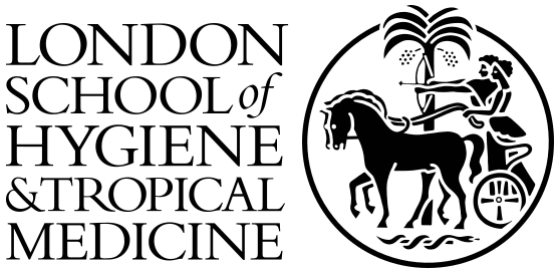

Baseline CD4 Count and Adherence to Antiretroviral Therapy: A Systematic Review and Meta-Analysis

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Background: In light of recent changes to antiretroviral treatment (ART) guidelines of the World Health Organization and ongoing concerns about adherence with earlier initiation of ART, we conducted a systematic review of published literature to review the association between baseline (pre-ART initiation) CD4 count and ART adherence among adults enrolled in ART programs worldwide.

Methods: We performed a systematic search of English language original studies published between January 1, 2004 and September 30, 2015 using Medline, Web of Science, LILACS, AIM, IMEMR, and WPIMR databases. We calculated the odds of being adherent at higher CD4 count compared with lower CD4 count according to study definitions and pooled data using random effects models.

Results: Twenty-eight articles were included in the review and 18 in the meta-analysis. The odds of being adherent was marginally lower for patients in the higher CD4 count group (pooled odds ratio, 0.90; 95% confidence interval, 0.84 to 0.96); however, the majority of studies found no difference in the odds of adherence when comparing CD4 count strata. In analyses restricted to comparisons above and below a CD4 count of 500 cells per microliter, there was no difference in adherence (pooled odds ratio, 1.01; 95% confidence interval: 0.97 to 1.05).

Conclusions: This review was unable to find consistent evidence of differences in adherence according to baseline CD4 count. Although this is encouraging for the new recommendations to treat all HIV-positive individuals irrespective of CD4 count, there is a need for additional high-quality studies, particularly among adults initiating ART at higher CD4 cell counts.

Key Words: adherence, antiretroviral therapy, CD4 count, HIV

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INTRODUCTION

There are 37 million people living with HIV (PLHIV) and more than 17 million people on antiretroviral treatment (ART) globally.[1] In 2015, after the publication of findings from 2 large randomized trials indicating the clinical benefit of starting ART at any CD4 cell count, the World Health Organization (WHO) issued updated guidelines recommending that ART should be started in all HIV-infected adults regardless of CD4 count or WHO stage.[2–6] Current UNAIDS targets for HIV treatment scale-up are for 90% of PLHIV to know their HIV status, 90% of those who know their status to be on ART, and 90% of those on ART to be virally suppressed.[7] Achieving these targets will require rapid further scale-up of testing and ART initiation and excellent adherence to treatment. Although many factors are known to influence adherence,[8] one frequently raised concern in the context of new WHO guidelines is the possibility that individuals starting ART at higher CD4 counts when generally clinically well may have lower adherence rates.[9,10]

Although there is strong evidence from individual-level, randomized, controlled trials for increased patient benefit when routinely initiating ART at CD4 counts greater than 500 cells per microliter, there is limited data informing how ART for all PLHIV will play out in programmatic settings, where the numbers of individuals receiving care and level of resources directed at retaining patients and maximizing adherence is likely to differ from well-resourced randomized trials. Concern has been expressed about potential increases in loss to follow-up, ART nonadherence, sexual disinhibition, and viral resistance among individuals starting treatment earlier, particularly in high-prevalence regions where health facilities are often overburdened.[11,12]

In light of steadily increasing number of adults starting ART at higher CD4 counts when clinically well and recent changes to WHO ART guidelines, we conducted a systematic

review of the published literature that reported the association between baseline CD4 count and adherence among adult patients enrolled in ART programs worldwide.

