Clinical Infectious Diseases

REVIEW ARTICLE

Contribution of Low CD4 Cell Counts and High Human Immunodeficiency Virus (HIV) Viral Load to the Efficacy of Preferred First-Line Antiretroviral Regimens for Treating HIV Infection: A Systematic Review and Meta-Analysis

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We assessed whether low CD4 count and high viral load (VL) affect the response to currently preferred ART. We performed a systematic review of randomized, controlled clinical trials that analyzed preferred first-line ART and a subgroup analysis by CD4 count (≤ or >200 CD4/μL) or VL (≤ or >100 000 copies/mL). We computed the odds ratio (OR) of treatment failure (TF) for each subgroup and individual treatment arm. Patients with ≤200 CD4 cells or VL ≥100 000 copies/mL showed an increased likelihood of TF at 48 weeks: OR, 1.94; 95% confidence interval (CI): 1.45–2.61 and OR, 1.75; 95% CI: 1.30–2.35, respectively. A similar increase in the risk of TF was observed at 96 weeks. There was no significant heterogeneity regarding integrase strand transfer inhibitor or nucleoside reverse transcriptase inhibitor backbone. Our results show that CD4 <200 cells/μL and VL ≥100,000 copies/mL impair ART efficacy in all preferred regimens.

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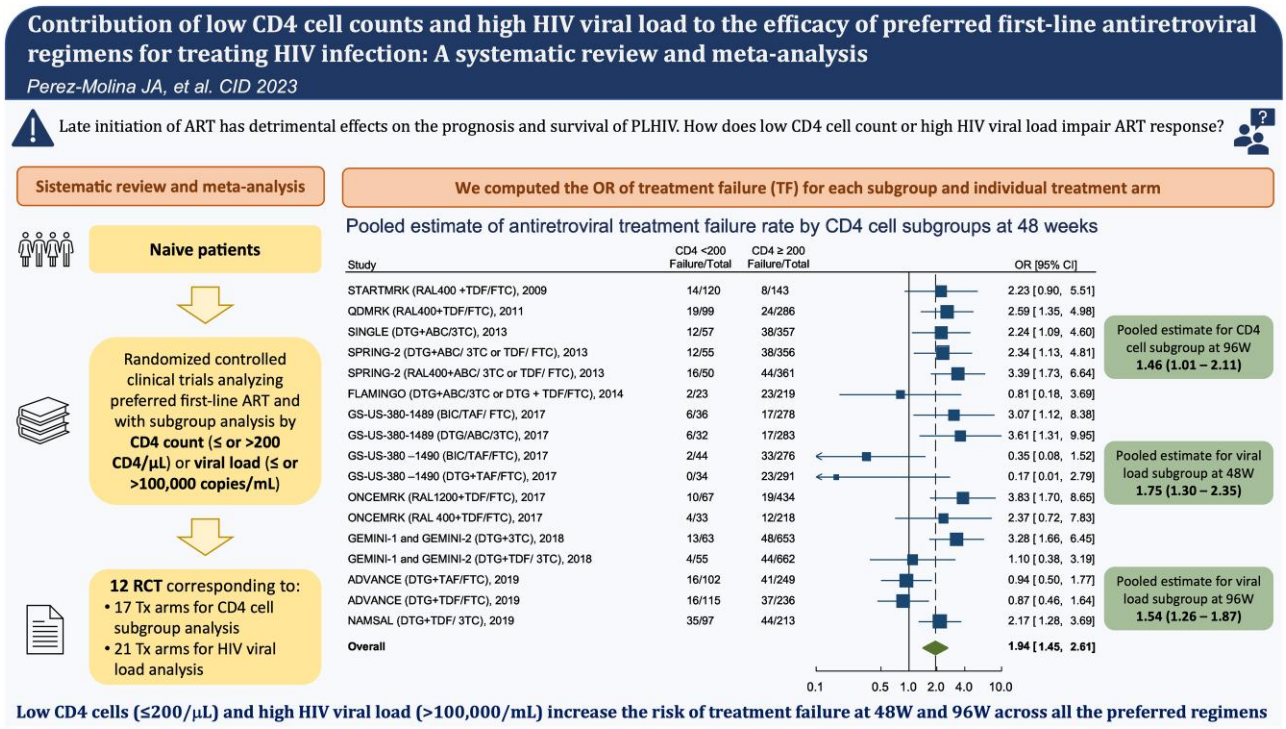
Graphical Abstract



Keywords. late presenter; antiretrovirals; CD4 cell; meta-analysis; systematic review.

Antiretroviral therapy (ART) aims to fully and durably suppress the replication of human immunodeficiency virus type 1 (HIV-1), thus reducing HIV-related morbidity, prolonging the duration and quality of survival, and preventing transmission of HIV. Early initiation of ART, regardless of CD4 count, can reduce the risk of AIDS-related and non–AIDS-related morbidity and mortality in people with HIV (PWH) [1, 2]. Nevertheless, many of these beneficial effects are lost when patients start therapy late with a CD4 count <350 cells/μL or with an AIDS-defining condition [3–5].

In ART-naive PWH, treatment guidelines consider pretreatment HIV RNA load and pretreatment CD4 count to be key factors when selecting an initial regimen. Furthermore, the US Food and Drug Administration guidance document for developing drugs for the treatment of HIV-1 infection advises sponsors of clinical trials to consider stratification of patients by baseline viral load (VL; <100 000 copies/mL vs ≥100 000 copies/mL) and CD4 count (<200 vs ≥200 cells/mm^3) [6].

A recent systematic review of the efficacy of initial ART in adults based on studies published from 1994 to July 2017 found a continuous improvement in the efficacy of ART, with newer regimens enabling a substantial proportion of PWH to achieve an HIV RNA load <50 copies/mL for up to 144 weeks [7]. Multivariable analysis revealed that both the type of anchor drug and the type of nucleoside reverse transcriptase inhibitor (NRTI) backbone were independent predictors of efficacy at weeks 48, week 96, and week 144, favoring the use of integrase strand transfer inhibitors (INSTIs) and tenofovir disoproxil fumarate-emtricitabine (TDF-FTC) or tenofovir alafenamide-emtricitabine (TAF-FTC). A higher baseline CD4 count was also independently associated with greater efficacy at weeks 48 and 144. In contrast, a lower baseline HIV RNA load was independently associated with greater efficacy at week 48 but not at week 144 [7].

