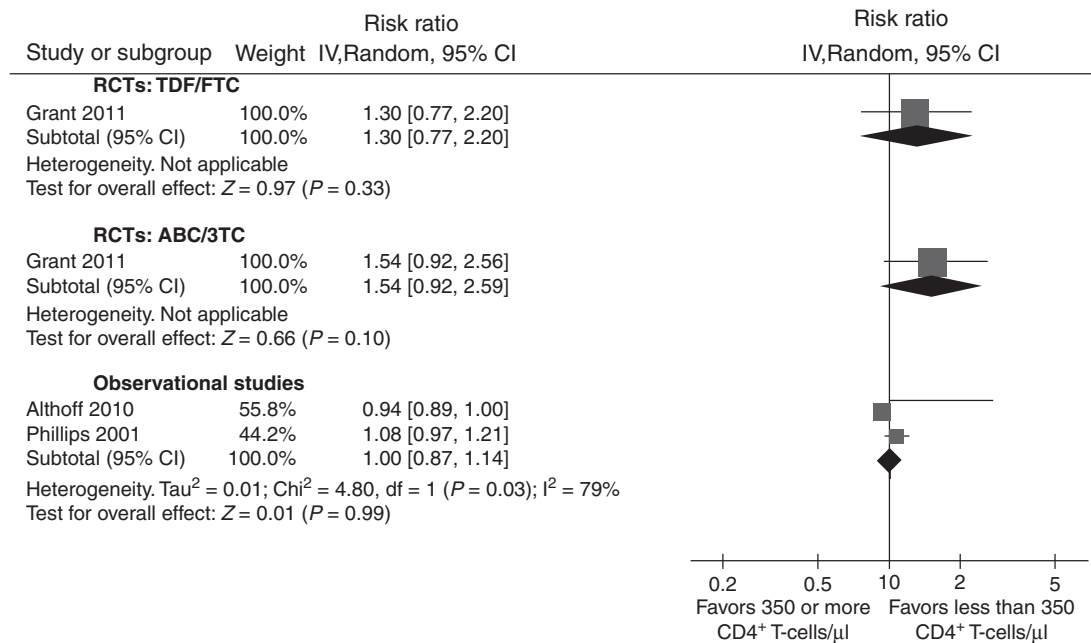


Fig. 6. Forest plot of virologic failure and virologic suppression. ABC/3TC, abacavir/lamivudine; CI, confidence interval; DF, degrees of freedom; IV, inverse variance; RCT, randomized controlled trial; TDF/FTC, tenofovir, emtricitabine.

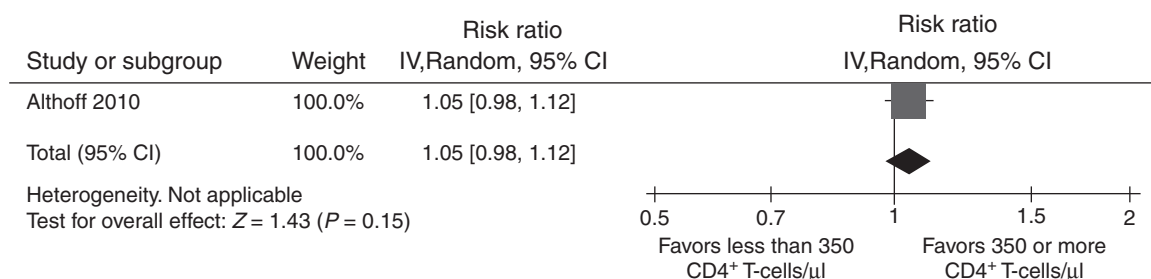


Fig. 7. Forest plot of immunologic recovery. CI, confidence interval; IV, inverse variance.

200 and 350 cells/ μl and those who initiated it between 351 and 500 cells/ μl [adjusted odds ratio (aOR) 0.94, 95% CI 0.56–1.58] [23]. Combining the results of these two studies, there was no evidence of a difference in CD4⁺ T-cell count recovery of at least 100 cells/ μl between the two groups (RR 1.05, 95% CI 0.98–1.12) (Fig. 7). The quality of this literature was rated as very poor based on its observational nature and overlap of patient populations between studies.

