

Efficacy of Antiretroviral Drugs in Reducing Mother-to-Child Transmission of HIV in Africa: A Meta-Analysis of Published Clinical Trials

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Abstract

Antiretroviral drugs (ARVs) have been shown to be efficacious in decreasing mother-to-child transmission (MTCT) of HIV. A summary estimate of the efficacy of ARVs in reducing MTCT is important for modeling and policy decisions. However, no one has hitherto attempted to generate this summary estimate for Africa, the continent with the greatest HIV/AIDS burden. This study estimates the efficacy of ARVs in reducing MTCT in Africa through a meta-analysis of published studies conducted in Africa. Using an a priori protocol, Medline, EMBASE, and the Cochrane Library were searched for primary studies that measured MTCT of HIV, had ARVs as the exposure to the mother, and were conducted in Africa. Extracted data included characteristics of the study, population, quality, exposure, and results. The data were analyzed using a random effects model with each trial arm as a data point. Ten randomized clinical trials conducted in West, East, and Southern Africa published from 1999 to 2007 satisfied the inclusion criteria. They ranged in sample size from 139 to 1797, and used different ARV regimens as the exposure to the mother antepartum, intrapartum, or postpartum, and to the baby. The combined effect estimate of using ARVs is 10.6% (95% CI: 8.6–13.1) transmission at 4–6 weeks and 21.0% (95% CI: 15.5–27.7) transmission for placebo. This represents approximately 50% efficacy. The result is stable and not driven by any single study. All regimens were well tolerated. We conclude that ARV use to reduce MTCT of HIV in Africa is efficacious and well tolerated.

Introduction

ACCORDING TO UNAIDS, approximately 2.3 million children are currently infected with the HIV virus and 2 million (87%) of these infections are in sub-Saharan Africa. This high proportion of pediatric infections in Africa is probably due to the following: sub-Saharan Africa is the region most severely affected by the HIV/AIDS epidemic with two-thirds of the world infections, the mode of HIV transmission between adults is predominantly heterosexual leading to more women infected, women in Africa have on average more babies compared to women in other regions, breastfeeding of babies is more common in Africa, and the use of interventions to reduce mother-to-child transmission (MTCT) of HIV is lowest in Africa. The majority of the infections in children are transmitted from the mother during pregnancy, at delivery, or during breastfeeding.¹

The risk factors for MTCT of HIV include advanced HIV disease (high viral load, low CD4 cell count),^{2,3} vaginal de-

livery (lacerations, episiotomies, instrument deliveries),⁴ infections (chorioamnionitis, prolonged rupture of membranes),⁵ and breastfeeding.⁶ Interventions that have been shown to substantially reduce MTCT in the developed countries include cesarian delivery, avoiding breastfeeding, and use of antiretroviral drugs (ARVs).^{7,8} Caesarian operations require theater facilities and trained personnel that are unavailable to most mothers delivering in Africa. The promise of formula feeding babies in Africa has to be counterweighed against the absence of clean water, and some studies have shown similar or greater mortality in formula-fed babies in Africa.^{9,10} Use of ARVs thus appears to be the most feasible means to reduce MTCT in Africa, and it may be the most cost-effective means as well. ARVs work by reducing the viral load in the mother and providing preexposure and postexposure prophylaxis to the baby.¹¹

The benefits of ARVs in reducing MTCT of HIV are well documented. The first prevention of mother-to-child transmission (PMTCT) clinical trial (ACTG 076) published in 1994

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was conducted in the United States and France in non-breastfeeding populations and it involved administration of five doses of zidovudine daily to the mother from as early as 14 weeks gestation, intravenous infusion of the drug during labor, and four doses of zidovudine syrup daily to the infant for 6 weeks. The regimen decreased HIV transmission by 67%.¹² Because women in developing countries often present to clinics late in pregnancy and breastfeed their babies, and because there are usually no facilities for drug infusions during labor, the next trials examined the use of shortened zidovudine regimens administered orally in Thailand, although the population was still nonbreastfeeding.^{13,14} Short-course zidovudine was 50% efficacious in reducing transmission. Several trials conducted in Africa then tested short and ultrashort course zidovudine regimens and other ARV regimens in breastfeeding populations.

Since publication of the ACTG 076 trial, all later trials have used different regimens of drugs or combinations, administered ante-, intra-, or postpartum to mother or baby, and administered for different durations. On February 18, 1998, the Centers for Disease Control (CDC) stopped placebo arms in its Thailand and Côte d'Ivoire studies citing preliminary data from the Thai study indicating 50% efficacy for short course zidovudine. The four studies that were in progress in Africa dropped their placebo arms for ethical reasons, and all later studies did head-to-head comparisons of different regimens to demonstrate equivalence, noninferiority, or superiority.^{15,16} While the questions answered by head-to-head comparisons are undoubtedly important, it has not been possible to determine how efficacious ARV use to prevent MTCT in Africa has been. Several systematic reviews have been done on the topic but none has attempted a statistical synthesis of the data to provide a summary statistic of how efficacious ARV use is in PMTCT.^{17,18} A summary efficacy statistic is especially useful for policy projections, decisions, and evaluation. This paper seeks to assess the efficacy of ARV drugs in reducing vertical transmission of HIV in Africa by doing a meta-analysis of published clinical trials. Only studies that were conducted in Africa are summarized in this analysis for two reasons: first, to generate an efficacy estimate directly relevant for policies on the continent that is worst affected by the HIV/AIDS epidemic, and second, to preempt the question on what is feasible in Africa (drug compliance, C-section rates, breastfeeding, late antenatal presentation, etc.) by considering only studies performed there.