In recent years, new drugs such as bictegravir (BIC) [8, 9], darunavir/cobicistat [10], and doravirine [11] and new treatment modalities such as 2-drug combinations with dolutegravir (DTG) and lamivudine (3TC) have been added to the antiretroviral armamentarium [12]. However, no data are available from randomized clinical trials comparing the efficacy of recommended first-line ART in patients with low CD4 counts (<200) and high HIV RNA load. Since antiretrovirals are one of the few modifiable factors in this situation, it is essential to have information on the efficacy of the regimens used. Our aim is this study was to provide a comprehensive overview of the contribution of baseline CD4 cell count and HIV RNA load to treatment efficacy and safety for recommended first-line treatment regimens in ART-naive PWH.

METHODS

We performed a systematic literature review and meta-analysis and used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement to report our findings [13] (Supplementary Materials, Supplementary Annex-1). The study protocol is available at https://osf.io/s7ahx.

Eligibility Criteria and Patient Population

We selected first-line ART as recommended in the leading guidelines (United States Department of Health and Human Services [US DHHS], International Antiviral Society-USA Panel [IAS-USA], European AIDS Clinical Society [EACS], and Grupo de estudio del sida GeSIDA-SEIMC [GeSIDA]) active in 2021 [14–17]. We included randomized, controlled clinical trials of treatment-naive adult patients with a follow-up of at least 48 weeks that provided subgroup analysis by CD4 cell count (<200 vs ≥200 cell/μL) or HIV VL (<100 000 vs ≥100 000 copies/mL) and information on response to treatment in at least 1 of the 2 subgroups analyzed. Studies of ART-experienced patients, pregnant or breastfeeding women, and patients who started ART and treatment for HIV-related opportunistic diseases were excluded.

Literature Search and Data Extraction

We performed a systematic search of Medline, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) limited to articles published from 1 January 2006 to 22 September 2022, with no language restrictions. The search terms included free text terms and the controlled vocabulary of the corresponding database (Supplementary Materials, Supplementary Annex 2). Each study could have 1 or more treatment arms. We performed a snowballing search by consulting the references of the articles included and scrutinized the abstracts of the main scientific meetings in HIV infection (CROI, IAS, and EACS) from the last 3 years.

Two reviewers (C. C.-A. and J. B.) independently identified eligible studies using Rayyan software for systematic reviews (https://www.rayyan.ai). A third investigator (J. A. P. M.) resolved disagreements. J. A. P. M. and C. C.-A. extracted the data using a prespecified data collection form. If available, we collected the primary and secondary end points for each study arm. We also collected variables related to the study design and the frequency of treatment-related adverse events. Two reviewers (J. A. P. M. and C. C.-A.) independently assessed the clinical applicability of the subgroup analysis for each study.

Evaluation of Risk of Bias

The likelihood of publication bias was evaluated through funnel plots and statistical tests for "small study effects" (Egger's test and Peter's test) [18]. Because we aimed to identify the differential treatment effect in 2 specific subgroups, we did not evaluate the risk of bias using ROB-2 but applied a specific tool to assess the credibility of the subgroup analyses performed in each study. We used the dimensions of evaluation proposed by Gil-Sierra et al [19], who recommend considering subgroup results in clinical decision-making. The applicability of such results is graded as probable, possible, doubtful, and null.

Statistical Analyses

We analyzed the primary outcome of efficacy for each arm of the studies included as the proportion of participants with an undetectable VL at 48 weeks by intent-to-treat analysis, as defined in the individual trial (time to virologic failure or using snapshot algorithms). This outcome is clearly established by regulatory agencies and subject to less subjective interpretation than treatment failure (TF), which includes causes other than virological failure. However, since this meta-analysis focuses on determining whether there was an increased risk of failure in specific subgroups, we pooled the rates of patients without an undetectable VL, whatever the cause.

TF was calculated as the proportion of patients without an undetectable VL at 48 weeks by intent-to-treat analysis. We also analyzed some secondary outcomes such as the proportion of participants without an undetectable VL at 96 weeks by intent-to-treat analysis, the proportion of participants without an undetectable VL at 48 weeks according to baseline HIV-RNA VL >500 000 copies/mL vs ≤500 000 copies/mL, the proportion and type of resistance mutations after virologic failure, and the proportion of patients with drug-related adverse events leading to discontinuation of the ART regimen.

To test the hypothesis that the effect of ART differs by subgroup, we calculated the ratio of the odds of TF at 48 weeks in the subgroup of patients with CD4 <200 cells/μL to the odds of the same outcome in the subgroup of patients with CD4 ≥200 cells/μL for each study arm. An odds ratio (OR) higher than 1 is interpreted as treatment having lower efficacy (ie, higher TF rate) in the subgroup of patients with CD4 <200 cells/μL than in the subgroup with CD4 ≥200 cells/μL. The same procedure was performed for the other subgroup of interest (VL >100 000 copies/mL vs ≤100 000 copies/mL) and for the remaining secondary outcomes. The effects measure (ie, OR) and its standard error were computed using each subgroup's raw count data. We pooled ORs across studies using a random effects model. Between studies, we calculated the I-square, and its significance was assessed using the Cochran Q test. For each pooled estimate, we provide the 95% confidence interval (CI) along with the corresponding prediction intervals. These represent the range of values within which the results of a new study will fall if it is performed under the same circumstances as the studies included in the review. Stata version 16 was used in all analyses (StataCorp, 2019. Stata Statistical Software, release 16; StataCorp LLC, College Station, TX).

