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Adherence to Antiretroviral Therapy During and After Pregnancy in Low-, Middle and High Income Countries: A Systematic Review and Meta-Analysis

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Abstract

Objective—To estimate ART adherence rates during pregnancy and postpartum in high-, middle- and low-income countries.

Design—Systematic review and meta-analysis

Methods—MEDLINE, EMBASE, SCI Web of Science, NLM Gateway and Google scholar databases were searched. We included all studies reporting adherence rates as a primary or secondary outcome among HIV-infected pregnant women. Two independent reviewers extracted data on adherence and study characteristics. A random-effects model was used to pool adherence rates; sensitivity, heterogeneity, and publication bias were assessed.

Results—Of 72 eligible articles, 51studies involving 20,153 HIV-infected pregnant women were included. Most studies were from United States (n=14, 27%) followed by Kenya (n=6, 12%), South Africa (n=5, 10%), and Zambia (n=5, 10%). The threshold defining good adherence to ART varied across studies (>80%, >90%, >95%, 100%). A pooled analysis of all studies indicated a pooled estimate of 73.5% (95% confidence interval [CI] 69·3–77·5%, I^2=97·7%) of pregnant women had adequate (>=80%) ART adherence. The pooled proportion of women with adequate adherence levels was higher during the antepartum (75·7%, 95% CI 71·5–79·7%) than during postpartum (53·0%, 95% 32.8% to 72·7%) (p=0·005). Selected reported barriers for non-adherence included physical, economic and emotional stresses, depression (especially post-delivery), alcohol or drug use, and ART dosing frequency or pill burden.

Conclusion—Our findings indicate that only 73·5% of pregnant women achieved optimal ART adherence. Reaching adequate ART adherence levels was a challenge in pregnancy, but especially during the postpartum period. Further research to investigate specific barriers and interventions to address them are urgently needed globally.

Keywords

HIV infection; pregnancy; antiretroviral therapy; adherence; PMTCT

INTRODUCTION

Globally, an estimated 1.4 million HIV-infected women give birth each year, 91% of whom reside in sub-Saharan Africa[1]. Antiretroviral therapy (ART) use during and after pregnancy is critical both for preserving maternal health and preventing mother-to-child HIV

transmission (PMTCT). In high-income countries, MTCT rates as low as 1–2% have been achieved with combination ART (cART) drug regimens during pregnancy, as well as use of elective Cesarean delivery in some circumstances and avoidance of breastfeeding [2]. In low- and middle-income countries where breastfeeding is common and access to PMTCT services can be problematic, MTCT rates can be as high as 25 to 48% [3, 4].

The 2010 World Health Organization (WHO) guidelines for ART drug use for treatment of pregnant women and preventing HIV infection in infants in low-resource settings have expanded recommendations for ART in pregnant women. These guidelines also recommended more complex combination ART regimens for PMTCT and the continuation of ART prophylaxis for either mother or infant thoughout the breastfeeding regardless of whether the woman requires immediate ART for her own health [5]. In low-income countries, there has been rapid scale-up of both ART coverage among treatment-eligible pregnant women, as well as total PMTCT coverage (prophylaxis and therapy). In such settings, an estimated 34% of treatment-eligible pregnant women received cART and an estimated 48% of HIV-infected pregnant women received the most effective ART regimens for PMTCT (excluding single-dose nevirapine) in 2010, up from 15% global PMTCT coverage in 2005; in sub-Saharan Africa, coverage was 54% [1, 6]. Given the rapid ART scale-up and availability of more effective PMTCT ART regimens, WHO has set a goal of virtual elimination of MTCT by 2015 [7].

Ensuring adherence to prescribed ART continues to be a major public health concern in both high-and low-income countries. Virologic and clinical success depend crucially on good adherence, and with poor adherence,, the virus may quickly develop therapy-limiting drug resistance [8]. Studies prior to 2005 using older cART regimens suggested that sustained virological suppression is achieved only if > 95% of prescribed doses are taken [9]. More recent studies of ritonavir-boosted protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs)(e.g. efavirenz)-based regimens suggest that virological suppression may be achieved at more moderate levels (70% to 80%) of ART adherence because the high potency and longer half-lives of these newer ART regimens making them more forgiving of occasional missed ART doses [10–12]. Nevertheless, higher ART adherence is associated with better virological outcomes in a linear dose-response fashion, thus maximum adherence should be encouraged in each patient [10–12]. Adherence is particularly important among pregnant and lactating women. In addition to non-adherence increasing the risk of virologic failure, maternal HIV disease progression and potential development of drug resistant virus, there may be increased risk of mother to child transmission. For treatment-eligible mothers, the ART regimen is continued during the postpartum period, and for those who are not eligible for treatment, continued use of triple ARV regimens for the duration of breastfeeding may be used to prevent postnatal HIV transmission. Thus, continued adherence to cART in the postpartum period is also critical for both maternal health and PMTCT.

A recent multinational randomized trial, HPTN 052 [13] found that initiation of treatment of HIV-infected individuals with CD4 counts between 350 and 550 cells/mm^3 significantly reduced transmission to their uninfected sexual partners compared to those who delayed treatment. Given high rates of HIV serodiscordance [14, 15] among married or cohabitating

couples affected by HIV in many settings, there is be increasing impetus to start effective ART for HIV-infected pregnant women, even if they do not meet current indications to start ART, further emphasizing the importance of good adherence in this population. Indeed, pregnant women (who are identifiable, seek care, and are clearly sexually active) would be a prime target for earlier treatment, with synergy for PMTCT.

Data on ART adherence during pregnancy are limited, and no systematic review of ART adherence in pregnancy has been published. These data are critical especially now that there is a global movement towards use of triple ART prophylaxis during pregnancy and breastfeeding for PMTCT. We conducted a meta-analysis to estimate the proportion of women with adequate ART adherence levels during pregnancy and postpartum in low-, middle- and high-income countries.

METHODS

Protocol and registration

The study background, rationale, methods were specified in advance and documented in a study protocol (Appendix 1). The study protocol was submitted and accepted to PROSPERO register (CRD42012002246).

