STUDY PROTOCOL:

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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Co-PI: Edward J Mills, PhD, MSc

Co-Investigator: Olalekan Uthman, MBBS, PhD

Background and Rationale

Worldwide, women are becoming increasingly burdened by the impact of the HIV/AIDS epidemic. Globally, almost 50% of the 37.2 million adults living with HIV are women. In sub-Saharan Africa, the worst affected region, nearly 60%, or 13.3 million adults infected with HIV are women, and this number is growing quickly[1]. A majority of women who are infected with HIV/AIDS are of child-bearing age, causing great concern regarding the direct transmission of HIV from mother to child and indirect effects such as loss of income and orphaning due to maternal HIV, as well as the consequences to the women's own health. 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.[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] Pregnancy status may reduce ART adherence due to nausea in early pregnancy, heartburn in later pregnancy, and physical, economic and emotional stresses as well as depression post-delivery. However, the motivation of women to adhere to ART to protect their babies might counteract some of these barriers during pregnancy.

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, other than single-doses ART, for PMTCT and the continuation of ART prophylaxis for either mother or infant thoughout breastfeeding regarding of whether the woman requires immediate ART for her own health.[5] Furthermore, 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]

However, ART adherence remains a major public health concern in both high-and low-income countries; virologic, clinical, and prevention of drug resistance depends critically on adherence to the prescribed ART regimen. Studies in the the mid-2000s using old unboosted protease inhibitors-based regimens suggested that sustained virological suppression can be achieved only if $\geq$ 95% of prescribed doses are taken.[8] More recent studies of the contemporary 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 of the high potency and longer half-lives of these newer ART regimens making them more forgiving of occasional missed ART doses. [9-11] Nevertheless, higher ART adherence is associated with better virological outcomes in a linear dose-response fashion and that maximum adherence should be encouraged in each patient.[9-11]

ART 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. The postpartum period includes not only ongoing ART for the treatment-eligible mother, but also ART

prophylaxis to the newborn, now recommended for a minimum of 4-6 weeks and potentially throughout the duration of breastfeeding.

A recent landmark multinational randomized trial, HPTN 052[12] 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[13,14] among married or cohabitating couples affected by HIV in many settings, there will 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.

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.

Primary Research Question:

1. What is the achievable ART adherence level in post- and during pregnancy globally?

Secondary Research Questions:

1. Are ART adherence rates in post and during pregnancy similar in low-, middle versus high income countries settings?
2. What is the achievable ART adherence rates to single-dose NVP vs. more complex pMTCT regimens?

Methodology:

Study Eligibility, Search Strategies, Studies Selections, Data Abstraction

We will retrieve published English language of both observational and randomized trials via PubMed, EMBASE, SCI Web of Science, NLM Gateway and Google scholar through August 2011. Our search terms will include: HIV or AIDS, pregnant*, “mother to child transmission”, "adherence", “compliance”, "antiretroviral therapy" “HIV”; “HAART”; “ART”; “cART”; “adherence”; “pregnancy”. Abstracts from major HIV/AIDS or infectious diseases conferences such as Conference on Retrovirus and Opportunistic Infections (CROI), International AIDS Society (IAS), International AIDS Conference, International Conference on Antimicrobials Agents and Chemotherapy (ICAAC) and Infectious Diseases Society of America (IDSA) were also reviewed for inclusion.

Two members of the investigative team will evaluate the eligibility of studies obtained from the literature search and will work independently to scan all abstracts and obtain full text of articles. In cases of discrepancy, agreement will be reached by consensus. Data will also be independently extracted and compared. For each study that met the selection criteria, details will be extracted on study design, study population characteristics, and adherence measures. We will report objective measures of ART adherence such as pill count or Medication Event Monitoring System [MEMS caps] measurements but as well as self-report but bearing in mind that the latter may tend to overestimate the true ART adherence rate.

