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SYSTEMATIC REVIEW AND META-ANALYSIS

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Adherence to Antiretroviral Therapy and Virologic Failure

A Meta-Analysis

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Abstract: The often cited need to achieve ≥95% (nearly perfect) adherence to antiretroviral therapy (ART) for successful virologic outcomes in HIV may present a barrier to initiation of therapy in the early stages of HIV.

This meta-analysis synthesized 43 studies (27,905 participants) performed across >26 countries, to determine the relationship between cut-off point for optimal adherence to ART and virologic outcomes.

Meta-analysis was performed using a random-effect model to calculate pooled odds ratios with corresponding 95% confidence intervals.

The mean rate of patients reporting optimal adherence was 63.4%. Compared with suboptimal adherence, optimal adherence was associated with a lower risk of virologic failure (0.34; 95% CI: 0.26–0.44). There were no significant differences in the pooled odds ratios among different optimal adherence thresholds (≥98–100%, ≥95%, ≥80–90%). Study design (randomized controlled trial vs observational study) (regression coefficient 0.74, 95% CI: 0.04–1.43, $P < 0.05$) and study region (developing vs developed countries; regression coefficient 0.56, 95% CI: 0.01–1.12, $P < 0.05$) remained as independent predictors of between-study heterogeneity, with more patients with optimal adherence from developing countries or randomized controlled trials experiencing virologic failure.

The threshold for optimal adherence to achieve better virologic outcomes appears to be wider than the commonly used cut-off point (≥95% adherence). The cut-off point for optimal adherence could be redefined to a slightly lower level to encourage the prescribing ART at an early stage of HIV infection.

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Abbreviations: AIDS = acquired immunodeficiency syndrome, ART = antiretroviral therapy, CAM = comprehensive meta-Analysis, HDI = United Nations human development index, HIV = human immunodeficiency virus, MEMS = medication event monitoring system, NNRTIs = nonnucleoside reverse transcriptase inhibitors, NRTIs = nucleoside/nucleotide reverse transcriptase inhibitors, PIs = protease inhibitors, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RevMan = review manager, RNA = ribonucleic acid, SD = standard deviation.

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INTRODUCTION

HIV/AIDS has been transformed into a manageable chronic disease with the advent of combination antiretroviral therapy (ART) initiated as the standard of care.[1] Three classes of HIV medications have been widely used in combination—nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs).[1] Despite the availability of effective treatment options, suboptimal adherence to treatment can result in insufficient viral suppression and promote the emergence of drug-resistant viral strains, resulting in regimen failure, progression to AIDS, and death.[2–4] Paterson et al suggested that at least 95% adherence to unboosted PIs was required for virologic suppression.[5] This 95% adherence cut-off point, based on what is now obsolete therapy, has been widely used as the level of optimal adherence needed to be met by patients taking newer agents and their combinations. The concern that patients may not achieve a near-perfect adherence presents a barrier for initiation of therapy in the early stages of HIV.[6]

This meta-analysis integrated finding from observational studies on ART adherence with 2 objectives: (a) to critically evaluate the association between optimal adherence to ART and virologic outcomes, and (b) to use meta-regression to determine methodological, regimen, and population factors that could moderate the relationship between adherence and virologic outcomes.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement in conducting this meta-analysis.[7] Studies eligible for inclusion were randomized controlled trials, retrospective analyses of data from trials, and cohort studies measuring the relationship between medication adherence to ART and virologic failure.

Search Strategy

WB carried out systematic literature searches of the electronic databases MEDLINE via PubMed, Cochrane Clinical Trials, and EMBASE from their inception date to 17 April 2015. This search used combinations of the following key words: medication adherence, patient compliance, antiretroviral therapy, antiretroviral agent, antiretroviral treatment, protease inhibitors, non-nucleoside reverse transcriptase inhibitors, virologic failure, and viral load. The reference lists of all articles included in this meta-analysis were also searched. Review articles, editorials, commentaries, government reports, and guidelines were excluded from this review. Titles and abstracts

of potentially relevant articles were screened independently by WB and YM. Full articles of potentially appropriate citations were screened for inclusion in this review if they fulfilled the following criteria: original research, participants aged 16 years or older, having a clear definition of medication adherence measurement and clear cut-off points for optimal and suboptimal adherence, and virologic failure stratified by optimal and suboptimal medication adherence groups. Ethical approval was not required as this study was based on published data and had no direct access to patient information.