Evaluation of Heterogeneity

We explored heterogeneity by fitting meta-regression models with the natural logarithm of the OR as the dependent variable

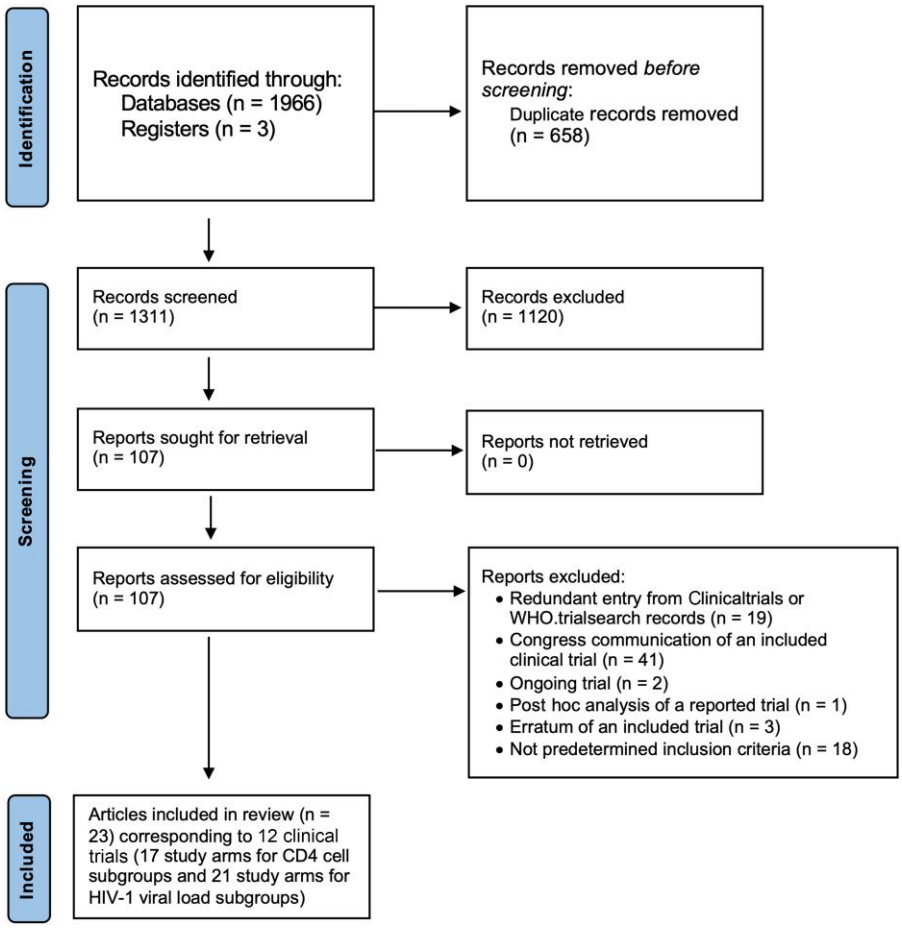


Figure 1. Flow chart of study selection process. Abbreviation: HIV-1, human immunodeficiency virus type 1.

and the year of publication as an independent term, weighted by the inverse of the standard error of the log (OR). We applied subgroup analysis to explore the following characteristics: type of INSTI or NRTI included in ART and clinical credibility of subgroup analysis.

We applied the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the quality of the evidence [20, 21]. We presented our results for each primary outcome in a "summary of findings" table.

RESULTS

We identified 1311 articles, from which we selected 23, corresponding to 12 randomized, controlled trials in treatment-naive patients, published from 2009 to 2019 [8, 9, 12, 22–41]. Only ART arms with preferred antiretroviral combinations were selected as follows: 17 arms (6597 participants) for CD4 subgroups and 21 arms (6846 participants) for HIV-1 VL subgroups (Figure 1, Table 1, Supplementary Table 1). Only 2 of the 12 studies were not industry-sponsored [35, 41]. No study had a CD4 count restriction as an inclusion criterion, while HIV-1 VL had to be detectable at different thresholds depending on the clinical trial: >500 [8, 9, 35, 37], >1000 [12, 23, 26, 28, 38, 41], or >5000 copies/mL [25, 30]. Only 1 study had an upper limit of HIV-1 VL (500 000 copies/mL) as an inclusion criterion [12]. The participants were primarily males; females represented a median of 15.5% (interquartile range [IQR], 12.5%–23.2%). Median age was 34 years (IQR, 33–37), the median percentage of HIV-1 VL >100 000 copies/mL was 26.4% (IQR, 20.6%–29.5%), and the median percentage of <200 CD4 cells/μL was 13.4% (IQR, 10.2%–29.1%). Two ART arms used BIC as the anchor drug, 5 used raltegravir (RAL), and 11 used DTG. As for the NRTI backbone, 1 ART arm included 3TC, 3 included abacavir/3TC, 3 included abacavir/3TC or TDF/FTC, 4 included TAF/FTC, and 7 included TDF/FTC.

A pooled analysis of the ART arms showed that starting ART with CD4 <200 vs ≥200 cells/μL or >100 000 copies/mL vs ≤100 000 copies/mL was associated with an increased OR of failure at 48 weeks: OR, 1.94 (95% CI: 1.45–2.61) and OR, 1.75 (95% CI: 1.30–2.35), respectively (Figures 2 and 3). The same increase in the risk of failure was observed at 96 weeks

Table 1. Characteristics and Efficacy Results by Subgroup of the Included Study Arms Included