Data analysis plan

We will first stabilize the raw ART adherence proportions from each study using the Freeman-Tukey variant of the arcsine square root transformed proportion[15] suitable for pooling. We will use a DerSimonian-Laird random effects model[16] due to anticipated variations in study population, health care delivery systems and epidemic course. To evaluate the stability of the results wewill apply several sensitivity analyses, including fixed effects analysis and used a one-study removed approach.[17] We will assess 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.[18,19] Also we will assess the possibility of publication bias by evaluating a funnel plot for asymmetry. Because graphical evaluation can be subjective, we will also conducted an Begg’s adjusted rank correlation test[20] and Egger’s regression asymmetry test[21] as formal statistical tests for publication bias.

The effect of study-level variables on the overall adherence rates will be explored using sub-group and meta-regression analyses, including the following subgroup 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).

Univariable and multivariable random-effects logistic regression analyses will be conducted to investigate the impact of study characteristics on the pooled adherence proportions. Univariable random-effects logistic regression analyses will be used to investigate the bivariate relationship between each study-level factor (listed above) and adherence estimates. Multivariable random-effects logistic regression analyses will be carried out to determine which study-level factors were independently associated with adherence estimates. Of note meta-analysis results will be reported as combined adherence proportions with 95% confidence intervals (CIs), while meta-regression results are reported as odds ratio with 95% CIs. Al P<.05 will be considered significant. Analyses will use Stata version 12 for Windows (Stata Corp, College Station, TX).

Timelines:

1. Mid-September 2011: complete the first round of literature search and database creation
2. End-September 2011: Complete first round of analysis
3. Oct 5th 2011: Draft abstract and Submission to the Conference on Retroviruses and Opportunistic Infections (CROI) 2012 to be held in Seattle, Washington, USA, March 3-6, 2012 (www.retroconference.org)
4. Mid-November 2011: Draft manuscript
5. December 2011: Manuscript Submission to a peer-reviewed Journal

Key Personnel Biography Information:

We have previously published extensively on the methods of meta-analysis, indirect comparisons, and multiple treatment Comparison meta-analysis. Our group has worked together to conduct meta-analyses and MTC analyses for peer-reviewed and technical reports addressing diseases as diverse as HIV/AIDS, COPD, cardiovascular disease, microbiology, and smoking cessation. Our MTC work has appeared in methods journals such as *Journal of Clinical Epidemiology, Clinical Trials, and Clinical Epidemiology & Prevention*, as well as disease specific journals such as *JAMA, J Am Coll Cardiol, Ann Clin Microbiol Antimicrob, and Quarterly Journal of Medicine.*

Jean B. Nachega, MD, MPH, DTM&H, PhD, is an Associate Scientist in the Departments of International Health and Epidemiology at Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; and Former John L. Mc Goldrick Fellow at Harvard School of Public Health, Boston, MA, USA. He is also a Professor of Medicine in the Department of Medicine and Director of the Center for Infectious Diseases at Stellenbosch University, Cape Town, South Africa. He is an infectious disease specialist physician trained in Epidemiology, International Health and Tropical Medicine in Belgium, the UK, and the United States. Dr Nachega has a long-term goal of optimizing clinical and public health outcomes in HIV-infected patients globally through novel and practical interventions to improve adherence and retention in care. Dr. Nachega's research, teaching, and professional activities include planning, design and implementation of clinical trials, cohort studies & programs for prevention and treatment of HIV/AIDS & tuberculosis in sub-Saharan Africa. His work is primarily funded by the U.S. NIH/NIAID, the European and Developing Countries Clinical Trial Partnership (EDCTP) and the Wellcome Trust. In addition, he is the Principal Investigator of the NIH/HRSA PEPFAR funded Medical Education Partnership (MEPI) at Stellenbosch University in Cape Town.

Edward Mills, PhD, is a Canada Research Chair and Associate Professor at University of Ottawa and McMaster University. Dr. Mills is Director of a McMaster University-University of Ottawa Evidence on Tap centre funded by Canadian Institutes of Health Research. He has published more than 70 peer-reviewed articles on meta-analysis and methods in addition to a further 100 articles in disease specific domains, including cancer. Since 2007, he has been working on meta-analysis related to indirect comparisons and network meta-analysis. He has published articles on the background concepts of indirect comparisons and network meta-analysis, Bayesian approaches to meta-analysis, and the

stability of inferences from indirect comparison meta-analysis. More recently, he has been examining the validity of indirect comparisons as well as the additive effects of combining drugs in meta-analysis that have not been combined as packaged interventions. This approach may more realistically reflect how medicine is practiced. In addition to network meta-analysis, Dr. Mills has published extensively on the use of randomized trial evidence, meta-analyses, and observational studies.