Data Collection and Outcome Measures

WB extracted data using standardized forms, with recording of authors, year of publication, country of study, study type, regimen, method of adherence measurement, cut-off points for good adherence, and virologic failure. The data were verified by a second reviewer (YM). Disagreements between reviewers were resolved through discussion until a consensus was reached. Study authors' grouping of patients into optimal and suboptimal adherence using the most objective measure was used. When a study reported >1 adherence measurement, the most reliable adherence measurement data was used, with reliability defined in following order: medication event monitoring system (MEMS) > pill count > pharmacy refill > self-reported adherence in the past week > self-reported adherence in the past month. When the number of virologic failures within each adherence group was not reported, we calculated virologic failure from the information provided in the paper or contacted the corresponding author. Studies were excluded when it was not possible to obtain virologic failure data in each adherence group. The United Nations Human Development Index (HDI) ranking was used to categories studies into low and high human development groups.[8]

Statistical Analyses

The data were analyzed using Review Manager (RevMan) version 5.3 (Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, 2014) and Comprehensive Meta-Analysis (CAM) version 3.3.070 (Biostat, Englewood, NJ). Each class of antiretroviral was considered in a separate analysis of the association between adherence and virologic failure in randomized clinical trials. Results are presented based on 9 categories, including study region, antiretroviral regimen, treatment experience, virologic failure cut-off points, adherence cut-off points, adherence measurement, study design, observation period, and year of publication. Adherence pooled odds ratios and 95% confidence intervals were calculated using a random effect model (DerSimonian and Lard)[9] that accommodated the random variation within studies and between-studies.[10]

Heterogeneity between-studies were examined using the Q and I^2 statistics.[9,11] The odds ratio was plotted against the inverse of standard error to identify the risk of publication bias by visually assessing the symmetry of funnel plots. Statistical significance was confirmed using Egger's test,[12] with a P value <0.05 considered suggestive of publication bias. A meta-regression was performed to examine major moderators of the between-studies heterogeneity. Results with P values <0.1 from univariate analyses were included in the multivariate meta-regression model.

RESULTS

Overall, 1796 studies were identified, of which 1449 were excluded after review of the title and abstract (Figure 1). The full text of the remaining 347 citations was screened, and 43 studies with 27,905 participants met the inclusion criteria. The included studies had wide a variation in sample sizes (range = 34–3607, mean = 649, SD = 805) and a slight majority of participants were men (57%). Twenty-five studies were prospective studies[5,13–36] that reported virologic failure according to adherence group. The remaining studies were randomized controlled trials (11)[37–47] and retrospective studies (7).[48–54] Characteristics of the included studies are shown in Table 1.

With respect to location, 14 studies were conducted in sub-Saharan Africa; 9 in the US; 6 in Canada; 5 in Europe; 5 in Asia; 1 in Australia; and 3 studies in several countries. Twenty-two (49%) studies included only treatment-naive patients and the remaining 21 studies included both treatment-naive and/or treatment-experienced patients. All studies reported cut-off points for optimal adherence and virologic failure. Thirty studies (70%) defined optimal adherence as ≥95%, with the remainder using 100%, 98%, 90%, 85%, and 80% as the cut-off points. Optimal adherence rates varied greatly across studies, partially due to the use of these different cut-off points and also different methods of measurement to assess adherence. The mean rate of achieving optimal adherence in adults was 63.4% (standard deviation [SD] = 23.7, range 5% to 97%, n = 43).

Meta-analysis and Meta-regression

Of a total 27,905 participants, 22,740 participants had a viral load and adherence measurement; 7056 (31%) had virologic failure. Overall, 3464 of 15,067 participants with optimal adherence to ART (23%), and 3592 of 7673 participants with suboptimal adherence (47%) participants had virologic failure (Figure 2). The pooled odds ratio for virologic failure for optimal adherence compared to suboptimal adherence was 0.34 (95% CI: 0.26–0.44). A high degree of heterogeneity was found: Q statistic $P < 0.001$ and $I^2 = 90\%$. The funnel plot did not show asymmetry (Figure 3), and the result of Egger's test was not statistically significant ($P = 0.68$). We conducted subgroup analyses to recalculate the pooled odds ratio according to study design, HDI rank, regimen, treatment experience, viral load cut-off points, adherence measurement, and adherence cut-off points (Table 2).