Author, Year (Study)	Study Arm	Female Sex, n (%)	VL >100 000 (%)	CD4 Count <200 (%)	Median Age, y	Plasma HIV-1 RNA <50 Copies/mL by CD4 Cells/mm^3 and VL Copies/mL at 48 wk; n/N (%)			
						CD4 Cell Count		HIV-1 RNA VL	
						<200	≥200	>100 000	≤100 000
Lennox et al, 2009 (STARTMRK) [30]	RAL400 + TDF/FTC	54 (19.2)	54.4	45.6	37	106/120 (88.3)	135/143 (94.4)	130/143 (90.9)	111/120 (92.5)
Eron et al, 2011 (QDMRK) [25]	RAL400 + TDF/FTC	90 (23.2)	39.4	25.7	38	80/99 (80.8)	262/286 (91.6)	128/152 (84.2)	215/234 (91.9)
Walmsley et al, 2013; Raffi et al, 2015 (SINGLE) [26, 34]	DTG + ABC/3TC	67 (16.2)	32.4	13.8	36	45/57 (78.9)	319/357 (89.4)	111/134 (82.8)	253/280 (90.4)
Raffi et al, 2013, 2015 (SPRING-2) [28, 34]	DTG + ABC/3TC or TDF/FTC[a]	63 (15.3)	27.7	13.4	37	43/55 (78.2)	318/356 (89.3)		
	DTG + ABC/3TC							30/37 (81.1)	115/132 (87.1)
	DTG + TDF/FTC							64/77 (83.1)	152/165 (92.1)
	RAL400 + ABC/3TC or TDF/FTC[a]	56 (13.6)	28.2	12.2	35	34/50 (68.0)	317/361 (87.8)		
	RAL + ABC/3TC							32/39 (82.0)	110/125 (88.0)
	RAL + TDF/FTC							55/77 (71.4)	154/170 (90.6)
Raffi et al, 2015; Clotet et al, 2014 (FLAMINGO) [34, 38]	DTG + ABC/3TC or TDF/FTC[a]	31 (12.8)	25.2	9.5	34	21/23 (91.3)	196/219 (89.5)		
	DTG + ABC/3TC							12/13 (92.3)	59/66 (89.4)
	DTG + TDF/FTC							45/48 (93.7)	101/115 (87.2)
Orell et al, 2017 (ARIA) [37]	DTG/ABC/3TC	248 (100)	27.8	52.4[b]	38	111/130 (85.4)	92/118 (77.9)	55/69 (79.7)	148/179 (82.7)
Gallant et al, 2017 (GS-1489) [9]	BIC/TAF/FTC	29 (9.2)	25.2	9.5	31	30/36 (83.3)	261/278 (93.9)	46/53 (86.8)	243/261 (93.1)
	DTG/ABC/3TC	33 (10.5)	15.9	10.2	32	26/32 (81.2)	266/283 (93.9)	45/50 (90.0)	249/265 (93.9)
Sax et al, 2017 (GS-1490) [8]	BIC/TAF/FTC	40 (12.5)	20.6	13.7	33	42/44 (95.4)	243/276 (88.0)	57/66 (86.7)	229/254 (90.1)
	DTG + TAF/FTC	37 (11.4)	16.6	10.5	34	34/34 (100)	268/291 (92.1)	51/54 (94.4)	252/271 (92.9)
Cahn et al, 2017 (ONCEMRK) [23]	RAL1200 + TDF/FTC	94 (17.1)	28.5	13.4	34	57/67 (85.1)	415/434 (95.6)	124/143 (86.7)	348/358 (97.2)
	RAL400 + TDF/FTC	32 (12.0)	29.5	13.1	35	29/33 (87.9)	206/218 (94.5)	62/74 (83.8)	173/177 (97.7)
Cahn et al, 2019 (GEMINI) [12]	DTG + 3TC	113 (15.8)	19.6	8.8	32	50/63 (79.4)	605/653 (92.6)	129/140 (92.1)	526/576 (91.3)
	DTG + TDF/FTC	98 (13.7)	21.3	7.7	33	51/55 (92.7)	618/662 (93.3)	138/153 (90.2)	531/564 (94.1)
Venter et al, 2019 (ADVANCE) [35]	DTG + TDF/FTC	208 (59)	20.2	32.7	32	99/115 (86.1)	199/236 (84.3)	63/71 (88.7)	235/280 (83.9)
	DTG + TAF/FTC	214 (61)	21.9	29.1	33	86/102 (84.3)	208/249 (83.5)	67/77 (87.0)	227/274 (82.4)
NAMSAL Study Group, 2019 (NAMSAL) [41]	DTG + TDF/FTC	197 (63.5)	66.8	31.3	38	62/97 (63.9)	169/213 (79.3)	137/207 (66.2)	94/103 (91.3)

Abbreviations: 3TC, lamivudine; ABC, abacavir; BIC, bictegravir; DTG, dolutegravir; FTC, emtricitabine; HIV-1, human immunodeficiency virus type 1; RAL400, raltegravir 400 mg; RAL1200, raltegravir 1200 mg; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate and emtricitabine; VL, HIV-1 viral load. Information only available by nucleoside pair for the viral load subgroups.

[a]In the ARIA study, CD4 cell stratification was ≤350 cells/mm and >350 cells/mm (these data were not included in the meta-analysis).

[b]Information only available by nucleoside pair for the viral load subgroups.