Eligibility Criteria

Type of studies: all studies (cross-sectional studies, cohort studies, randomised controlled trials) that reported ART adherence rates as a primary or secondary outcome. No language, publication date or publication status restrictions were imposed. Types of participants: HIV-infected pregnant women on ART during antenatal care or postnatal period or both. Types of interventions: any type of ART. Types of outcome measures: adherence rates regardless of measures (such as self-reported, pill count, etc.).

Information Sources and Search Strategy

Two of the authors (YSH, OAU) conducted searches on the following electronic databases (from inception to November 2011): PubMed, EMBASE, SCI Web of Science, NLM Gateway and Google scholar. We used the following keywords: HIV or AIDS, pregnant*, “mother to child transmission”, "adherence", “compliance”, "antiretroviral therapy" (see Appendix 1 for the full PubMed search strategy). We searched abstract of relevant conference proceedings from 2006 onward (the most recent ones that may not have been indexed in NLM Gateway meeting abstracts). In addition, the bibliographies of relevant review articles and selected articles were examined for pertinent studies.

Study selection

Two authors (JBN and OAU) evaluated the eligibility of studies obtained from the literature search, and worked independently to scan all abstracts and obtain full text of articles. In cases of discrepancy, agreement was reached by consensus.

Data abstraction

JBN and OAU independently extracted and compared the data. For each study that met the selection criteria, details were extracted on study design, study population characteristics, and adherence measures.

Data Analysis

For the meta-analysis, we first stabilized the raw ART adherence proportions from each study using the Freeman-Tukey variant of the arcsine square root transformed proportion [16] suitable for pooling. We used a DerSimonian-Laird random effects model [17] due to anticipated variations in study population, health care delivery systems and epidemic course. To evaluate the stability of the results we applied several sensitivity analyses, including fixed effects analysis and used a one-study removed approach [18]. The purpose of this analysis was to evaluate the influence of individual studies, by estimating pooled estimate in the absence of each study. We assessed heterogeneity among trials by inspecting the forest plots and using the chi-squared test for heterogeneity with a 10% level of statistical significance, and using the I^2 statistic where we interpret a value of 50% as representing moderate heterogeneity [19, 20]. We assessed the possibility of publication bias by evaluating a funnel plot for asymmetry. Because graphical evaluation can be subjective, we also conducted a Begg's adjusted rank correlation test [21] and Egger's regression asymmetry test [22] as formal statistical tests for publication bias.

The effect of study-level variables on the overall adherence rates was explored using subgroup and meta-regression analyses: stage of pregnancy (antepartum vs. postpartum), publication type (conference abstract vs. journal article), study design (observational vs. PMTCT interventional studies [e.g., adherence data collected as part of a clinical trial evaluating efficacy of PMTCT regimens, not ART adherence interventions]), study location (low- and middle income versus high-income countries), type of ART regimen (zidovudine[ZDV], single-dose nevirapine [sdNVP], and combined ART [cART]), adherence threshold (>80%, >90%, > 95% and 100%), and measure of adherence (pharmacy refills and claims-based, pill counts, self-reported and blood drug concentration). In addition, we conducted another subgroup analysis based on countries income-group, after excluding studies that administered sdNVP and limited to studies that used 80% or more as threshold for good ART adherence levels, to evaluate whether there are differential proportion of women that achieved adequate adherence levels based on country-income group in studies that administered complex regimens as opposed to studies of single-dose NVP and studies that used high threshold of adherence levels.

Univariable and multivariable random-effects logistic regression analyses were conducted to investigate the impact of study characteristics on the pooled adherence proportions. Univariable random-effects logistic regression analyses were used to investigate the bivariate relationship between each study-level factor (listed above) and adherence estimates. Multivariable random-effects logistic regression analyses were carried out to determine which study-level factors were independently associated with adherence estimates. Meta-analysis results were reported as combined adherence proportions with 95% confidence intervals (CIs), while meta-regression results are reported as odds ratio with 95% CIs.

Pearson correlation coefficient was used to examine the association between adherence rates and mother-to-child transmission of HIV. The Pearson correlation analyses were stratified by type of ART and type of study design. All P values are exact and P<·05 was considered significant. Analyses were conducted using Stata version 12 for Windows (Stata Corp, College Station, Texas). This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (http://www.prisma-statement.org) [23, 24]. PRISMA checklist is provided in the Appendix 2.

RESULTS

Search results and study characteristics

Figure 1 shows the study selection flow diagram. The literature search yielded 560 articles. After review, 72 articles were selected for critical reading. Twenty-one studies did not meet the inclusion criteria and were excluded (see Appendix 3 for list of excluded studies). The other 51 studies [25–74] involving 20,153 HIV-infected pregnant women were included; 48 studies reporting 71 adherence estimates were included in the meta-analysis. The remaining three studies [56, 64, 75] reported ART adherence as mean or median adherence and could not be included in the meta-analysis. Kappa agreement was 0.96 between JBN and OUA for inclusion of studies in this meta-analysis.

Table 1 presents the characteristics of the included studies. The studies were carried out between 1986 and 2011 and reported between 1998 and 2011. Most were reported as journal articles (n=46, 90%); five were presented as conference abstracts (10%). The preponderance of the studies (n=38, 74%) were observational and thirteen (26%) were RCTs evaluating PMTCT regimens. Most were carried out in the United States (n=14, 27%) followed by Kenya (n=6, 12%), South Africa (n=5, 10%), and Zambia (n=5, 10%). Most studies included pregnant women on triple regimen ART (n=23, 45%). Fifteen (29%) and twelve (24%) studies report adherence rates among HIV-infected pregnant women on zidovudine (ZDV) and single dose nevirapine (sdNVP), respectively. One study compared adherence between ZDV and triple regimen ART. Most (11 out of 12) of the sdNVP studies reported adherence among pregnant women who ingested the sdNVP at onset of labour at home. Only one study [61] reported adherence in both pregnant women who ingested sdNVP at home and those who ingested sdNVP during labour at least two hours before delivery. The threshold used to define ART adherence varied across studies (>80%, >90%, >95%, and 100%). Most studies measured adherence using self-reported questionnaires (n=26, 51%), followed by pill counting (n=9, 18%), and pharmacy refills or claims-based (n=5, 10%). Five studies (9%) used blood drug concentrations (cord blood [43, 44, 50, 74] and red blood cells [36]) to measure ART adherence; one study used electronic medication-events-monitoring system (MEMS caps) [64]. Most of the studies reported adherence during antepartum period (n=39, 76%), four (8%) reported adherence during postpartum period, and eight (16%) reported both antepartum and postpartum adherence rates.