Severe adverse events and laboratory abnormalities

One RCT found no difference in risk of severe adverse events between early and deferred treatment cohorts (RR 1.06, 95% CI 0.84–1.33), but found a significantly increased risk of grade 3 or 4 lab abnormalities in patients who started ART early when compared to patients who delayed starting ART ($P < 0.001$) [18] (Fig. 8). The grade 3–4 laboratory abnormalities that were significantly higher in the early treatment group, including neutropenia and total hyperbilirubinemia, were of unclear clinical significance. The quality of this literature for these outcomes was high with no observed study limitations.

Methodological quality of included studies

No observational study suffered from obvious selection bias; all observational studies had study populations that were either truly or somewhat representative of average, HIV-infected persons, and all participants were drawn from the same community. Additionally, all treatment data were ascertained through healthcare records, and outcomes or interests were not present at the start of the study. The comparability between intervention arms was good as all studies adjusted for confounding

factors such as age or sex. Outcomes were adequately assessed in all studies either through independent blind assessment or record linkage, follow-up was long enough for outcomes to occur in all studies, but two observational studies did not report follow-up rates of participants [27,29] (Appendix 3, <http://links.lww.com/QAD/A491>).

All three RCTs adequately described how the randomization sequence was generated, and all allocation was adequately concealed prior to assignment. No studies suffered from attrition bias resulting from incomplete outcome data reporting (e.g. follow-up in all studies was adequate), and no study suffered from reporting bias resulting from selective outcome reporting. Two of the three RCTs may have potentially been biased because of a lack of blinding of assigned treatment (treatment was determined by predetermined clinical characteristics) [12,18].

Discussion

We found evidence to suggest early ART initiation (with baseline CD4⁺ ≥ 350 T-cells/ μl) can reduce the risk of progression to AIDS or death, can increase the likelihood of immunologic recovery (CD4⁺ T-cell count reaching 800 cells/ μl or more after ART) and can reduce the risk of being diagnosed with a non-AIDS-defining illness. We also found that grade 3 or 4 laboratory abnormalities are more commonly found among patients treated early, but these are of unclear clinical significance. The quality of the evidence is strongest in the GRADE system for the risk of severe adverse events or grade 3 or 4 laboratory

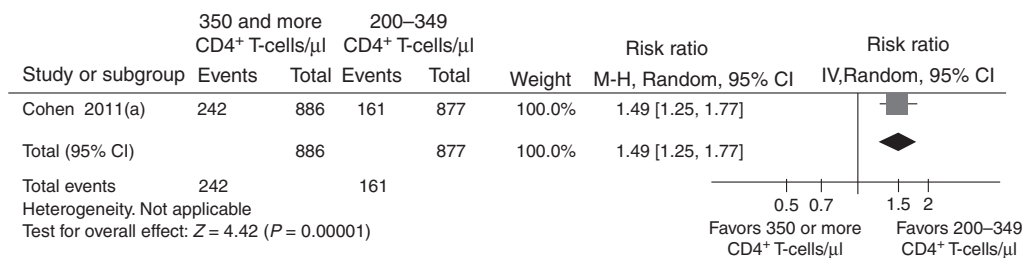


Fig. 8. Forest plot of risk of grade 3 or 4 laboratory abnormalities. CI, confidence interval; M-H, Mantel–Haenszel; RCT, randomized controlled trial.

abnormalities. Additionally, there was fairly consistent agreement between the RCT literature and the large observational literature, although this is not captured in the GRADE system. It should be noted that, apart from the laboratory abnormalities, early treatment does not appear to cause additional harms. Additionally, although not a specific outcome we reviewed, it may be associated with lower likelihood of patients being lost to follow-up before they begin ART [47].