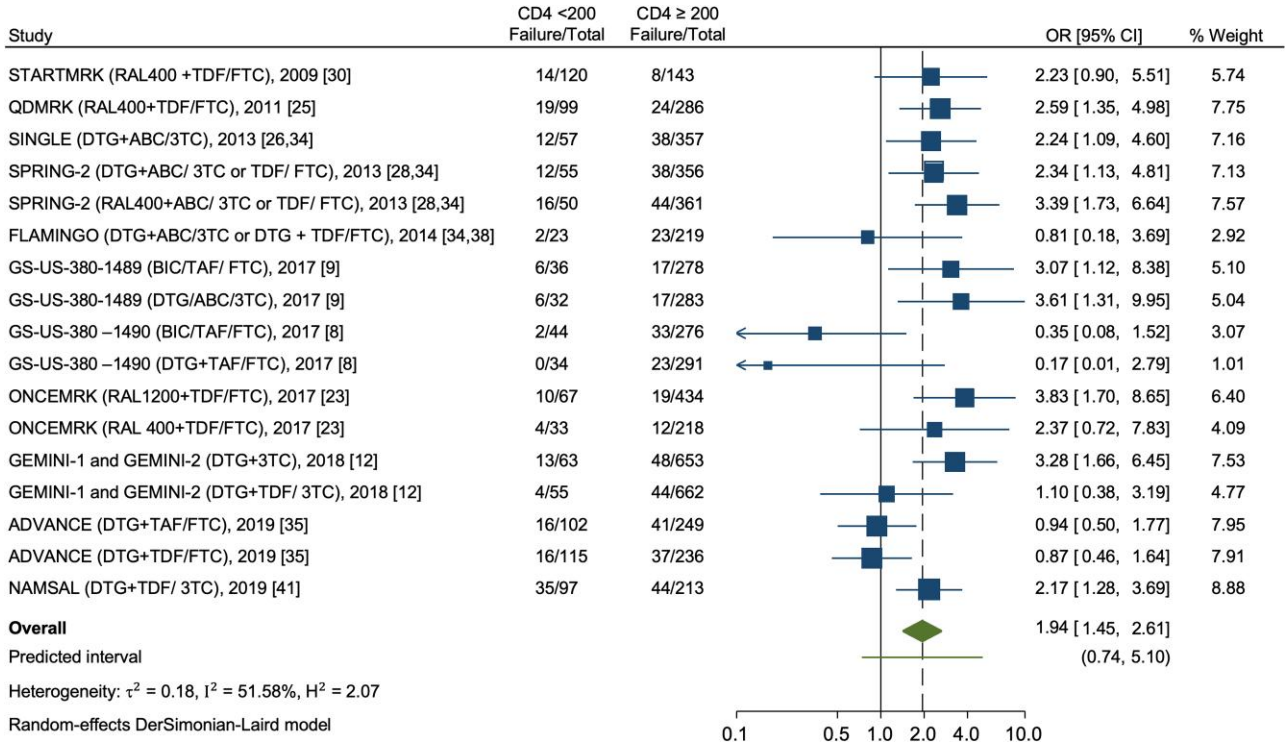


Figure 2. Pooled estimate of antiretroviral treatment failure rate by CD4 cell subgroups (<200 cells/μL vs ≥200 cells/μL) at 48 weeks. Abbreviations: 3TC, lamivudine; ABC, abacavir; CI, confidence interval; DTG, dolutegravir; FTC, emtricitabine; OR, odds ratio; RAL400, raltegravir 400 mg; RAL1200, raltegravir 1200 mg; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

for the CD4 and VL thresholds: OR, 1.46 (95% CI: 1.01–2.11) and OR, 1.54 (95% CI: 1.26–1.88), respectively (Figures 4 and 5). As for studies that analyzed treatment response at the threshold of 500 000 copies/mL, the pooled TF estimation was an OR, 2.73 (95% CI: 1.65–4.53; Figure 6).

When we excluded arms based on DTG plus 3TC from the analysis, pooled estimates were not substantially different. The OR for TF at 48 weeks for the threshold of <200 CD4 cells/μL and >100 000 copies/mL was 1.86 (95% CI:1.37–2.53) and 1.82 (95% CI: 1.35–2.46), respectively, and for TF at 96 weeks, the OR was 1.32 (95% CI: 0.94–1.87) and 1.56 (95% CI: 1.26–1.93), respectively.

We examined sources of heterogeneity that could affect TF estimations. No consistent significant effects on TF rates were observed for the year of publication, the type of NRTI backbone, or the anchor drug (Supplementary Figures 1–11). Sensitivity analyses excluding those studies with lower credibility for clinical decision-making did not significantly affect pooled estimates (data not shown). Likewise, we did not detect publication bias in the funnel plot graphics or with the Egger and Peter tests (Supplementary Figure 12).

We could not evaluate discontinuation rates secondary to adverse events by subgroup (ie, according to CD4 count and HIV VL) because such information was not specified. When analyzed overall for each treatment arm, discontinuation rates, irrespective of their association with the study drugs, were very low and ranged from 0% to 4% at 48 weeks to an additional 1% to 2% at 96 weeks (Supplementary Table 2). There were no remarkable differences between the study arms. As for treatment-emergent resistance mutations at failure, the highest incidence of mutations conferring resistance to INSTI and NRTIs was observed in the study arms that included RAL. In contrast, study arms that included DTG or BIC showed no emerging INSTI resistance mutations at the time of failure, with only 2 patients developing resistance to 3TC (M184V mutation) in the ADVANCE trial (1 at 48 weeks and 1 at 96 weeks) [35, 36].

We graded the certainty of evidence of the primary outcomes using the GRADE approach (Table 2). The evidence was graded as moderate mostly because of inconsistency between study results.

DISCUSSION

The results of our meta-analysis showed that CD4 cell counts <200 cells/μL and VL >100 000 copies/mL were associated with poorer ART outcomes in treatment-naive patients. This effect was consistent for both end points at 48 and 96 weeks and did not seem to be associated with the individual drugs comprising the ART regimen. The consequences of TF were