METHODS

Eligibility

As we were interested in the relationship between baseline CD4 count and adherence in routine program settings, controlled trials were excluded from review. The age of 15 years was used for eligibility because this is the commonly used age cutoff for the management of ART patients at the "adult clinic" for clinical reasons, including drug formulation and dosage. Studies reporting on women starting ART for the prevention of mother-to-child transmission, and use of antiretrovirals for preexposure prophylaxis were also excluded because adherence trends in these populations are not representative of the general population initiating ART.[13,14]

Search Strategy and Study Selection

This study has been designed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[15] We performed a systematic search of English language, original studies published between January 1, 2004 and September 30, 2015 for studies reporting on ART adherence among adults aged ≥15 years according to baseline CD4 count. A limit of January 2004 was used to align with the start of the ART rollout in public health systems in many high-burden countries. Baseline CD4 count was defined as the most recent CD4 count reported before initiating ART and the publishing authors definition of adherence was used for each included study. Medline, Web of Science, LILACS, AIM IMEMR, and WPIMR databases were searched using a compound search strategy incorporating terms for antiretrovirals, adherence, and CD4 count defined in a study protocol (available from the corresponding author). Published abstracts from all Conferences of the International AIDS Society and the Conference on Retroviruses and Opportunistic Infections were searched from 2011 to 2015 to identify data that may have been presented but not yet published in full.

Selection of Studies and Data Extraction

The primary investigator (P.B.) conducted all searches and reviewed all relevant abstracts, conference presentations,

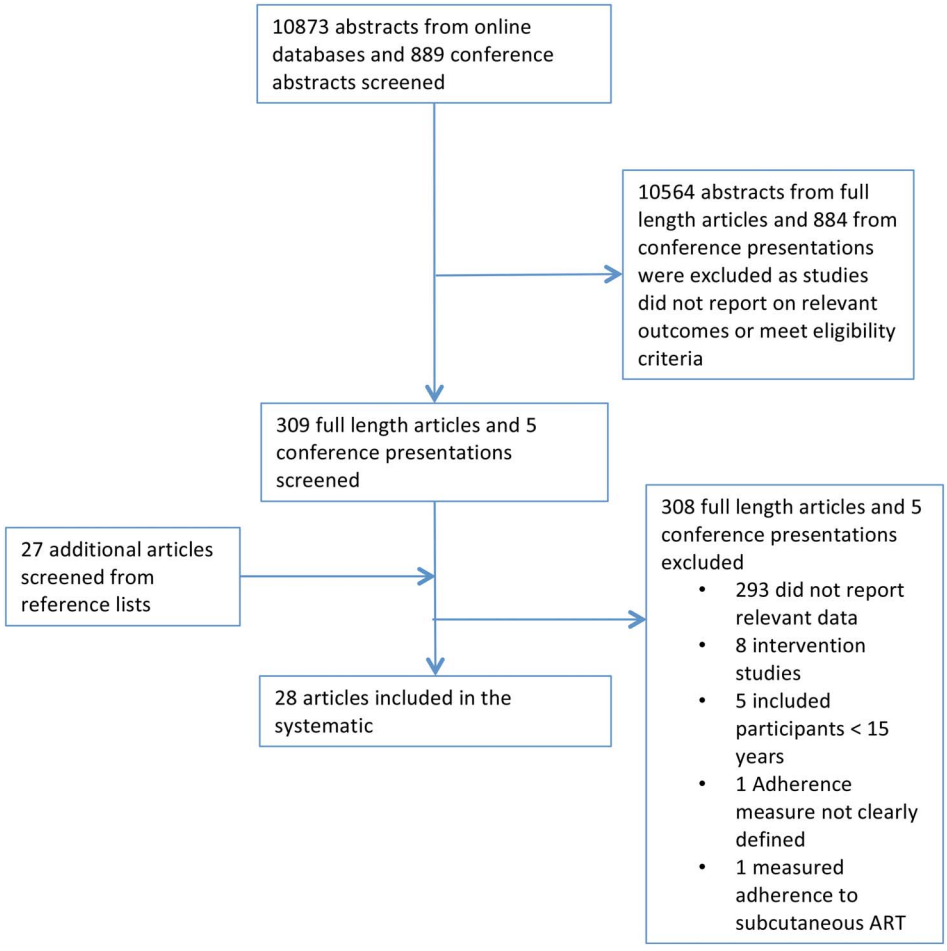

FIGURE 1. Study selection process.