The results of univariate meta-regression analyses for different moderators are shown in Table 3. Based on virologic failure cut-off points, studies were classified into three sets including: ≤100 copies/mL, 11 studies (N = 5646); between 100 copies/mL and 400 copies/mL, 17 studies (N = 9351); and between 500 copies/mL and 1000 copies/mL, 14 studies (N = 7383). The pooled odds ratio for virologic failure for optimal adherence compared to suboptimal adherence for the studies with the lowest virologic failure cut-off was higher (0.55; 95% CI: 0.41–0.74, $I^2 = 56\%$) than for the studies with an intermediate virologic failure cut-off (0.37; 95% CI: 0.26–0.54, $I^2 = 88\%$). The group using a virologic failure cut-off >500 copies/mL had the lowest pooled odds ratio for virologic failure (0.25; 95% CI: 0.16–0.41, $I^2 = 92\%$). Studies with the lowest virologic failure cut-off reported a significantly different pooled odds ratio compared with studies with a virologic failure cut-off > 500 copies/mL (regression coefficient −0.75; 95% CI: −1.39 to −0.12, $P = 0.02$).

According to participants' treatment experience, studies were grouped into 3 sets: treatment-naive patients only, 22 studies (N = 17,010); treatment-experienced patients only, 12 studies (N = 4009), and both treatment-naive and experienced patients, 9 studies (N = 1721). The pooled odds ratio for optimal

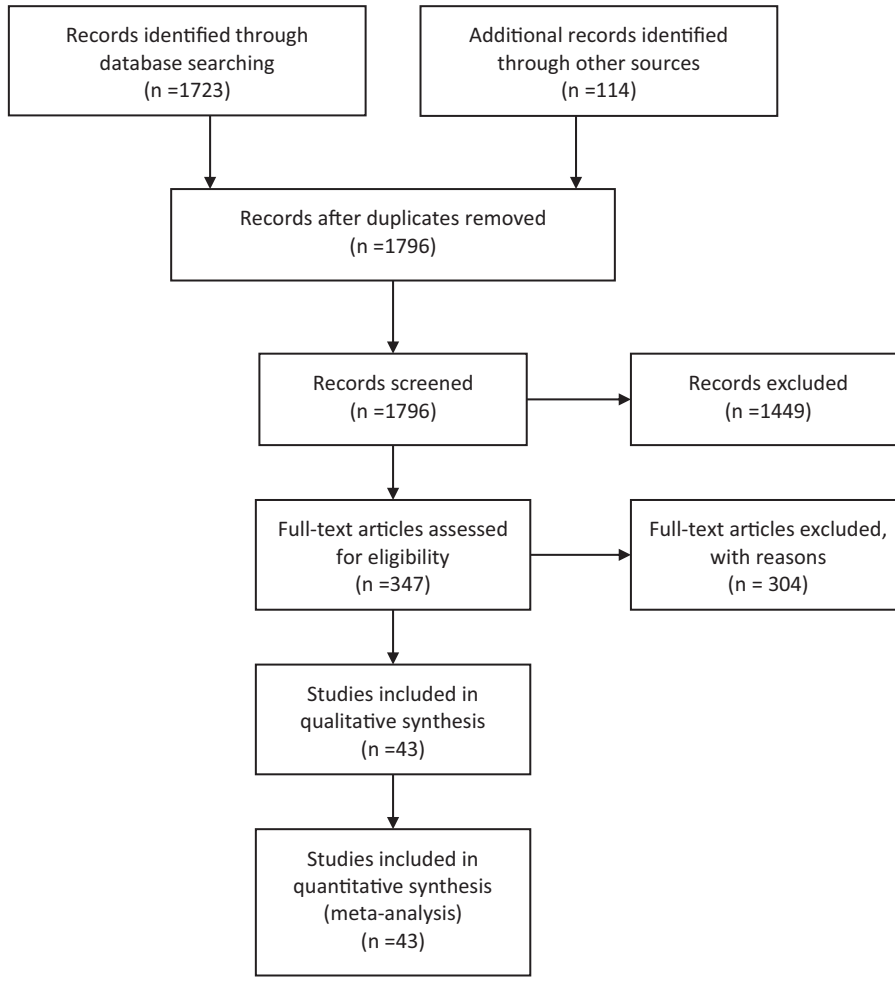

FIGURE 1. Flow diagram of study selection.

adherence compared to suboptimal adherence for virologic failure for treatment-experienced patients was the highest (Table 2); however, no statistically significant difference in pooled odds ratio was found between the 3 groups.

The relationship between adherence and virologic outcomes varied with type of adherence measurement. The pooled odds ratio for the self-report adherence measure (0.45; 95% CI: 0.37–0.55, $I^2 = 31\%$) was higher than the pooled odds ratio for the pharmacy refill (0.29; 95% CI: 0.20–0.41, $I^2 = 94\%$). The group using MEMS adherence measure had the lowest pooled odd ratio (0.15; 95% CI: 0.06–0.37, $I^2 = 35\%$) for optimal adherence compared to suboptimal adherence for virologic failure. There was a trend toward significant difference across the odds of virologic failure between self-report and MEMS (regression coefficient −1.00; 95% CI: −2.05, 0.06, $P = 0.06$), but not between self-report and pharmacy refill (regression coefficient −0.22; 95% CI: −0.78, 0.34, $P = 0.45$).