Olalekan A. Uthman, MD, MPH &PhD is a public health physician and systematic reviewer. Dr. Olalekan has worked across a wide range of health technology assessments with a focus on meta-analytical research, HIV/AIDS, and other infectious diseases. He is an experienced Cochrane author and Cochrane Infectious Disease Group Editor. His research area aims to conduct high quality systematic reviews, and to investigate aspects of clinical trial and systematic review methodology. He is proficient in advanced methods in systematic review, such as mixed treatment comparison; Bayesian generalized evidence synthesis and trial sequential analysis. Dr Olalekan has published several systematic reviews and cost-effectiveness models on HIV/AIDS. He is trained in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to grading the quality of evidence and strength of recommendations. He has contributed to several recent UK National Institute for Health and Clinical Excellence public health and intervention guidelines and World Health Organization policies on antiretroviral therapies

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PubMed Search Strategy

#1	HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw]))
#2	Antiretroviral Therapy, Highly Active[MeSH] OR Anti-Retroviral Agents[MeSH] OR Antiviral Agents[MeSH:NoExp] OR ((anti) AND (hiv[tw])) OR antiretroviral*[tw] OR ((anti) AND (retroviral*[tw])) OR HAART[tw] OR ((anti) AND (acquired immunodeficiency[tw])) OR ((anti) AND (acquired immunedeficiency[tw])) OR ((anti) AND (acquired immuno-deficiency[tw])) OR ((anti) AND (acquired immune-deficiency[tw])) OR ((anti) AND (acquired immun*) AND (deficiency[tw])) OR NEVIRAPINE OR ZIDOVUDINE
#3	MOTHER-TO-CHILD TRANSMISSION OR MTCT OR DISEASE TRANSMISSION, VERTICAL OR prevention of mother-to-child transmission OR PMTCT
#4	"pregnan*" OR antenatal OR ante-natal OR Adheren* OR complian*
#5	#1 AND #2 AND #3 AND #4

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8-9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-10
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9-10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10-11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12-13, 19
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13-14
DISCUSSIONS			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18-19

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

Excluded studies

Study	Reason
Bhadrakom, 2000[1]	No relevant outcome reported
Desai, 2003[2]	Case study
MMWR, 2004[3]	No relevant outcome reported
Ciambrone, 2006[4]	Qualitative study on issues affecting adherence (no threshold reported)
Szyld, 2006 [5]	No relevant outcome reported
Abatemarco, 2008[6]	No relevant outcome reported
Black, 2008[7]	No relevant outcome reported
Coffie, 2008 [8]	Adherence threshold <80% (poor adherence was defined as having taken only one-half)
Varga, 2008 [9]	No relevant outcome reported
Delvaux, 2009 [10]	Case-control study
Mandala, 2009 [11]	No relevant outcome reported
Melekhin, 2009 [12]	No relevant outcome reported
Katz, 2010[13]	No relevant outcome reported
Melekhin, 2010 [14]	No relevant outcome reported
Mirkuzie, 2010[15]	No relevant outcome reported
Awiti Ujiji, 2011[16]	No relevant outcome reported
El-Khatib, 2011[17]	Mixed population
Kurewa, 2011 [18]	No relevant outcome reported
Panditrao, 2011[19]	No relevant outcome reported
Tshabalala, 2011[20]	No relevant outcome reported
Wang, 2011[21]	No relevant outcome reported

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eTable 1: Factors associated with adherence as reported by individual studies