and full-length articles. All steps in the search process were verified by a second investigator (A.N. or A.J.) (Fig. 1). Disagreements were resolved through consensus. Data extraction followed the same verification procedure, and it included patient and program characteristics according to a predefined data extraction form. Where studies reported both subjective and objectives measures of adherence, the objective measure was used based on the assumption that this was likely to be more accurate. Risk of bias was assessed by the assessment of the following criteria: (1) objective versus subjective adherence measure, (2) baseline differences (other than CD4 count) balanced or adjusted for at analysis, (3) prospective versus retrospective or cross-sectional study design, and (4) and nondifferential loss to follow-up with respect to likelihood of being adherent. We used GRADE to assess the overall quality of the evidence.[16]

Data Analysis

Our primary effect measure was the odds of being adherent at higher CD4 count compared with lower CD4 count as defined by the studies. Studies that provided raw data on the number of adherent patients or odds ratios (ORs) for adherence by CD4-cell count strata were included in a meta-analysis that estimated ORs and corresponding 95% confidence intervals (CIs) comparing adherence at lower and higher CD4 counts at baseline; data were pooled using a DerSimonian and Laird[17] random effects model. Where studies reported multiple CD4 count group comparisons, we included data from the comparison of the lowest and highest CD4 count groups. Where studies reported ORs adjusted for potential confounders, these estimates were used; otherwise, crude estimates were used as indicated in Figure 2. Because the I^2 statistic does not work well with observational studies,[18] heterogeneity was assessed by visual inspection of forest plots. Predefined subgroup analyses were run to explore potential differences by income status (as defined by World Bank Income Classification)[19]; we further undertook a post hoc subgroup analysis to assess the potential influence of the 2010 WHO guideline change in treatment eligibility (from CD4 200 cells/μL to 350 cells/μL) by assessing differences before and after 2010. We used STATA version 12.0 (StataCorp LP, College Station, TX) for all analysis. All P values were 2 sided, with a P value less than 0·05 regarded as statistically significant.

RESULTS

From an initial screen of more than 10,873 abstracts, 27 full-length articles met the inclusion criteria[20–46]; 1 additional article was identified from bibliography screen,[47] yielding 28 articles in total included in this review (Fig. 1 and Table 1). The majority of studies (18) were from low-income and middle-income countries.[20–22,24,25,27–30,33–35,40–44,46] Studies provided data for 72,119 participants, sample sizes ranged from 76 to 3700 adults, with 31,011 men and 40,669 women included (1 study did not disaggregate data by sex).[46] Median baseline CD4 count ranged from 104 to 486 cells per microliter and was