The pooled odds ratios were also estimated by grouping studies using cut-off points for optimal adherence studies with a cut-off point between 98% and 100%, 7 studies (N = 3940); studies with a cut-off point of ≥95%, 30 studies (N = 17,779); and studies with a cut-off point of 80% to 90%, 6 studies (N = 1021). The pooled odds ratios for virologic failure for optimal adherence compared to suboptimal adherence for each cut-off point were similar, with no statistically significant differences.

The pooled odds ratio for optimal adherence compared to suboptimal adherence for observational studies was significantly greater than randomized controlled studies (regression coefficient, 0.66; 95% CI: 0.10, 1.21, $P = 0.02$). Studies were aggregated into three subgroups according to HIV-medication regimens: NNRTI-based, boosted PI-based, and unboosted PI-based. The pooled odds ratio for virologic failure for optimal adherence compared to suboptimal adherence for patients taking NNRTI-containing regimens was the highest, but the differences in pooled odds ratios between the regimens were not statistically significant.

Studies were subgrouped into 2 groups based on the HDI of the country in which the study was performed: very high HDI, 21 studies (N = 10,466); low HDI, 19 studies (N = 9945). The pooled odds ratio for optimal adherence compared to suboptimal adherence for countries with low HDI (0.50; 95% CI: 0.35–0.72) was significantly higher than countries with very high HDI (0.23; 95% CI: 0.15–0.33).

A multivariate meta-regression model was built-in to examine the specific moderators of the between-study heterogeneity, including the following: study region, threshold used to define virologic failure, adherence measurement, study design,

TABLE 1. Characteristics of Included Studies in Meta-Analysis of Adherence to Antiretroviral Therapy and Virologic Failure

Study	Country	Study Type	Definition of Virologic Failure (Copies/mL)	Adherence Measures	Cut-off Point for Optimal Adherence %	Observation Period
Pasternak et al 2012[37]	Netherlands	Randomized controlled trial	≥50	MEMS∗	100	9 months
Okonjio et al 2012[38]	Kenya	Randomized controlled trial	≥400	Pill count	≥95	24 weeks
Murphy et al 2012[48]	South Africa	Retrospective study	≥50	Pharmacy refill	>90	24 months
Nolan et al 2011[49]	Canada	Retrospective study	≥500	Pharmacy refill	≥95	Median 51 months
El-Khatib et al 2011b[50]	South Africa	Retrospective study	>50	Pharmacy refill	≥95	Median 44 months
Messou et al 2011[13]	Côte d'Ivoire	Prospective study	≥300	Pharmacy refill	≥95	12 months
Lima et al 2010[51]	Canada	Retrospective study	>400	Pharmacy refill	≥95	Median 2 years
Ford et al 2010[14]	South Africa	Prospective study	>5000	Self-report	≥95	5 years
Nellen et al 2009[15]	Netherlands	Prospective study	>400	Pharmacy refill	≥85	2 years
San et al 2008[16]	Mozambique	Prospective study	≥1000	Pill count	>95	1 year