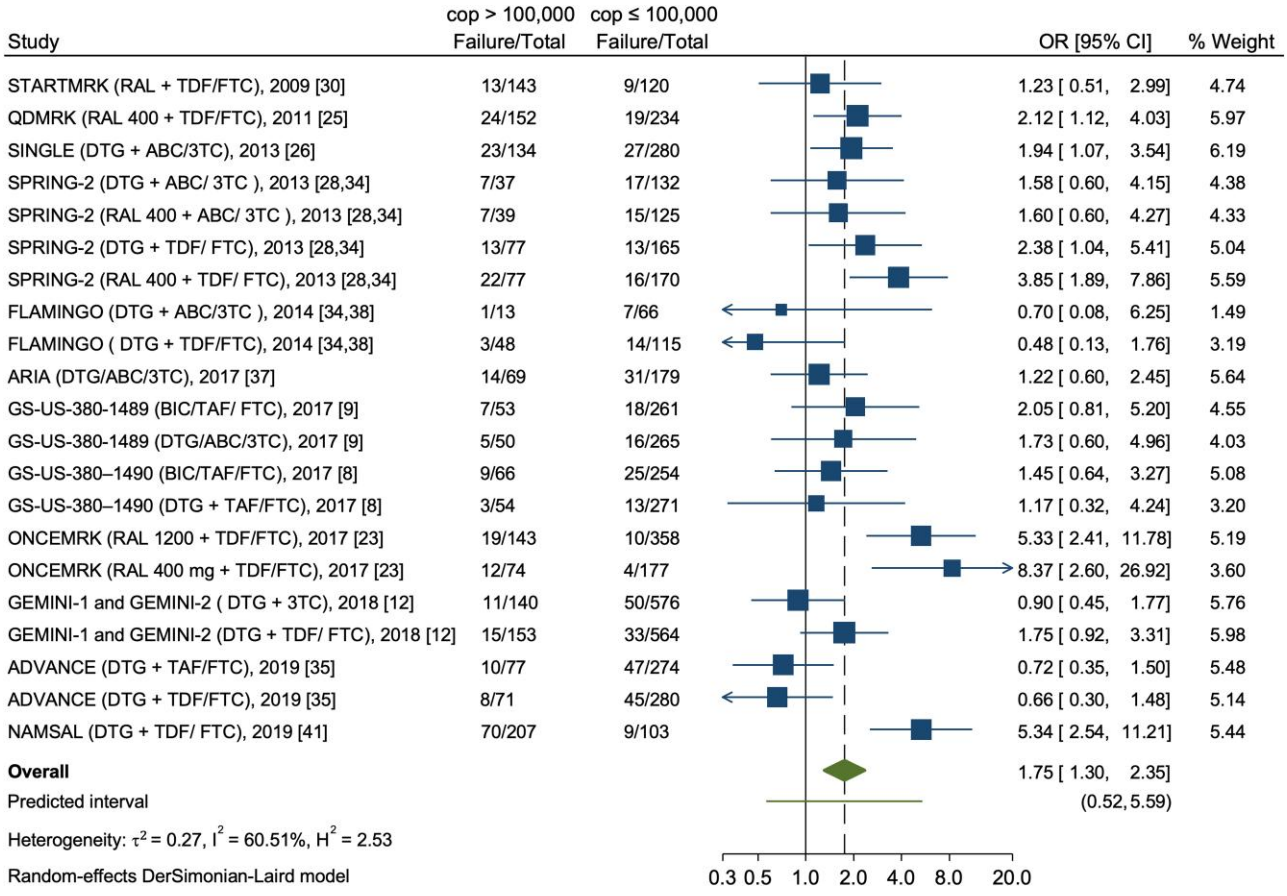


Figure 3. Pooled estimate of antiretroviral treatment failure rate by viral load (>100 000 copies/mL vs ≤100 000 copies/mL) at 48 weeks. Abbreviations: 3TC, lamivudine; ABC, abacavir; CI, confidence interval; cop, copies; DTG, dolutegravir; FTC, emtricitabine; OR, odds ratio; RAL400, raltegravir 400 mg; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

not the same for all regimens, with a higher selection of resistance mutations in RAL-containing arms. However, more information is needed, given the moderate uncertainty of the estimations.

Despite the benefits of early identification and treatment of HIV infection, late diagnosis of HIV remains common in Europe and North America (slightly below 50%), with no significant changes in recent decades [3, 42, 43]. Consequently, median CD4 cell counts at diagnosis or at initiation of ART are generally <350 mm^3 [42, 44]. Late diagnosis of HIV and initiation of ART are widely recognized as a major public health problem that is closely related to increased morbidity and mortality among PWH [4, 5, 45, 46]. In addition, delayed ART leads to poorer immunovirological response [47], increases ART toxicity [48], is a key factor in HIV transmission [49], and has been linked to more intensive use of healthcare resources and increased costs [50].

ART is a potentially modifiable factor with prognostic implications for late diagnosis. A key question is whether a specific combination of drugs may work better in this setting. In 2012, we conducted a meta-analysis in which we found that starting ART with low CD4 counts was consistently associated with poorer outcomes and not with specific antiretrovirals [51]. The OR of undetectable VL at 48 weeks and 96 weeks was lower for those participants who initiated antiretroviral treatment with ≤200 cells/μL vs >200: 0.68 (95% CI: .59–.78) and 0.91 (95% CI: .76–1.08), respectively. In this study, most anchor drugs were boosted protease inhibitors followed by nonnucleoside reverse-transcriptase inhibitor. Ten years later, and with more potent and better-tolerated antiretrovirals, the detrimental effect of low CD4 counts and high VL on response to ART remained unchanged, with no drug regimen performing significantly better than the others. In addition, no integrase inhibitor or nucleoside backbone was significantly associated with a higher likelihood of TF. Although the results are somewhat heterogeneous, the increase in the OR for TF was consistent across many estimations, with few instances falling outside the bounds of the pooled estimates for CD4 cells and VL. The characteristics of the population studied, the way the studies were conducted,