Study	Factors reported
Albrecht[63]	Maternal non-adherence was associated with home births (OR: 3·2; 95% CI: 1·3 to 7·4), no high school education (OR: 2·4; 95% CI: 1·1 to 5·3), and low newborn birth weight (OR: 4·6; 95% CI: 1·3 to 20·1).
Bardequez[6]	The odds of perfect adherence were significantly higher for women who initiated ART during pregnancy (P <0·01), did not have AIDS (P = 0·02), never missed prenatal vitamins (P <0·01), never used marijuana (P = 0·05), or felt happy all or most of the time (P < 0·01).
Barige[62]	Women were more likely to ingest NVP if they were from study villages, preferred home administration or presented at a more advanced stage of pregnancy.
Bii[66]	Mothers who deliver in a health facility were more likely to adherence to sdNVP. Women attending ANC for two times or less, young women under 20 years of age and single women were less likely to swallow their sdNVP (p<0·05).
Cohn[65]	In multivariate analyses, those who had ever used illicit drugs had 5.95 times higher odds (p = 0·002) and those who missed prenatal vitamins had 4·84 times higher odds (p = 0·001) of ART nonadherence.
Demas[36]	Participation in HIV support groups and disclosure to the participant's mother were associated with better adherence.
Durante[58]	Adherence is associated with an understanding and belief in the effectiveness of antiretroviral therapy
Ickovics[57]	Those who were prescribed ZDV only 1–2 times per day had significantly higher adherence than those prescribed ZDV 3–5 times per day (58·1% vs. 40·3%, respectively, *p* = ·05).
Imbaya[30]	Adherence to ART was significantly associated with level of education (p=0.0117) and economic status (p=0·0109).
Kirsen[35]	Women who stated to have disclosed their HIV status were significantly more adherent in the pre-delivery period than women who did not (P = 0·004).
Kuonza[61]	Non-adherence to the maternal dose of nevirapine was associated with lack of

Study	Factors reported
	maternal secondary education (OR = 2·38; 95%CI: 1·05-3·39) and multi-parity (OR = 2·66; 95%CI: 1·05-6·72), while previous maternal exposure to the PMTCT programme (OR = 0·22; 95%CI: 0·08-0·57) and giving the mother a NVP tablet to take home during antenatal care (OR = 0·03; 95%CI: 0·01-0·09) were associated with improved maternal adherence to nevirapine.
Laine[7]	The adjusted OR of adherence for black (OR 0·47, 95% confidence interval [CI] 0·30, 0·75) and Hispanic (OR 0·49, 95% CI 0·29, 0·82) women were nearly 50% lower than for white women. The OR of adherence was 0·32 (95% CI 0·12, 0·90) for teenagers compared with women aged 25–29 years and 0·56 (95% CI 0·34, 0·92) for women in New York City versus those residing elsewhere. Women on antiretroviral therapy before pregnancy were more likely to adhere (OR 1·55, 95% CI 1·02, 2·35).
Louis[42]	Women with a viral load ≥ 1000 copies per milliliter at delivery were less likely to report medication adherence, (50·0% vs 87·8%, P < .001).
Mellins[33]	Factors associated with non-adherence included advanced HIV disease status, higher HIV-RNA viral load, more health-related symptoms and alcohol and tobacco use.
Mirkuzie[48]	Mother-infant pairs attended in health facilities at birth were more likely (OR 6·7 95% CI 2·90-21·65) to ingest their medication than those who were attended at home.
Nassali[68]	Previous attendance of a routine postnatal review and having access to a phone were significantly associated with adherence to PMTCT among mothers older than 25 years (odds ratio (OR) 3·6 (95% confidence interval (CI); 1·2-10·4)) and (OR 3·1 (95% CI; 1·3-7·1)), respectively. On the other hand, Christianity (OR 3·2 (95% CI; 1·1 - 9·0) was significantly associated with adherence to PN-PMTCT among mothers below 25 years of age. Mothers' perceived benefits of the PN-PMTCT program, easy access to the program, and presence of social support from a spouse were important motivators for mothers to adhere to PN-PMTCT.
Peltzer[49]	In multivariate analysis it was found that women with better PMTCT knowledge, term delivery and those who had told their partner about nevirapine had a higher maternal nevirapine adherence.