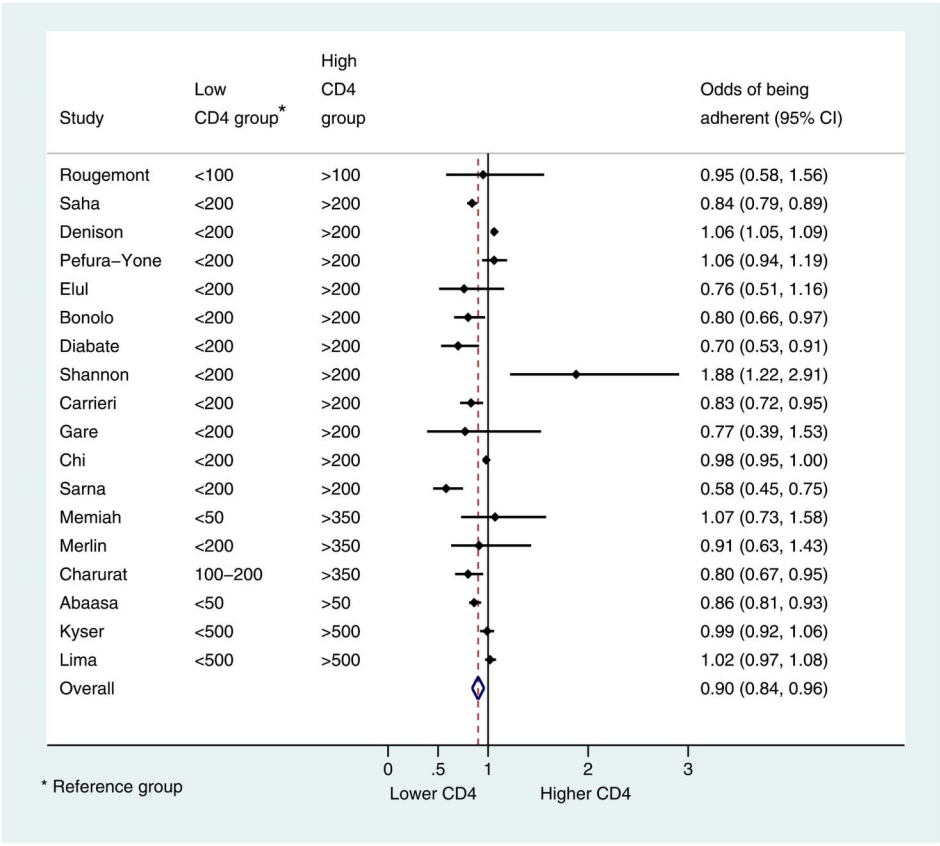

FIGURE 2. Forest plot of the odds of being adherence when comparing patients who started ART in the higher CD4 category with those who start ART in the lower baseline CD4 category.

TABLE 1. Overview of Review Studies

First Author	Publication Year	Country	Study Type	No. Participants	Period of Initiating ART
Abaasa[20]	2008	Uganda	Retrospective cohort	897	2004–2006
Bonolo Pde[21]	2005	Brazil	Prospective cohort	306	Not indicated
Byakika-Tusiime[22]	2013	Uganda	Prospective cohort	76	2002–2007
Carrieri[23]	2006	France	Prospective cohort	1110	1997–1999
Charurat[24]	2010	Nigeria	Retrospective cohort	5760	2005–2006
Chi[25]	2009	Zambia	Retrospective cohort	37,039	2004–2007
Conen[26]	2013	Switzerland	Retrospective cohort	2928	2005–2012
Deloria-Knoll[47]	2004	United States	Cross-sectional survey within cohort	255	March–Nov 1999
Denison[27]	2015	Tanzania, Uganda, and Zambia	Cross-sectional survey within cohort	4489	2004–2010
Diabate[28]	2007	Cotê d'Ivoire	Prospective cohort	591	2005
Elul[29]	2013	Rwanda	Cross-sectional survey within cohort	1951	2002–2007
Gare[30]	2015	Papua New Guinea	Cross-sectional survey within cohort	102	2004–2011
Kyser[31]	2011	United States	Retrospective cohort	528	2004–2006
Lima[32]	2015	Canada	Retrospective cohort	4120	2000–2012
Maqutu[33]	2010	South Africa	Retrospective cohort	688	2004–2006
Maqutu[34]	2011	South Africa	Retrospective cohort	688	2004–2006
Memiah[35]	2013	Nigeria, Uganda, Zambia, and Tanzania	Cross-sectional survey within cohort	2344	2004–2005
Merlin[36]	2012	United States	Retrospective cohort	1521	2007–2011
Moore[37]	2010	Canada	Retrospective cohort	1707	2000–2006
Murphy[38]	2013	United States	Retrospective cohort	2090	1994–2002
Palepu[39]	2006	Canada	Retrospective cohort	276	1996–2003
Pefura-Yone[40]	2013	Cameroon	Cross-sectional survey within cohort	889	Before 2011
Ramadhani[41]	2007	Tanzania	Retrospective cohort	150	2005
Rougemont[42]	2009	Cameroon	Prospective cohort	312	2006
Saha[43]	2014	India	Cross-sectional survey within cohort	370	2005–2006
Sarna[44]	2008	India	Cross-sectional survey within cohort	310	2004
Shannon[45]	2006	Canada	Retrospective cohort	184	Before 2002
Weiser[46]	2014	Uganda	Prospective cohort	438	2005–2010