Overall adherence to ART during and after pregnancy

Proportion of women who achieved adequate adherence levels and 95% CIs from individual studies with a pooled estimate are shown in Figure 2. The pooled ART adherence

proportions for all studies yielded an estimate of 73·5% (95% CI 69·3–77·5%) of patients with adequate ART adherence (>80%). The I^2 statistics was 97.7%, indicating statistically significant heterogeneity among the studies. We found no significant publication bias (Egger's test, p=0·467 and Begg's test, p =0·996). The results of leave-one-study-out sensitivity analyses showed that no study had undue influence on pooled adherence estimate. Adherence estimates of the three studies not included in the meta-analysis were as follows: Chung et al. [56] reported ART adherence was 96% by pill count. Using MEMS caps, Ickovics[64] reported that the mean adherence to antepartum ZDV was extremely low (50·0%), with a statistically significant decline in mean postpartum adherence after three weeks (34·1%) (p=0·04). Leisegang et al. [75] estimated median overall pharmacy claims-based ART adherence of women who were pregnant when starting ART at 54·0%.

Adherence to ART by different subgroups

The results of subgroup analyses are shown in Figure 3. The pooled proportion of patients who achieved adequate adherence levels was significantly higher during the antepartum (75·7%, 95% CI 71·5–79·7%) than during the postpartum period (53·0%, 95% CI 32·8% to 72·7%) (p=0·005). Similarly, the pooled adherence of patients with good adherence rate was significantly higher in low- and middle-income countries (76·1%. 95% CI 72·2–79·7%) than in high-income countries (62·0%, 95% CI 50·1% to 73·3%) (p=0·021). However, the differential proportion of women that achieved adequate adherence levels between low-and middle-income vs. high-income countries became non-significant when we excluded sdNVP studies (74·3% vs. 62·0%, p=0·062) and when analyses were limited to >90% thresholds (74·8% vs. 69·7%, p=0·071) and 100% thresholds (78·3% vs. 74·0%, p=0·103).

Adherence proportions from RCTs evaluating PMTCT regimens were non-significantly higher than observational studies in proportion of patients with adequate ART adherence (79.6% vs. 70.4%, p=0.086). Also, the pooled proportions were higher among women on ZDV (79.0%, 95% CI 70.2–86.6%) and women on sdNVP (78.6%, 95% CI 73.5–83.4%) than those on triple regimens combination ART (63.5%, 95% CI 55.8–70.8%) (p=0.006). Studies that used pill counts (73.0%, 95% CI 60.7–83.7%) (p=0.017) and self-reported questionnaires (74·2%, 95% CI 60·7–83·7%) (p=0·015) tended to report higher adherence proportions than those studies that used pharmacy refills or claims-based measures (44·7%, 95% CI 20·4–70·4%).

Association between maternal ART adherence and mother-to-child transmission (MTC) of HIV

Fifteen studies reported 22 estimates of MTC rates (all from LMIC). When reported, the MTC rates ranged from 0·4% to 30·3% (median = 8·7%). There was negative but not statistically significantly correlation between maternal ART adherence rates and MTC rates (Pearson correlation r = −0·072, p= 0·751). As shown in Figure 4, the negative association between maternal ART adherence and MTC rates tended to be stronger for women on ZDV or sdNVP (r = −0·439, p=0·102) than women on HAART (r = − 0·175, p=0·708).

Factors modifying adherence estimates as identified by meta-regression analyses

Factors associated with adherence estimates and proportion of explained variability in adherence estimates as identified by both unadjusted and adjusted logistic random-effect modelling are shown in Table 2. In the multivariable model, only ART type and adherence measure remained being statistically significantly associated with ART adherence. Adherence estimates from cART studies were lower than those from sdNVP studies (OR=0·48, 95% CI 0·28 to 0·80) and lower among studies that used pharmacy-based measures than other measures (OR=0·25, 95% CI 0·09 to 0·70). The four factors included in the adjusted model jointly account for almost one-third (29%) of the variability in the adherence estimates.

Factors associated with adherence rates as reported in individual studies

Twenty-two studies (45%) reported factors associated with adherence. Appendices eTable 1 and eTable 2 provides study specific data on factors associated with adherence in individual studies.

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis to summarize the available data regarding ART adherence during and after pregnancy. The pooled proportion of pregnant women with adequate (>80%) ART adherence was only about 72%. Importantly, a recent literature review of gender and ART adherence in high-income countries concluded that female gender was associated with lower adherence than men, although it did not address pregnancy issues [76]. This is potentially related to the association between family and other care-taking responsibilities and lower adherence rates [77, 78]. Many HIV-infected women are first diagnosed during pregnancy and are still dealing with the implications of this diagnosis when they are prescribed ART drugs. Our study confirms that optimal adherence is a challenge during pregnancy and the postpartum period. The finding of better adherence during pregnacy than postpartum may be attributable to maternal concerns during the antepartum period regarding health of the fetus and prevention of MTCT. However, even during pregnancy, adherence was lower than is thought to be required for viral suppression and prevention of drug resistance [8, 10–12].

“Morning sickness” is common in early pregnancy and may contribute to reduced adherence during this period [79]. Nausea and vomiting affect 70–85% of pregnant women in early pregnancy and may be exacerbated by other medications (e.g., ZDV), particularly those that may also have common gastrointestinal side effects. Heartburn also occurs in later pregnancy and may affect medication-taking behaviors. Post delivery, physical, economic and emotional stresses, including the stresses and demands of caring for a new baby might make adherence more difficult. Postpartum depression (PPD) may also impact adherence. PPD is a subset of major depressive disorder that crosses cultures and affects approximately 13% of women[80]; a recent systematic review [81] found that the prevalence of PPD among women in developing countries was 31·3% (95% CI, 21·3%-43·5%), higher than PPD prevalence among women from developed countries. Adherence in early pregnancy may also be affected by maternal concerns about safety of ART drugs for the fetus.