Our findings are subject to multiple limitations. As with all systematic reviews, we are limited by the sensitivity of our search and our ability to identify relevant studies. We comprehensively searched four key scientific databases and used broad inclusion criteria to identify studies. We carefully reviewed the bibliographies of included studies, as well as abstracts from recent conferences, to assure the completeness of our search. However, the large bulk of this literature comes from Europe, North America and Australia, with little contribution from Africa, Asia and South America, which may somewhat limit its generalizability to areas where the bulk of patients in need of ART live. Additionally, we are potentially limited by publication bias, but given the highly inclusive nature of the large synthesized cohorts, such as NA-ACCORD, EUROSIDA, ICONA, CASCADE, HIV-CAUSAL and others, we suspect that publication bias was not an issue in this review. Additionally, we developed estimates of efficacy from RCTs and effectiveness from cohort studies. Whereas the three RCTs provide evidence of efficacy, the pooled estimates are unstable because of small numerators for rare outcomes, and using GRADE criteria, we had to mark the overall quality of the RCT literature as poor, for some major clinical outcomes, like mortality and progression, because of this. For this reason, we also examined cohort studies that provide a lower quality of evidence, usually because of their inability to control for unmeasured confounding. Eleven of the 13 observational studies reported mortality data from many of the same cohorts, potentially biasing our overall effectiveness estimates. We conducted sensitivity analyses to examine how much potential bias there was. When we examined two studies, one from Germany [43] and one from the United States [32], which had no overlap with other studies, and the two large studies primarily from North America [37] and Europe [29] that minimally overlapped each other, we found similar pooled risks of mortality, suggesting that whatever overlap there was did not materially influence our estimates. Clearly to understand the impact of cohorts being reported in more than one publication, we would need to do an individual patient database meta-analysis for each outcome variable. Cohorts can also suffer from lead-time bias, that is, patients who may have benefited from therapy, but died before entering the cohort, are not counted and, as a result, may bias results [23,24]. Several of the more recent reports attempted in various ways to control for this, and the pooled RR we found in

sensitivity analysis of nonoverlapping reports that reported attempting to control for lead-time bias for outcomes of mortality was significantly lower in overall pooled estimates to that from nonoverlapping studies in our other sensitivity analysis. Finally, the GRADE system for rating the quality of the literature is relatively new [48,49] and a recent evaluation of its use at WHO found some challenges with its use [50]. It is, however, the current gold standard and has been adopted by WHO for its guideline development process [51].

In conclusion, our findings provide evidence, albeit of differing quality, depending on the outcome in question, of the efficacy and effectiveness of initiating ART at CD4⁺ T-cell counts of between 350 and 499 cells/ μ l compared to initiating it later in the course of disease when CD4⁺ T-cell counts have fallen below 350 cells/ μ l. The literature for beginning ART at CD4⁺ T-cell counts of at least 500 cells/ μ l is much less robust and awaits new data from the large trials and combination cohort studies to provide additional evidence of the effectiveness of even earlier initiation [52,53]. As a result of the process in which these data were used, the 2013 WHO treatment guidelines strongly recommend that ART be initiated in adults and adolescents with CD4⁺ T-cell counts of 500 cells/ μ l or less in addition to patients who have stage 3 or 4 clinical disease, tuberculosis, HBV infection with evidence of severe chronic liver disease, infected partners in serodiscordant couples and pregnant and breastfeeding women, regardless of CD4⁺ T-cell count [5]. However, we believe that this is a question that has not been fully answered, and we are in strong support of awaiting results of two RCTs that are currently in the field – Strategic Timing of AntiRetroviral Treatment (START) study [52] and Tolérance/efficacité à 30 mois d'un traitement ARV précoce +/- prophylaxie antiTB par INH: essai randomisé de phase 3 (TEMPRANO) [53] – in hopes that they will add additional high-quality evidence to answer the question of when to start ART definitively.

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Conflicts of interest

The authors declare that they have no conflicts of interest. This work was supported under a contract with the WHO (APW 200671213).

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