Nachega et al 2007[17]	South Africa	Prospective study	>400	Pharmacy refill	100	Median 2.2 years
Gross et al 2006[18]	Canada	Prospective study	>1000	Pharmacy refill	>95	Median 29 months
Moore et al 2005[19]	Canada	Prospective study	≥500	Pharmacy refill	>95	Median 44.7 months
Kitahata et al 2004[52]	USA	Retrospective study	>500	Pharmacy refill	>90	Median 89 weeks
Cahn et al 2004[39]	Argentina, Brazil, Mexico, Italy, Thailand, Canada	Randomized controlled trial	≥400	Self-report	≥95	48 weeks
Arnsten et al 2001[20]	USA	Prospective study	>500	MEMS	≥90	5.1 months
McNabb et al 2001[21]	USA	Prospective study	≥400	MEMS	>95	3 months
Parienti et al 2010[22]	USA	Prospective study	≥50 (400)	MEMS	>95	2 years
Bangsberg et al 2000[23]	USA	Prospective study	≥400	MEMS	≥98	Median 9.4 weeks
Paterson et al 2000[5]	USA	Prospective study	≥400	MEMS	≥95	Median 6 months
Tuldra et al 2000[40]	Spain	Randomized controlled trial	>400	Self-report	≥95	48 weeks
Meresse et al 2013[41]	Cameroon	Randomized controlled trial	≥40	Self-report	≥80	24 months
Abah et al 2014[53]	Nigeria	Retrospective study	>1000	Pharmacy refill	≥95	Median 12 months
Neogi et al 2013[24]	India	Prospective study	>400	Self-report	100	2 years
Li et al 2012[25]	USA	Prospective study	≥200	Self-report and Pill count	≥95	32 months
McMahon et al 2013[54]	India	Retrospective study	≥200	Pharmacy refill	>95	12 months
Ekstrand et al 2011[26]	India	Prospective study	>1000	Self-report	≥95	2 years
Lower-Beer et al 2000[27]	Canada	Prospective study	>500	Pharmacy refill	≥95	Median 19 months
Carr et al 2000[42]	Australia	Randomized controlled trial	≥50	Self-report	100	52 months
Cohen et al 2013[43]	21 countries	Randomized controlled trial	≥50	Self-report	>95	96 weeks
Haubrich et al 1999[44]	USA	Randomized controlled trial	<500	Self-report	≥95	6 months
Muyingo et al 2008[45]	Uganda and Zimbabwe	Randomized controlled trial	>50 (400)	Pharmacy refill	100	48 weeks
Anude et al 2013[28]	Nigeria	Prospective study	≥400	Pharmacy refill	≥95	12 months
Nelson et al 2010[46]	26 countries	Randomized controlled trial	≥50	Self-report	>95	96 weeks
Biswas et al 2014[29]	USA	Prospective study	≥40	Self-report	>95	3 years
Ti et al 2014[30]	Canada	Prospective study	≥500	Pharmacy refill	≥95	Median 32 months
El-Khatib et al 2011b[31]	South Africa	Prospective study	≥400	Pill count	≥95	24 weeks
Glass et al 2006[32]	Switzerland	Prospective study	≥50 (400)	Self-report	≥95	12 months
Jordan et al 2009[33]	Vietnam	Prospective study	≥1000	Self-report	≥95	16.65 months
Goldman et al 2008[34]	Zambia	Prospective study	≥400	Pharmacy refill	≥95	744 days
Court et al 2014[35]	South Africa	Prospective study	>1000	Pharmacy refill	≥90	27 months
Shet et al 2014[47]	India	Randomized controlled trial	>400	Pill count	≥95	96 weeks
Carrieri et al 2003[36]	France	Prospective study	200, 400, and 500	Self-report	100	36 months