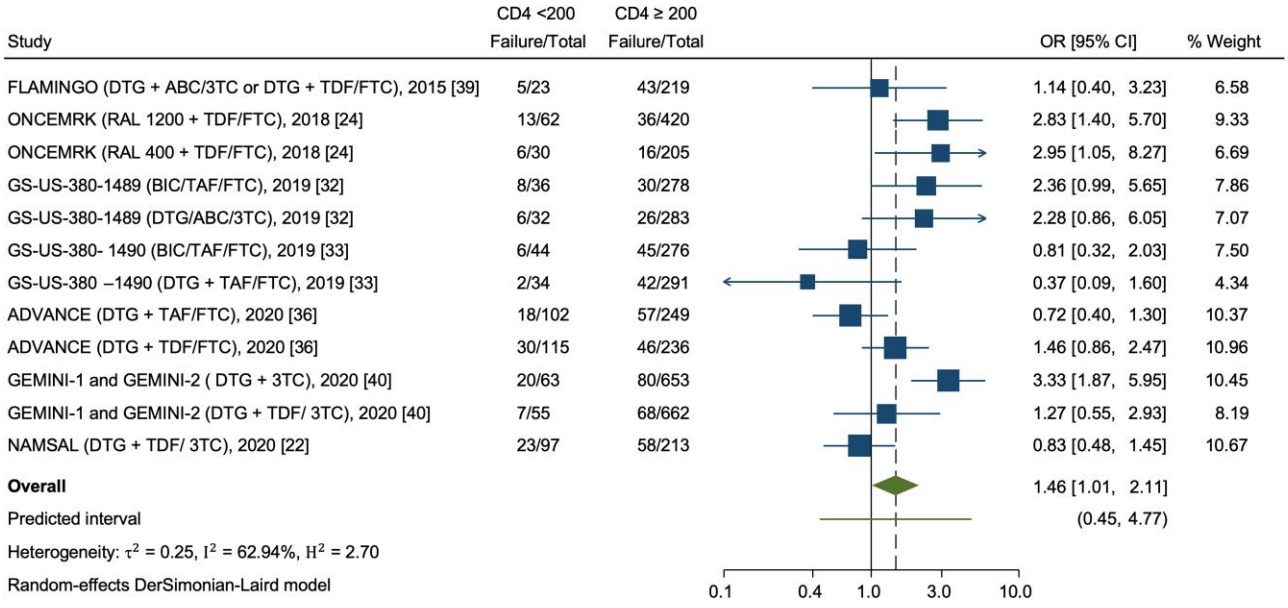


Figure 4. Pooled estimate of antiretroviral treatment failure rate by CD4 cell subgroups (<200 cells/μL vs ≥200 cells/μL) at 96 weeks. Abbreviations: 3TC, lamivudine; ABC, abacavir; CI, confidence interval; DTG, dolutegravir; FTC, emtricitabine; OR, odds ratio; RAL400, raltegravir 400 mg; RAL1200, raltegravir 1200 mg; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

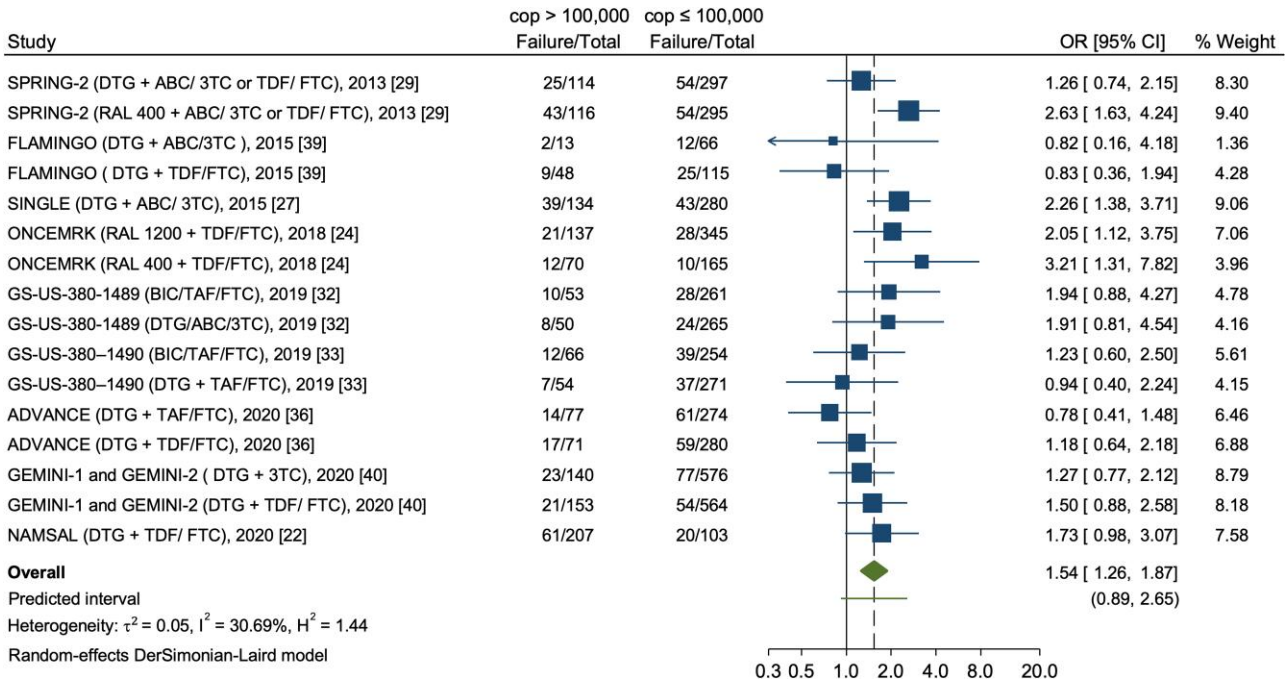


Figure 5. Pooled estimate of antiretroviral treatment failure rate by viral load (>100 000 copies/mL vs ≤100 000 copies/mL) at 96 weeks. Abbreviations: 3TC, lamivudine; ABC, abacavir; CI, confidence interval; cop, copies; DTG, dolutegravir; FTC, emtricitabine; OR, odds ratio; RAL400, raltegravir 400 mg; RAL1200, raltegravir 1200 mg; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

and the small number of patients with CD4 counts <200 cells/μL in some trials may have influenced the variability of the estimates.

RAL-containing arms appear to have been more affected by low CD4 counts and elevated HIV VL. However, this finding should be interpreted with caution given the heterogeneity

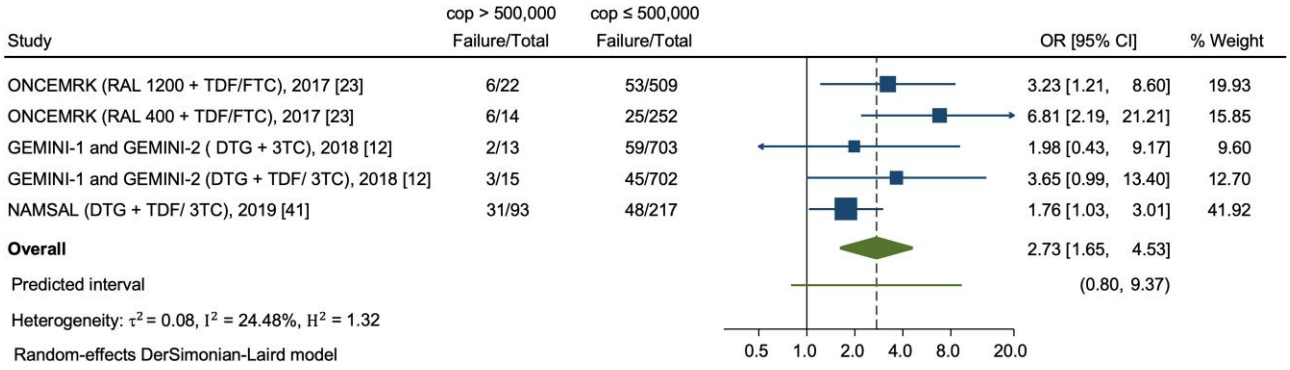


Figure 6. Pooled estimate of antiretroviral treatment failure rate by viral load (>500 000 copies/mL vs ≤500 000 copies/mL) at 48 weeks. Abbreviations: 3TC, lamivudine; CI, confidence interval; cop, copies; DTG, dolutegravir; FTC, emtricitabine; OR, odds ratio; TDF, tenofovir disoproxil fumarate.