As documented in the studies evaluated in this review, pregnancy status can be associated with reduced ART adherence due to health factors associated with non-adherence such as advanced AIDS stage and health-related symptoms (nausea, fatigue, etc.) related to pregnancy, HIV disease, or toxicity of the ART regimen itself. In addition, there was a high prevalence of individual level barriers to ART adherence such as physical, economic and emotional stresses, depression (especially post-delivery), alcohol or drug use, and drug regimen frequency or pill burden. Of note, key factors associated with high ART adherence reported in several studies were disclosure of HIV status as well as social support, in agreement with other studies in the general population [82, 83].

Our study has several implications. Evaluation and management of mental health and illicit drug use during and following pregnancy should be a high priority for healthcare workers in charge of all HIV-infected pregnant women [84]. Social support and facilitation of HIV-serostatus disclosure, whenever feasible and safe, should be encouraged since it is effective in improving adherence to PMTCT [48, 49, 53]. The use of cART is recommended by WHO in pregnancy and after delivery when women meet indications for treatment. The recent changes in WHO recommendations to consider where feasible, the use of cART (instead of single-dose NVP) for prophylaxis in pregnant women reflect the increased effectiveness in PMTCT of longer and more complex regimens [2, 85–87] for the mother coupled with extension of maternal or infant prophylaxis during the neonatal/breastfeeding period [88–90]. The WHO has also endorsed consideration of the approach of initiating life-long cART in all pregnant women regardless of CD4 count, which has been adopted as national policy in Malawi [91, 92]. These new recommendations reflect the benefits of earlier initiation of ART for maternal health and infant survival, as well as to optimize PMTCT. However, they also magnify the challenges to good adherence. The findings of our study have implications for the WHO goal of elimination of mother-to-child transmission by 2015 [7], since the ability to reduce transmission to the greatest extent possible depends not only on the availability and accessibility of the most effective regimens, but also on the ability of women to take these medications appropriately and to give full prophylactic regimens to their infants. There is a critical and urgent need to assist HIV providers to more reliably monitor adherence and develop evidence-based interventions to improve and/or maintain adherence in HIV-infected individuals[85], particularly pregnant and postpartum women as PMTCT programs move toward universal use of cART, potentially lifelong, for all pregnant women. Without close monitoring and adherence support, sub-optimal adherence levels would likely to increase the likelihood of multi-class drug resistance acquisition for both the mother and infant and compromise the safety and scale-up of PMTCT with cART [93, 94].

In many programs, non-medical personnel such as lay or peer counselors play an important role [86]. A number of programs have documented the feasibility and acceptance of this method of supplementing clinic-based staff [87]. However, there are limited data on the impact of these support staff on the overall effectiveness of PMTCT programs and ART adherence, particularly in pregnant and postpartum women. While some observational studies seem to suggest that peer support can improve ART prophylaxis adherence in pregnant womans [88, 89], more research is needed to better evaluate the effectiveness and cost-effectiveness of such interventions. Indeed, a trial with peer mentors to improve maternal ART adherence antenatally and at the time of birth is underway in South Africa

[90]. Furthermore, using a mathematical model McCabe et al. [91] found that programs aimed at optimizing ART adherence using directly observed therapy would be cost-effective to decrease MTCT. Another trial, also underway in South Africa, is investing the role of male involvement on PMTCT ART adherence [92]. The use of regimens with easier dosing requirements, reduced pill burden and better tolerability profiles may also help optimize ART adherence in pregnant women [85, 93].

Strengths of our study include its novelty, timeliness and the comprehensive search of several databases and sources to identify studies globally. We found no evidence of publication bias[94], and used random-effect models to produce a robust pooled adherence estimate. In addition, we also conducted meta-regression analyses to investigate whether any particular study-level factor explained the results and could account for the observed variations between studies.

There are also some limitations of our study. Adherence estimates from different study designs and settings were pooled in this meta-analysis, and as expected high heterogeneity between studies was found in the meta-analysis. Considerable amount of this heterogeneity could be explained by factors such population, regimens, or study methodology. However, even in the presence of high heterogeneity, meta-analysis has been suggested as preferred option to qualitative or narrative interpretation of the results, because narrative synthesis can lead to misleading or wrong conclusions [95]. Quantitative accuracy is an important feature of meta-analysis, one of the reasons for avoiding narrative interpretation without synthesis [95]. Heterogeneity appeared to be the norm rather than exception in published ART adherence meta-analyses [96–99]. Another limitation is the possibility of information bias that can be introduced by the methods used for measuring adherence. Indeed, most of the studies included in this meta-analysis used self-reported or pill count adherence which may overestimate adherence levels, and only a few studies used objective methods such as MEMS caps and blood drug concentrations. However, there is a conservative bias with self-report and pill counts, leading to possible overestimation of adherence and potentially actual levels of ART adherence being even lower than what we are reporting. To date, however, there is no established gold standard to measure ART adherence as each measurement method has unique strengths and weaknesses [85]. Finally, the meta-regression analysis has several limitations. Meta-regression represents an observational association and suffers from ecological fallacy [100]. In addition, meta-regression has low statistical power to detect an association and easily influenced by an outlier [101].