First Author	Minimum Age of Participant (yrs)	Median Age of Participant (yrs)	Median Baseline CD4 Cell Count (Cells/mL)	Adherence Measure	Adherence Cutoff (%)	Overall Reported Adherence (%)
Abaasa[20]	15	37	Not indicated	Self report: VASand pill count	95	78
Bonolo Pde[21]	18	Not indicated	Not indicated	Self report: 3 d recall	95	Not indicated
Byakika-Tusiime[22]	15	36	56	Self report: VAS and number of doses missed	Linear	96
Carrieri[23]	Not indicated	37	Not indicated	Self report: 4 d recall	100	63
Charurat[24]	Not indicated	35	121	Pharmacy pill count	95	25
Chi[25]	15	Not indicated	132	MPR based on pharmacy pill count	100	63
Conen[26]	16	39	269	Unscheduled treatment interruption	No interruption ≥7 mo	85
Deloria-Knoll[47]	Not indicated	41	229 and 234	Self report: 3 d recall	Not indicated	NA
Denison[27]	18	40	Not indicated	Self report: treatment interruption	No interruption ≥48 h	96.8
Diabate[28]	Not indicated	36 to 39	124	Self report: 4 d recall	95	74
Elul[29]	18	38	130 to 221	Self report: 3 and 30 d recall	100	94 and 78 at 3 and 30 d
Gare[30]	20	Not indicated	264	Self report: 1 mo and pill count	100	82
Kyser[31]	18	41	486	Self report: 3 d recall	95	84
Lima[32]	19	42	Not indicated	Pharmacy pill count	95	70 to 80
Maqutu[33]	Not indicated	32.5	108	Pharmacy pill count	95	79

(*continued on next page*)

TABLE 1. (*Continued*) Overview of Review Studies

First Author	Minimum Age of Participant (yrs)	Median Age of Participant (yrs)	Median Baseline CD4 Cell Count (Cells/mL)	Adherence Measure	Adherence Cutoff (%)	Overall Reported Adherence (%)
Maqutu[34]	Not indicated	32.5	107	Pharmacy pill count	95	58 at 1 mo to 86 at 17 mo
Memiah[35]	16	38	227	Self report: 7 d recall	95	76
Merlin[36]	19	44	NA	Self report: 2 wk recall	100	71
Moore[37]	18	39 to 43	150 and 170	Unscheduled treatment interruption -3 mo	No interruption ≥3 mo	61 to 81
Murphy[38]	18	39 to 41	206 to 221	Self report	95	73–80 across race groups
Palepu[39]	Not indicated	35.3 to 36.3	270 and 229	Pharmacy pill count	95	50
Pefura-Yone[40]	18	40	122	Self report: case index	Case index score >10	78
Ramadhani[41]	18	41	114	Self report: questionnaire	100	16
Rougemont[42]	18	37	104	Pharmacy pill count	100	85
Saha[43]	18	34	241	Self report: 4 d recall	100	88
Sarna[44]	18	36 to 39	Not indicated	Self report: 4 d recall	90	93
Shannon[45]	16	42	270	Pharmacy pill count	95	30
Weiser[46]	18	38	137	Self report: VAS	90	61

MPR, medicine possession ratio; VAS, visual analogue scale.

<200 cells per microliter for 12 studies.[21,23,25,27–31,40,43–45] Twenty-seven studies reported adherence as a binary outcome and one as a linear outcome, detail of which is presented in Table 1.[22] Twelve used <95% adherence to antiretroviral doses as a threshold for poor adherence, 2 used <90%, and 8 used <100%. Three studies reported on unscheduled treatment interruption of 2 days, 7 days, and 3 months, respectively.[26,27,37] One cross-sectional study used a case index score generated by a questionnaire of greater than "10" to generate a binary definition of adherence versus nonadherence (case index score <10).[40] None of the studies specifically assessed adherence by CD4 count as the primary outcome.

Studies varied in their reporting of adherence with respect to time on ART. The majority of studies in this review presented multiple pooled estimates of adherence measurements from individuals on ART for durations ranging from 0 to >7 years. Two studies reported adherence from initiation to a cutoff time on ART (1 month and 6 months).[33,42] A further 9 studies excluded participants on ART for less than 3,[24,30] 6,[27,29,41] or 12[23,25,28] months of ART. Where studies reported adherence at multiple time points, the data at the measurement taken at the longest duration of ART was used for analysis.