Table 2. Summary of Outcomes and Certainty of Evidence

Outcome	No. of Participants	Certainty of the Evidence (GRADE)	Relative Effect (95% Confidence Interval)	Anticipated Absolute Effects: Risk With ≥200 CD4 or VL $<10^5$	Anticipated Absolute Effects: Difference in Risk With ≤200 CD4 or VL $>10^5$
Treatment failure by CD4 cell at 48 wk (<200 vs ≥200)	6597 (17 ART arms)[a]	⊕⊕⊕◯ Moderate[b]	OR 1.94 (1.45–2.61)	92 per 1000	73 more per 1000 (36 more to 118 more)
Treatment failure by CD4 cell at 96 wk (<200 vs ≥200)	4783 (12 ART arms)[c]	⊕⊕⊕◯ Moderate[d]	OR 1.46 (1.01–2.11)	137 per 1000	51 more per 1000 (1 more to 114 more)
Treatment failure by VL at 48 wk (>100 000 vs ≤100 000)	6846 (21 ART arms)[e]	⊕⊕⊕◯ Moderate[f]	OR 1.75 (1.30–2.35)	88 per 1000	57 more per 1000 (23 more to 97 more)
Treatment failure by VL at 96 wk (>100 000 vs ≤100 000)	5914 (16 ART arms)[g]	⊕⊕⊕◯ Moderate[h]	OR 1.54 (1.26–1.87)	142 per 1000	61 more per 1000 (30 more to 94 more)

Based on GRADE. The risk in the group with ≤200 CD4 cells/μL (and its 95% confidence interval [CI]) is based on the assumed risk in the group with >200 CD4 cells/μL and the relative effect of the ART (and its 95% CI).

GRADE Working Group grades of evidence as follows:

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Abbreviations: ART, antiretroviral treatment; CD4, CD4 cell count/μL; GRADE, Grading of Recommendations Assessment, Development and Evaluation; OR, odds ratio; VL, viral load (copies/mL).

Explanations.

[a]Treatment arms corresponding to 11 clinical trials.

[b]Serious inconsistency: I square is 51.6% and prediction interval includes the null effect.

[c]Treatment arms corresponding to 7 clinical trials.

[d]Serious inconsistency: I square is 62.9% and prediction interval includes the null effect.

[e]Treatment arms corresponding to 12 clinical trials.

[f]Serious inconsistency: I square is 60.5% and prediction interval includes the null effect.

[g]Treatment arms corresponding to 9 clinical trials.

[h]Serious inconsistency: I square is 30.7% and prediction interval includes the null effect.

and inconsistency of the results. The highest incidence of emerging mutations inducing resistance to INSTI and NRTI was recorded in study arms with RAL as the anchor drug, showing that the consequences of failure differ depending on the antiretrovirals used. Similarly, for NRTIs, there were no significant differences in the OR for TF between groups that were consistent for the CD4 and VL subgroups. As for the Gemini study, estimates were not significantly different from the pooled results of the VL analysis at 48 and 96 weeks and the CD4 analysis at 48 weeks. The difference observed at 96 weeks in the CD4 subgroup is probably related to a less precise estimation (because of the small number of studies). In fact, the OR for failure was equivalent at 48 and 96 weeks (3.28 vs 3.33).

One limitation of a meta-analysis that examines data from subgroup analyses is that patients are not necessarily randomized by subgroup (ie, CD4 lymphocyte count and HIV-1 VL). Consequently, the groups may not be homogeneous in terms of these and other prognostic factors. Variables such as viral

hepatitis coinfection, HIV transmission group categories, and socioeconomic status could be associated with a poorer response to ART and, simultaneously, with a low CD4 cell count or baseline HIV-1 VL >100 000 copies/mL. Unfortunately, this potential confounding bias cannot be addressed in a meta-analysis of pooled data. The only way to resolve the issue satisfactorily would be to perform a meta-analysis of individual patient data. Nevertheless, the credibility of the subgroup analysis for clinical decision-making was considered appropriate for most studies. Finally, as we did not intend to evaluate the effect of low CD4 count or high HIV-1 VL on treatment efficacy overall but only for recommended first-line regimens, some studies with other treatment regimens were not evaluated.

Prediction intervals for TF estimates in our study at 48 and 96 weeks (Figures 2–6) include the null result, thus reflecting the heterogeneity of some estimates and the fact that the effect size of a new study would range from a decrease to an increase in the risk of TF.

The results of this meta-analysis show that CD4 count <200 cells/μL and HIV VL >100 000 copies/mL impair the efficacy of ART across all the preferred regimens. A definitive answer to whether some drug regimens perform better than others in this demanding scenario would require comparative clinical trials in late presenters. The Laptop study (NCT03696160) and the Dolce study (NCT04880395) are testing different ART combinations in patients with CD4 counts <200 cells/μL. The Laptop study is comparing bictegravir/TAF/emtricitabine with darunavir/cobicistat/TAF/emtricitabine, whereas the Dolce study is comparing DTG/3TC with DTG/tenofovir disoproxil fumarate/emtricitabine or 3TC. The results of these and other studies will increase our understanding of whether specific antiretroviral combinations work best in the demanding setting of severely immunosuppressed patients. Until more information becomes available, our findings can be used when deciding on initiation of antiretroviral therapy. Success of treatment in patients with low CD4 counts and/or high VLs seems to be independent of the drugs included in the ART regimen, provided they are currently recommended first-choice options.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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