In conclusion, our meta-analysis showed ART adherence during pregnancy is significantly below that recommended for adequate virologic suppression. Optimal adherence remains a challenge in pregnancy, in both high- and low-income countries, and particularly during the postpartum period. It is crucial to monitor ART adherence, investigate specific barriers for non-adherence and develop interventions to assist ante-and post-partum women in adhering to ART and ensure the long-term efficacy of such an approach for both maternal health and PMTCT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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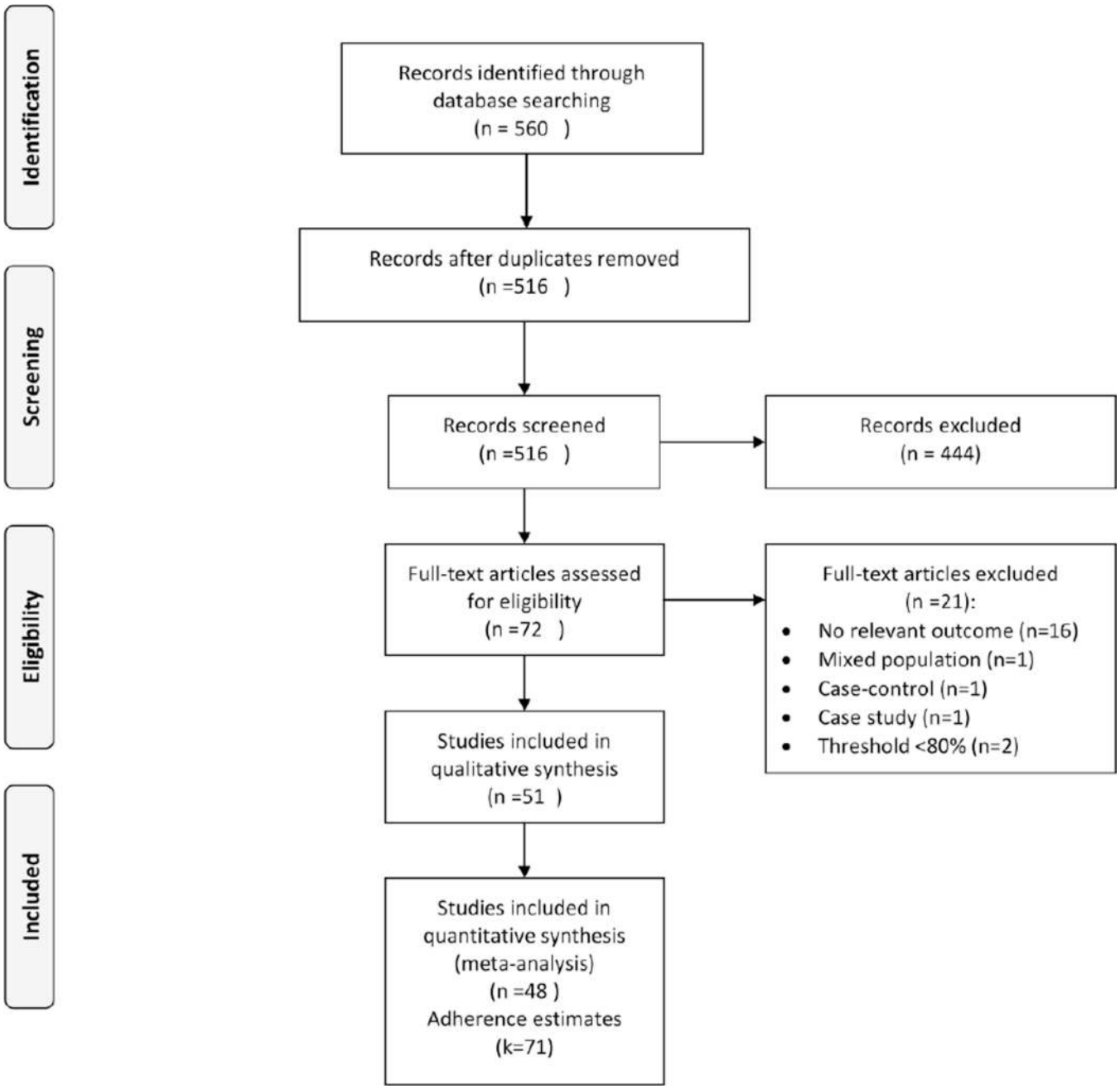