Risk of bias was judged to be moderate based on the characteristics outlined below (see Supplemental Digital Content, http://links.lww.com/QAI/A841). Retrospective designs (21 studies) and subjective measures of adherence (16 studies) were used most commonly. In the majority (24 studies), baseline differences other than CD4 counts were balanced at baseline or adjusted for in analysis; loss to follow-up was judged to be nondifferential with respect to adherence in 5 of the 10 studies, where the relevant information was provided. Overall, the quality of the evidence was judged to be low.

Eighteen studies provided data on 62,823 participants that could be included in the meta-analysis,[20,21,23,24,27–32,35,36,40,42,44,45,48,49] among which 11 provided adjusted estimates (Fig. 2).[20,23–25,28,29,31,35,36,42,44] Overall, the odds of being adherent was slightly lower for patients in the higher CD4 count group (pooled OR, 0·90; 95% CI: 0·84 to 0·96); however, the majority of studies found no difference in the odds of adherence comparing lower and higher CD4 count strata, and there was little evidence of heterogeneity (Fig. 2). Results were not different when studies were restricted to comparisons above and below a CD4 count of 200 cells per microliter (pooled OR, 0·88; 95% CI: 0·80 to 0·96) compared with higher thresholds. When restricting the analysis to studies reporting adherence above and below 350 cells per microliter, results were again similar to the overall result (3 studies; pooled OR, 0·85; 95% CI: 0·73 to 0·97)[24,35,36]; however, 2 of the 3 studies contributing to this analysis found no difference in adherence.[35,36] Two studies compared adherence above and below 500 cells per microliter and found no difference in adherence (pooled OR, 1·01; 95% CI: 0·97 to 1.05).[31,32] Subgroup analysis by income classification found decreased adherence at higher CD4 counts in low-income and middle-income countries (OR, 0·88; 95% CI: 0·80 to 0·96), whereas for high-income countries, there was no difference (OR, 0·97; 95% CI: 0·87 to 1·07). Studies published before 2010 found decreased adherence at higher CD4 counts (OR, 0.85; 95% CI: 0.76 to 0.93), whereas studies published after 2010 found no difference (OR, 0·97; 95% CI: 0·87 to 1·07).

Five studies from low-income and middle-income settings,[22,33,34,41,46] and 5 from high-income settings[26,37–39,45] provided insufficient data for inclusion in the meta-analysis. Of these, 7 studies presented adjusted ORs of the association between adherence and a numerical baseline CD4 count[22,26,33,34,38,39,46]; one presented adjusted ORs of adherence by median baseline CD4 count[41] and a further 2 studies[37,47] presented a crude comparison of median baseline CD4 between adherent and nonadherent

TABLE 2. Overview of Data From Studies Not Included in the Meta-Analysis

Author	Year	Country	Measure of Baseline CD4	Adjusted Analysis	Association With Adherence
Deloria-Knoll	2004	United States	Median CD4 count comparison between adherent and nonadherent groups	No	Mean baseline CD4: adherent group = 378 cells/mL. Nonadherent group = 336 cells/mL; $P = 0.18$
Byakika-Tusiime	2013	Uganda	Numerical baseline CD4 count	Yes	Adjusted OR, 0.99 (95% CI: 0.997 to 0.999)
Conen	2013	Switzerland	Baseline CD4 cell count per 100 cells/mL increase	Yes	Adjusted OR, 1.20 (95% CI: 1.14 to 1.26)
Maqutu	2010	South Africa	Numerical baseline CD4 count	Yes	Adjusted OR, 0.995 (95% CI: 0.992 to 0.999)
Maqutu	2011	South Africa	Numerical baseline CD4 count	Yes	Adjusted OR, 1.000 (95% CI: 0.998 to 1.001)
Moore	2010	Canada	Median CD4 count comparison between adherent and nonadherent groups	No	Median baseline CD4: adherent group = 150 cells/mL. Nonadherent group = 170 cells/mL; $P < 0.001$
Murphy	2013	United States	Baseline CD4 cell count per 100 cells/mL increase	Yes	Adjusted OR, 1.07 (95% CI: 1.01 to 1.14)
Palepu	2006	Canada	Baseline CD4 cell count per 100 cells/mL increase	Yes	Adjusted OR, 0.90 (95% CI: 0.83 to 0.99)
Ramadhani	2007	Tanzania	Baseline median CD4 count	Yes	Adjusted OR, 1.0 (95% CI: 1.0 to 1.0)
Weiser	2014	Uganda	Baseline CD4 cell count per 100 cells/mL increase	Yes	Adjusted OR, 0.90 (95% CI: 0.78 to 1.05)