Study	Factors reported
Peltzer[53]	In multivariate analysis, it was found that women with higher HIV status disclosure and less discrimination were better in maternal ZDV adherence, women with higher male involvement were better in maternal and infant nevirapine adherence.
Turner[38]	Full adherence varied by race (29% of blacks vs 45% of whites), delivery site (29% New York city vs 46% rest-of state), prenatal care (29% adequate vs 46% inadequate).
Turner[39]	In multivariate models, older maternal age, prior illicit drug users, more recent year of delivery and women treated by a provider offering HIV-focused services were more likely to be adherent according to this pharmacy measure. Multiparous women, complete Medicaid eligibility, greater number of prescribed antiretroviral medications and with longer duration of prescribed therapy and had lower odds of pharmacy-based adherence.
Vaz[57]	In multivariate regression analysis, age >29 years (OR= 3·58, 95% CI 0·10–0·75, P=0·011), and mean number of pills/day <6 (OR 2·53, CI 95% 1·07–6·01, P=0·035)
Wilson[67]	In multivariate analyses having missed ZDV doses was positively associated with prenatal illicit drug use (OR= 3·49; 95% CI 1·30-9·42; *P* < ·05) and missing prenatal vitamins (OR= 2·71; 95% CI 1·30-5·67; *P* < ·01)

cART: combined antiretroviral therapy, sdNVP: single dose nevirapine, ZDV: Zidovudine, AIDS: acquired mmunodeficiency syndrome; ANC: antenatal care; ART: antiretroviral therapy, PMTCT: prevention of mother-to-child transmission; PN-PMTCT: postnatal prevention of mother-to-child transmission; RNA: ribonucleic acid, OR: odds ratio, CI: confidence interval

eTable 2: Overview of factors associated with adherence as reported by individual studies

	Albrecht[24]	Bardequez[30]	Barige[36]	Bil[26]	Cohn[27]	Demas[14]	Durante[58]	Ickovics[57]	Imbaya[30]	Kirsen[35]	Kuonza[61]	Iaine[7]	Louis[42]	Mellins[33]	Mirkuzie[48]	Nasaali[68]	Peltzer[49]	Peltzer[53]	Turner[38]	Turner[39]	Vaz[57]	Wilson[67]
Higher education	+								+		+											
Higher income									+											+		
Place of residence			+									+							+			
Media access																						
Younger women				−								−				−				−	−	
Single women				−																		
Black												−							−			
Christianity																+						
Multiparity											−									−		

	Albrecht[24]	Bardequez[30]	Barige[36]	Bii[26]	Cohn[27]	Demas[14]	Durante[58]	Ickovics[57]	Imbaya[30]	Kirsen[35]	Kuonza[61]	Iaine[7]	Louis[42]	Mellins[33]	Mirkuzie[48]	Nasaali[68]	Peltzer[49]	Peltzer[53]	Turner[38]	Turner[39]	Vaz[57]	Wilson[67]
Knowledge/beliefs about PMTCT							+									+	+					
Previous PMTCT											+					+						
Disclosure						+				+							+	+				
Partner support																+		+				
Access to phone																+						
Drug use		–			–									–						+		–
Depression		–																				
AIDS / advanced disease		–												–								
Home births	–			–											–							
Poor pregnancy outcomes	–																					
Advanced stage of pregnancy			+																			
Frequent ANC attendance				+															+			
Use of prenatal vitamin		+			+																	+

	Albrecht[24]	Bardequez[30]	Barige[36]	Bii[26]	Cohn[27]	Demas[14]	Durante[58]	Ickovics[57]	Imbaya[30]	Kirsen[35]	Kuonza[61]	laine[7]	Louis[42]	Mellins[33]	Mirkuzie[48]	Nasaali[68]	Peltzer[49]	Peltzer[53]	Turner[38]	Turner[39]	Vaz[57]	Wilson[67]
Home administration			+								+											
Focused service/support groups						+										+				+		
Number of pills/long duration								−												−	−	
On lifelong ART		+										+										
Higher viral load													−	−								

+ Positive association (promoter or facilitator of better adherence)

− Negative association (barrier to better adherence)

AIDS: acquired mmunodeficiency syndrome; PMTCT: prevention of mother-to-child transmission; ANC: antenatal care; ART: antiretroviral therapy