Figure 1.
Study selection flow diagram

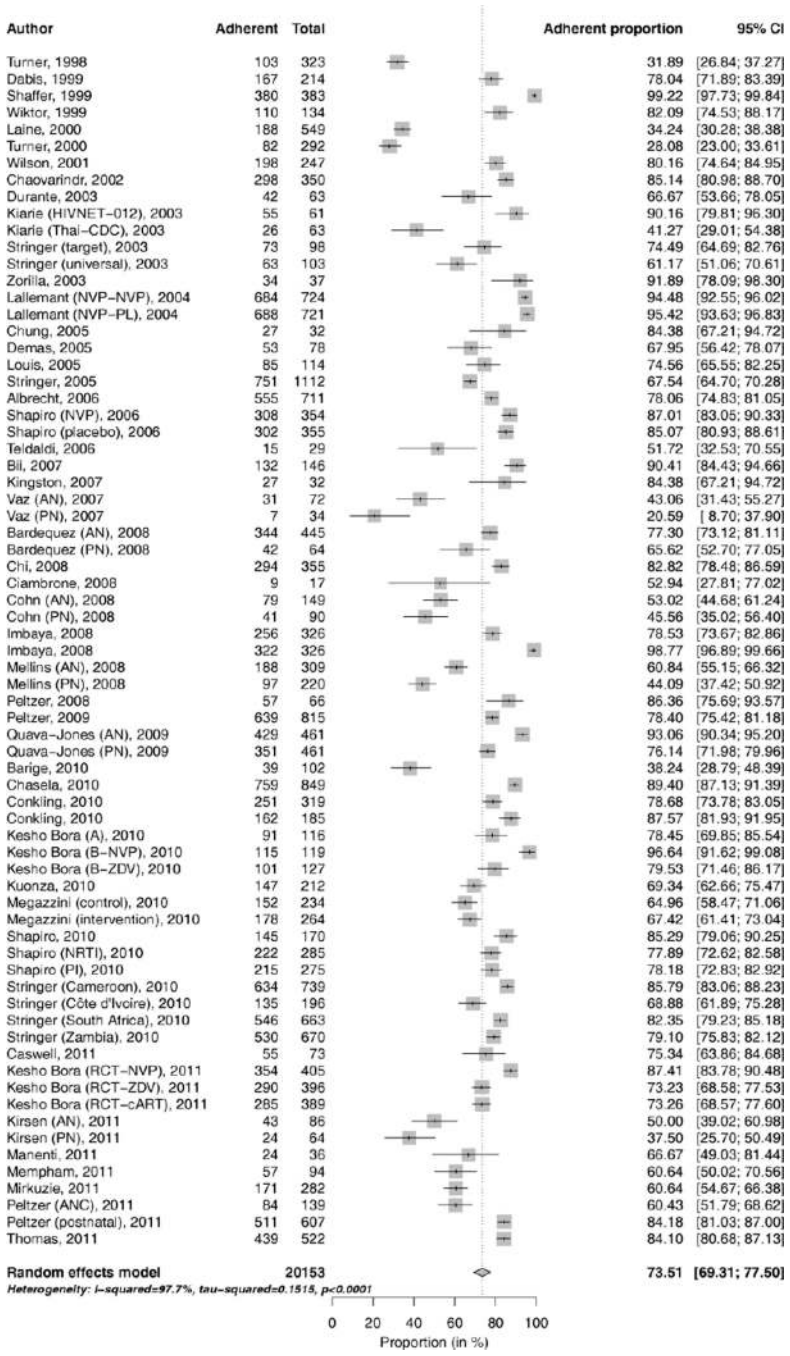

Figure 2.
Pooled proportion of pregnant women to antiretroviral therapy

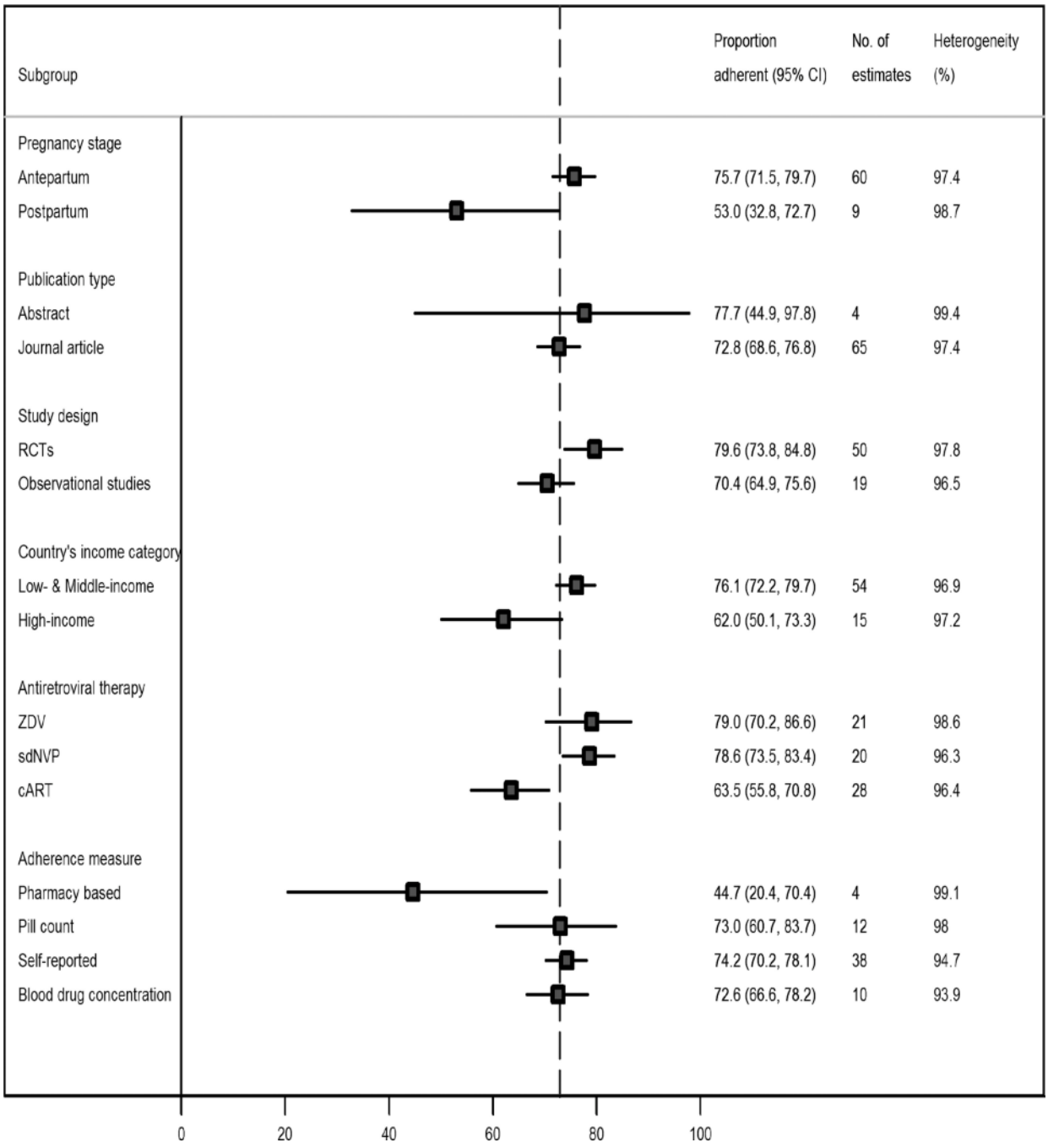

Figure 3.