groups. The results of these studies are presented in Table 2. Overall median baseline CD4 count ranged from 56 to 270 cells per microliter, and 6 studies reported a median CD4 count of <200 cells per microliter.[22,33,34,37,41,46] Two studies showed increased adherence with increased CD4 count (1·01 to 1·14 per 100 cells per microliter increase in baseline CD4 count),[26,38] 4 studies reported a decrease in adherence at higher CD4 count,[22,33,37,39] and 4 reported no difference.[34,41,46,47]

DISCUSSION

Overall, the findings of this review showed decreased adherence at higher baseline CD4 count (OR, 0.90; 95% CI: 0.84 to 0.96), although results were inconsistent across studies. Of the 28 studies, 15 showed an individual difference with 11 reporting decreased adherence[20–24,28,33,37,39,43,44] and 4[26,27,38,45] reporting increased adherence at higher baseline CD4 count. The odds of being adherent ranged from 0.58 (95% CI: 0.45 to 0.75)[44] to 1.8 (95% CI: 1.22 to 2.91).[45] Interpretation of these findings is limited by variability in the definition of higher and lower CD4 count categories between studies. When studies were restricted to a threshold of >500 vs ≤500 cells per microliter, no differences were observed.

Reported barriers to adherence are multifactorial. A recent systematic review of the predictors of adherence identified a number of factors associated with adherence, including self-efficacy, substance use, depressive symptoms, concerns about ART, beliefs about the utility of ART, satisfaction with the care provider, stigma, and social support.[50] Qualitative studies have identified a number of patient-reported barriers to adherence, including forgetfulness, limited understanding of the importance of treatment, drug side effects, pill burden, disruptions to daily routine, and competing priorities.[51] Some studies have reported that feeling sick is a more frequent barrier to adherence than feeling healthy[52]; this may in part be related to the higher pill burden associated with the treatment of comorbodities.[53] The relationship between baseline CD4 count and adherence to ART is complex and contextual, and other factors are likely as important or more important in determining adherence, as suggested by the variability in adherence levels between studies included in this review. Although adherence counseling needs to be adapted to respond to the growing number of people starting ART without having experienced an illness event, focusing on any single factor as the cause of poor adherence is unlikely to lead to the necessary support for patients in a way that will lead to optimal health outcomes over time.

Strengths of this review include the comprehensive search of the available literature that allowed us to assess outcomes among over 72,000 adults initiating ART. Nevertheless, the findings of this review are judged to be based on low-quality evidence. This was driven in large part by differences in CD4 count thresholds and adherence definitions applied between studies, which to a degree reflect differences in ART initiation thresholds applied in different settings. We present forest plots to display between-study heterogeneity and used random effects models. Another limitation with respect to informing current ART guideline changes is that many of the studies included in this review were done at a time when ART was initiated at a low threshold of CD4 count 200 or 350 cells per microliter.[2] In such settings, patients initiating ART at higher CD4 counts represent specific patient populations (eg, pregnant women or tuberculosis-HIV coinfected patients) who may not be representative of the broader patient population, and only 4 studies adjusted for the presence of WHO defining illness at ART initiation in the analysis of adherence.[23,25,40,42] Duration of ART may also be an important factor affecting adherence, although this relationship was inconsistent with some studies showing an increased adherence over time[54] and some showing a decreased adherence.[24,32] Therefore, a further

important limitation is the marked heterogeneity and the lack of reporting of the duration on ART at which adherence was measured.

In conclusion, this review was unable to find strong evidence supporting consistent differences in adherence according to baseline CD4 count, particularly at CD4 counts >500 cells per microliter. Although this may be encouraging for the implementation of the new WHO ART guidelines, the quality of the limited published evidence to date is variable. Further studies with improved standardization of methods for monitoring and reporting ART adherence are therefore encouraged as HIV programs shift toward starting treatment irrespective of immune status.

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