MEMS = medication event monitoring system.

and year of publication. Study design (observational study versus randomized controlled trials; regression coefficient 0.74, 95% CI: 0.04–1.43, $P < 0.05$) and study region (developed versus developing countries; regression coefficient 0.56, 95% CI: 0.01–1.12, $P < 0.05$) remained as independent predictors of between-study heterogeneity.

DISCUSSION

This meta-analysis of 43 studies, involving 27,905 participants, addresses a gap in the current HIV treatment adherence literature with a quantitative evaluation of the association between level of adherence and virologic outcomes among

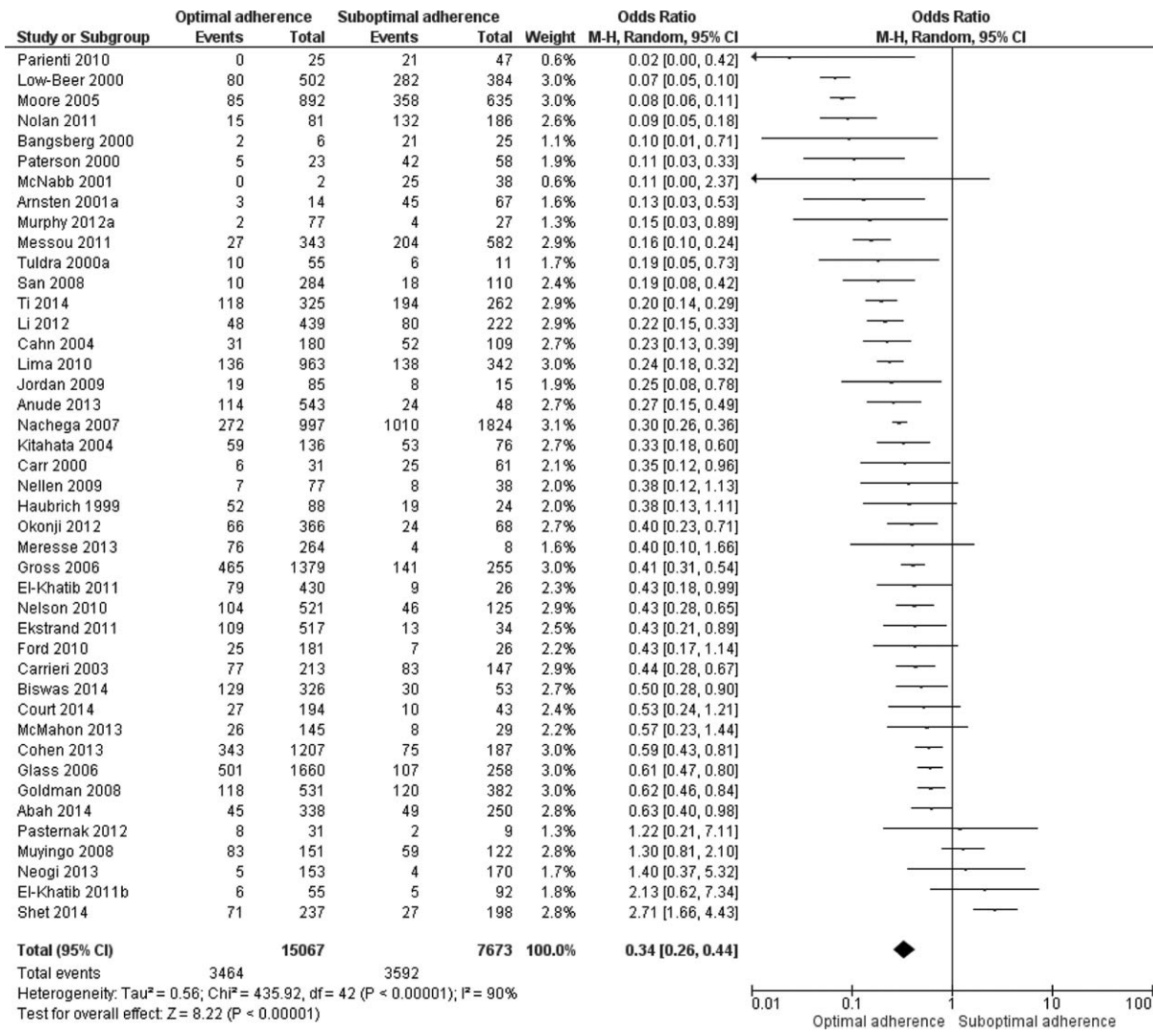

FIGURE 2. Association between adherence to antiretroviral therapy and virologic failure.

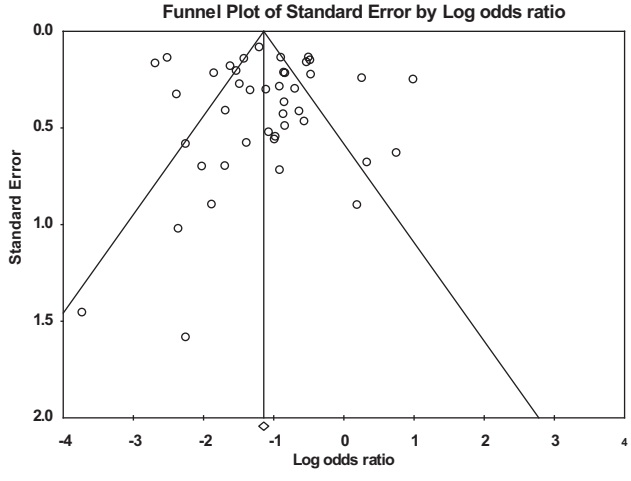

FIGURE 3. Funnel plot for the association between adherence to antiretroviral therapy and virologic failure ($P = 0.68$ at Egger's test).

adults taking ART. This study revealed that adherence levels as low as 80% to 90% may be adequate for viral suppression in patients taking newer antiretroviral drugs. Our data also showed that pooled odds ratios for virologic failure for optimal adherence compared to suboptimal adherence were similar between NNRTI-based and boosted PI-based regimens. The effectiveness of newer antiretroviral agents at the lower level of adherence may encourage the prescribing of ART at an early stage of HIV infection.