Pooled proportion of pregnant women to antiretroviral therapy, by different sub-groups

cART: combined antiretroviral therapy, sdNVP: single dose nevirapine, ZDV: Zidovudine

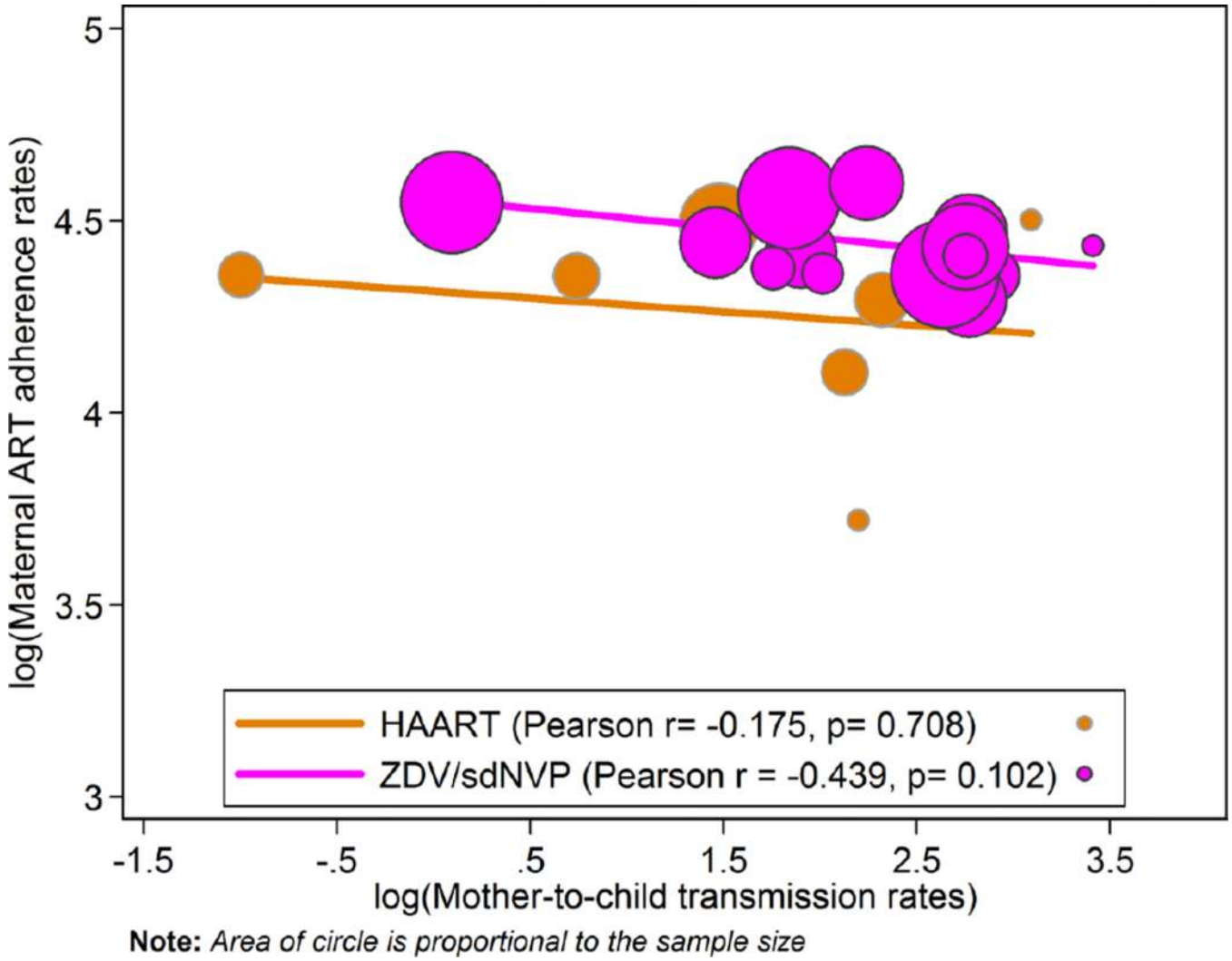

Figure 4.
Association between maternal antiretroviral therapy adherence rates and mother-to-child transmission rates

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Table 1

Overall characteristics of included studies

First Author	Publication year	Type of publication	Study year	Study design	Country	Income group	ARTs	Threshold	Adherence measure	Sample	Stage
Turner[38]	1998	Abstract	NR	Obs.	USA	High	cART	80	Pharmacy-based	323	AN
Dabis[25]	1999	Journal	1995–1998	RCT	Burkina Faso	Low	ZDV	80	Pill count	214	AN
Shaffer[69]	1999	Full	1996–1997	RCT	Thailand	Middle	ZDV	100	Pill count	383	AN
Wiktor[68]	1999	Full	1996–1998	RCT	Côte d'Ivoire	Middle	ZDV	100	Self-reported	134	AN
Laine[7]	2000	Full	1993–1996	Obs.	USA	High	ZDV	80	Pharmacy-based	549	AN
Turner[39]	2000	Full	1993–1996	Obs.	USA	High	ZDV	80	Pharmacy-based	292	PN
Wilson[67]	2001	Full	1998	Obs.	USA	High	AZT	100	Pill count	247	AN
Chaovarindr[27]	2002	Abstract	1999–2001	Obs.	Thailand	Middle	ZDV	100	Self-reported	350	AN
Ickovics[64]	2002	Full	1997–1998	Obs.	USA	High	ZDV or cART	NR	MEMS	53	AN&PN
Durante[58]	2003	Full	1998	Obs.	USA	High	cART	100	Self-reported	63	AN
Kiarie[45]	2003	Full	1999–2001	Obs./RCT	Kenya	Low	cART	80	Self-reported	61/63	AN
Stringer[44]	2003	Full	2000–2001	RCT	Zambia	Middle	sdNVP	NR	Cord blood	98/103	AN
Zorilla[55]	2003	Full	NR	Obs.	USA	High	cART	100	Self-reported	37	AN
Lallemant[70]	2004	Full	2001–2003	Obs//RCT	Thailand	Middle	ZDV	90	Pill count	724/721	AN
Chung[40]	2005	Full	2003	RCT	Kenya	Low	ZDV	100	Pill count	32	AN
Louis[42]	2005	Full	1999–2004	Obs.	USA	High	cART	100	Self-reported	114	AN
Stringer[50]	2005	Full	2003	Obs.	Zambia	Middle	sdNVP	100	cord blood	1112	AN
Albrecht[63]	2006	Full	2001–2003	Obs.	Zambia	Middle	sdNVP	100	Self-reported	711	AN