The findings indicated that the mean proportion of patients who were reported to demonstrate optimal adherence worldwide was 63.4%, which is similar to a meta-analysis of 84 studies that reported 62% of patients take $\geq$90% of their prescribed ART.[55] The results of this study demonstrate that adherence is robustly associated with virologic outcomes across the various types of adherence measure, ART regimen, study population, and reporting. The odds of virologic failure were almost 3 times higher for participants with suboptimal adherence compared with those with optimal adherence. This confirms that achieving long-term optimal adherence is indeed Achilles' heel of successful virologic outcomes.[56] The need for

TABLE 2. Subgroup Analysis Adherence to Antiretroviral Therapy and Virologic Failure

Analysis Group	No of Studies	Pooled Odds Ratio (95% CI)	Tests for Heterogeneity	
			P Value (Q Statistic)	I^2 (%)
Study design				
Randomized controlled trial	11	0.55 (0.33–0.92)	<0.001	85
Observational study	32	0.29 (0.22–0.38)	<0.001	90
HDI rank				
High HDI	21	0.23 (0.15–0.33)	<0.001	91
Low HDI	19	0.50 (0.35–0.72)	<0.001	87
Regimen				
NNRTI-based	17	0.54 (0.38–0.77)	<0.001	88
Boosted PI-based	4	0.31 (0.14–0.71)	0.06	59
Unboosted PI-based	5	0.25 (0.13–0.47)	0.11	47
Treatment experience				
Naive	22	0.33 (0.23–0.47)	<0.001	94
Experienced	12	0.52 (0.41–0.66)	0.36	9
Naive and experienced	9	0.28 (0.17–0.46)	0.001	69
Threshold used to define virological failure				
≤100 copies/mL	11	0.55 (0.41–0.74)	0.01	56
100–400 copies/mL	17	0.37 (0.26–0.54)	<0.001	88
≥500 copies/mL	14	0.25 (0.16–0.41)	<0.001	92
Threshold used to define optimal adherence group				
≥98–100%	7	0.54 (0.29–1.00)	<0.001	85
≥95%	30	0.34 (0.24–0.47)	<0.001	92
≥80–90%	6	0.34 (0.23–0.51)	0.57	0
Measurement				
Self-report	14	0.45 (0.37–0.55)	0.13	31
Pharmacy refill	18	0.29 (0.20–0.41)	<0.001	94
MEMS	6	0.15 (0.06–0.37)	0.18	35
Pill count	4	0.80 (0.21–3.02)	<0.001	93

CI = confidence interval, HDI = United Nations human development index, MEMS = medication event monitoring system, NNRTIs = nonnucleoside reverse transcriptase inhibitors, PIs = protease inhibitors.

clinicians to exert concerted efforts to maintain continuing optimal adherence to antiretroviral therapy is indisputable.

Classifying patients according to various optimal adherence thresholds (≥98–100%, ≥95%, and 80–90%) did not result in statistically significant differences in the odds of virologic failure. This finding is consistent with a meta-analysis of 37 studies in children that reported no significant group differences in virologic outcomes between different thresholds of good adherence.[57] This suggests that patients who achieved ''perfect'' (100%) or ''near perfect'' (≥95%) adherence did not necessarily have better virologic outcomes than patients who had achieved ''good enough'' (≥80–90%) adherence. This finding has clinical importance and is in line with previous studies[58,59] that indicated that although the need to maintain high levels of adherence to achieve long-term virologic suppression is clear, the level of adherence behavior capable of sustaining viral suppression is broader than previously thought.

Considerable variation in the relationship between adherence and virologic outcomes was found based on the type of adherence measurement used in the studies we reviewed. For studies using self-reported adherence, the odds of virologic failure in participants with optimal adherence was about half that of participants with suboptimal adherence. The odds of virologic failure for optimal adherence were about one-third and one-seventh that of the participants with suboptimal adherence using pharmacy refill and MEMS, respectively. Our meta-analysis undermines the validity of using self-reported adherence to distinguish virologic outcomes. A high proportion of patients with optimal self-reported adherence experienced virologic failure. Self-reported adherence is potentially confounded by social desirability and recall bias, which leads patients to overestimate their actual adherence;[60] this method is inferior to MEMS in its ability to explain virologic outcomes.

Despite the findings[17,61] of previous studies suggesting the need for different levels of optimal adherence between antiretroviral regimens for achieving similar virologic outcomes, classifying patients based on regimen did not result in statistically significant differences in the odds of virologic outcomes in this meta-analysis.

The pooled odds ratio for optimal adherence compared to suboptimal adherence for virologic failure for studies with virologic failure cut-offs < 100 copies/mL were significantly higher than studies with virologic failure cut-offs between 500 copies/mL and 1000 copies/mL. The rate of virologic failure detected in patients with good adherence increased when studies defined a virologic failure at a low level of HIV-1 ribonucleic acid (RNA). The relationship between adherence and viral load improved when the level of detection of HIV-1 RNA increased. The tighter the definition of virologic failure the more likely it is to unmask suboptimal adherence.

TABLE 3. Meta-Regression Analysis of Moderators for the Association Between Antiretroviral Adherence and Virologic Failure

Moderator	Category 1	Category 2	Regression Coefficient (95%CI)	*P* Value	I^2 Inconsistency *Q* Statistic
Region	Developing countries	Developed countries	0.79 (0.25, 1.32)	0.004	89.2%; 352.4 (38 df), $P < 0.001$
Regimen	NNRTIs	Boosted PIs	0.58 (−0.42, 1.59)	0.257	88.8%; 349.11 (39 df), $P < 0.001$
Treatment experience	Experienced	Naive	0.38 (−0.27, 1.04)	0.250	90.1%; 404.22 (40 df), $P < 0.001$
Threshold used to define virologic failure	100–400 copies/mL	≤100 copies/mL	−0.30 (−0.92, 0.33)	0.353	87.5%; 312.53 (39 df), $P < 0.001$
	≥500 copies/mL	≤100 copies/mL	−0.75 (−1.39, −0.12)	0.020	
Threshold used to define optimal adherence group	≥80–90%	≥98–100%	−0.56 (−1.62, −0.51)	0.304	90.7%; 430.21 (40 df), $P < 0.001$
	≥95%	≥98–100%	−0.54 (−1.31, 0.23)	0.171	
Measurement	Pharmacy refill	Self-report	−0.22 (−0.78, 0.34)	0.446	90.2%; 398.75 (df 39), $P < 0.001$
	MEMS	Self-report	−1.00 (−2.05, 0.06)	0.064	
	Pill count	Self-report	0.17 (−0.89, 1.24)	0.749	
Study design	RCT	Observational study	0.66 (0.10, 1.21)	0.020	88.7%; 364.17 (41 df), $P < 0.001$
Observation period	≤ 1 year	>1 year	0.15 (−0.38, 0.69)	0.574	90.1%; 413.84 (31 df), $P < 0.001$
Year of publication	≥2005	<2005	0.67 (0.07, 1.28)	0.028	89.6%; 394.36 (41 df), $P < 0.001$
Multivariate					
Region	Developing countries	Developed	0.56 (0.01, 1.12)	0.048	82.6%; 172.5 (30 df), $P < 0.001$
Threshold used to define virologic failure	≥500 copies/mL	≤100 copies/mL	−0.46 (−1.23, 0.30)	0.238	
Measurement	MEMS	Self-report	−0.50 (−1.58, 0.58)	0.366	
Study design	RCT	Observational study	0.74 (0.04, 1.43)	0.038	
Year of publication	≥2005	<2005	0.43 (−0.37, 1.23)	0.291	

MEMS = medication event monitoring system, NNRTIs = nonnucleoside reverse transcriptase inhibitors, PIs = protease inhibitors.

The odds of virologic failure for optimal adherence were about half and one-third that of the patients with suboptimal adherence in countries with a low HDI and high HDI, respectively. More patients with optimal adherence experienced virologic failure in countries with low HDI than in countries with high HDI. This review indicates that patients with equal or better levels of optimal adherence in developing countries compared to developed countries[62] does not necessarily translate into better virologic outcomes. This might be associated with the increase in pretreatment antiretroviral drug resistance[63] and unavailability of baseline HIV drug resistance testing before initiation of ART[64] in resource-limited settings that have a potential to contribute to the increasing rates of virologic failure in optimally adherent patients. We support moves toward the use viral load monitoring at the point of care in resource-limited settings[65] to improve treatment outcomes.

Study design (observational study vs randomized controlled trials) was an independent predictor of between-study heterogeneity. More patients with optimal adherence experienced virologic failure in randomized controlled trials than in observational studies. Differences in estimated magnitude of treatment effect are very common between randomized controlled trials and observational studies.[66] This difference in virologic outcomes between study designs might be related with selection bias in observational studies[67] and higher quality and rigor of randomized controlled trials.

This meta-analysis shares the limitations intrinsic to meta-analysis in general and with studies of adherence in particular. We only included studies published in English, so we may have missed studies that were relevant to our research question during the literature search. When the included studies were stratified and analyzed based on regimen, virologic failure cut-off, adherence cut-off and type of adherence measurement, heterogeneity between-studies remained high for most of the subgroups. Because of this high degree of heterogeneity, which was not entirely described either by subgroup analysis or by meta-regression, our pooled results need to be viewed with caution.

CONCLUSION

Irrespective of the cut-off point for optimal adherence, our findings support the tenet that optimal adherence to ART is associated with positive clinical outcomes. The threshold for optimal adherence to achieve better virologic outcomes appears to be wider than the commonly used cut-off point (≥95% adherence). Though patients taking ART should be instructed to attain ≥95% adherence, apprehensions of slightly lower adherence should not deter prescribing ART regimens at an early stage of HIV infection.

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