First Author	Publication year	Type of publication	Study year	Study design	Country	Income group	ARTs	Threshold	Adherence measure	Sample	Stage
Shapiro[60]	2006	Full	2002–2003	RCT	Botswana	Middle	ZDV	100	Self-reported	354/355	AN
Teldaldi[46]	2006	Full	1997–1998	Obs.	USA	High	cART	100	Self-reported	29	PN
Bii[66]	2007	Full	2005	Obs.	Kenya	Low	sdNVP	100	NR	146	AN
Cohn[65]	2007	Full	2002–2005	Obs.	USA	High	cART	95	Self-reported	149	AN&PN
Kingston[32]	2007	Full	2004–2005	Obs.	UK	High	cART	100	NR	32	AN
Vaz[57]	2007	Full	2001–2002	Obs.	Brazil	Middle	cART	95	Pill count	72	AN&PN
Bardequez[34]	2008	Full	2002–2005	Obs.	USA	High	cART	100	Self-reported	445	AN&PN
Chi[28]	2008	Full	2005–2007	RCT	Zambia	Middle	ZDV	100	pharmacy refills	355	AN
Chung[56]	2008	Full	2003–2006	RCT	Kenya	Low	cART	NR	NR	58	AN&PN
Ciambrone[29]	2008	Full	2003	Obs.	USA	Middle	cART	100	Self-reported	17	AN
Demas[36]	2008	Full	1997–1998	Obs.	USA	High	ZDV	NR	red blood cell	78	AN
Imbaya[30]	2008	Abstract	NR	Obs.	Kenya	Low	sdNVP/ZDV	100	NR	326	AN
Peltzer[54]	2008	Full	2006–2007	Obs.	South Africa	Middle	sdNVP	100	Self-reported	66	AN
Quava-Jones[26]	2009	Abstract	2002–2008	Obs.	Trinidad & Tobago	High	cART	NR	Self-reported	461	AN & PN
Peltzer[49]	2010	Full	2008–2009	Obs.	South Africa	Middle	sdNVP	100	Self-reported	815	AN
Barige[62]	2010	Full	2002–2007	Obs.	Uganda	Low	sdNVP	100	Self-reported	102	AN
Chasela[59]	2010	Full	NR	RCT	Malawi	Low	cART	100	Self-reported	849	PN
Conkling[47]	2010	Full	1986–1994	Obs.	Rwanda/Zambia	Low/Middle	sdNVP	100	Self-reported	185/319	AN

First Author	Publication year	Type of publication	Study year	Study design	Country	Income group	ARTs	Threshold	Adherence measure	Sample	Stage
Kesho Bora[51]	2010	Full	2005–2006	Obs.	Burkina Faso & Kenya	Low	ZDV/sdNVP	100	Self-reported	116/319/127	AN
Kuonza[61]	2010	Full	2008	Obs.	Zimbabwe	Low	sdNVP	100	Self-reported	212	AN
Megazzini[43]	2010	Full	2005–2006	RCT	Zambia	Middle	sdNVP	100	Cord blood	234/264	AN
Mellins[33]	2010	Full	2001–2005	Obs.	USA	High	cART	100	Self-reported	309	AN&PN
Shapiro[37]	2010	Full	2006–2008	Obs./RCT	Botswana	Middle	cART	100	Self-reported	170/285/275	AN
Stringer[74]	2010	Full	2007–2008	Obs.	Cameroon, Cote d'Ivoire, South Africa & Zambia	Low & Middle	sdNVP	100	Blood concentration	739/196/663/670	AN
Caswell[73]	2011	Full	2004–2007	Obs.	UK	High	cART	100	NR	73	AN
Kesho Bora[71]	2011	Full	2005–2008	RCT	Burkina Faso, Kenya, South Africa	Low/Middle	cART	100	Self-reported	389/405/396	AN
Kirsen[35]	2011	Full	2008–2009	Obs.	Tanzania	Low	cART	95	Pill count	86	AN&PN
Leisegang[75]	2011	Abstract	NR	Obs.	South Africa	Middle	cART	NR	Pharmacy-based	293	NR
Manenti[52]	2011	Full	2007	Obs.	Brazil	Middle	cART	NR	Self-reported	36	AN
Mempham[41]	2011	Full	2008	Obs.	South Africa	Middle	cART	95	Pill count	94	AN
Mirkuzie[48]	2011	Full	2009	Obs.	Ethiopia	Low	cART	100	Self-reported	282	AN
Peltzer[53]	2011	Full	2009	Obs.	South Africa	Middle	AZT	100	self-reported	AN: 139/PN:607	AN
Thomas[72]	2011	Full	2003–2009	RCT	Kenya	Low	ZDV	100	Pill count	522	PN

cART: combined antiretroviral therapy, sdNVP: single dose nevirapine, ZDV: Zidovudine; NR: not reported; AN: antepartum; PN: postpartum; MEMS: Medication Events Monitoring System; Obs: Observation studies; RCT: randomised controlled trial; NR: not reported

Table 2

Factors associated with adherence estimatates identified by unadjusted and adjusted meta-regression

	Univariable (unadjusted)			Multivariable (adjusted)		
Factor	**OR (95% CI)**	**p-value**	**R^2**	**OR (95% CI)**	**p-value**	**R^2**
Antepartum (vs. postpartum)	2·88 (1·38, 6·01)	0·005	10·6	1·88 (0·93, 3·80)	0·077	29·4%
Abstract (vs. journal article)	1·60 (0·52, 4·92)	0·408	0·0	Ni		
RCTs (vs observational) studies	1·65 (0·93, 2·93)	0·086	3·5	Ni		
LMIC (vs. high-income)	2·07 (1·12, 3·82)	0·021	8·4	1·05 (0·56, 1·98)	0·871	
ZDV (vs. sdNVP)	1·68 (0·97, 2·93)	0·066	4·2	Ni		
cART (vs.sdNVP)	0·44 (0·27, 0·71)	0·001	15·0	0·48 (0·29, 0·80)	0·006	
Pharmacy refills (vs. others)	0·25 (0·09, 0·72)	0·011	10·1	0·25 (0·09, 0·70)	0·009	

R^2 :Proportion of variability (statistical heterogeneity) in adherence estimates explained by study level factors; OR: odds ratio; CI: confidence interval; LMIC: low- and middle-income countroes; cART: triple regimes, combined antiretroviral therapy; Ni: not included in the adjusted model

* proportion of variance jointly explained by the four factors included in the adjusted model