Materials and Methods

We developed an a priori protocol for literature search, data extraction, and analysis.

Literature search

We searched Medline (using PubMed), EMBASE, and the Cochrane Library for published articles on the use of ARVs to prevent MTCT of HIV. We divided the search to capture the themes of (1) prevention, control, or therapy and (2) disease transmission or infection, vertical or mother-to-child or maternal-fetal or perinatal, (3) HIV infection or AIDS, (4) antiretroviral drugs, agents, or therapy, and (5) Africa.

We developed search terms for these themes, combined the terms using OR for each theme, and then combined the different theme searches using AND. For Medline, we used

medical subject headings (MeSH terms) in an exploding search, supplemented by text and part-text words. We also used some of the search terms published as part of the "Comprehensive African HIV/AIDS RCT search strategy for PubMed" and checked the studies included in the African HIV/AIDS database.¹⁹ Similarly, for EMBASE we used Emtree terms programmed to map to preferred terminology, to include subterms and derivatives in an exploding search, and search as free text. We searched the combined Medline and EMBASE databases using the EMBASE tools. From the Cochrane Library, we performed a search of all clinical trials on HIV/AIDS conducted in Africa, from which we then selected those on MTCT with ARV exposures. We also checked the references of the published systematic reviews on the topic for studies cited. To accommodate the lag between publishing and database indexing, we limited all searches to articles published (including e-published ahead of print) on or before December 31, 2006. The final database searches were performed in June 2007.

Inclusion and exclusion criteria

We screened all titles and abstracts from the individual database search results, pooled the unique potentially eligible studies, retrieved full-text articles, and then assessed whether they met the inclusion criteria. We restricted inclusion to publications of clinical trials that reported primary data, measured HIV transmission from mothers to babies, had antiretroviral drugs as the exposure to the mother, and were performed in Africa. We excluded publications that did not report primary data (commentaries, perspectives, laboratory studies, secondary and meta-analyses, etc.), phase one and two trials, and studies done on Africans living outside the continent.

Data extraction

P. Chigwedere extracted the data and M. Essex supervised the process; inconsistencies were resolved by discussion with all authors. We extracted the data using a standardized form. We extracted details of the study (citation, publication date, study name, location, and dates carried out), the subjects (demographic characteristics, inclusion/exclusion criteria, number enrolled, loss to follow-up), the exposure (ARV regimen used for each arm, dosage, duration, adverse events), the endpoint (HIV transmission rates to babies, when the endpoint was measured, how the endpoint was measured), and other data relevant for transmission (mode of delivery, breastfeeding).

Methodological quality

We assessed the quality of studies using the Jadad criteria for assessing clinical trials.²⁰ We described how randomization was generated, the adequacy of blinding, and loss to follow-up; we, however, did not assign a quantitative score for quality. We also assessed adherence to medications and the test used to determine HIV status in the baby.

Statistical analysis

Because it is not meaningful to statistically summarize the efficacy across studies with different comparison groups, each differing from the next in regimen and/or duration, we

chose the cumulative incidence of HIV transmissions as the metamer. This treats each arm within a trial as a data point, rather than the whole trial being the data point. We used the raw data of number of transmissions/sample size as given in the papers. Where raw data were not given or incomplete, we used the transmission rate estimate calculated from survival analysis methods (as published) and the sample size randomized for that arm. We chose transmission at 4–6 weeks postpartum to capture combined antepartum and intrapartum transmission, although this may include some early transmission from breastfeeding. For studies that did not report data or estimates at 4–6 weeks, we used data closest to 4 weeks but not less than 3 weeks, for this may miss some intrapartum transmission.²¹ For studies with multiple publications, we used the estimate reported first since we intended to do a cumulative meta-analysis showing when the data were first available. We converted the different data formats into a single format of event rate and standard error.

We used the software Comprehensive Meta-Analysis (CMA version 2 Professional Package) from Biostat Inc., Englewood, NJ for the analysis.²² We a priori chose the DerSimonian and Laird random effects model for the analysis.²³ The sources of heterogeneity evident before analysis include the use of different regimens, different durations, and an endpoint measured over a period from 4–6 weeks. Accordingly, the random effects model, which does not assume that all studies are estimating the same true effect, is appropriate. For the summary statistics, we grouped all study arms that used an ARV regimen and, separately, study arms that used no ARVs (placebo), then ran the analysis. Although we do not necessarily assume that combined ARV arms are comparable to combined placebo arms, as would be in a randomized study, we calculated efficacy of ARV use to prevent MTCT as $1 - T_{ARV}/T_{placebo}$ where T_{ARV} is the combined transmission rate in trial arms that used ARVs and $T_{placebo}$ is the combined transmission rate in the placebo arms.²⁴ To check if the result was qualitatively sensitive to the model used, we also ran the analyses using the Mantel-Haenszel fixed effects model.²⁵ We ran a one-study-removed analysis for both the ARV use group and placebo group to determine if there was one study disproportionately driving the combined estimate. We ran a cumulative meta-analysis ordered chronologically by date of publication to determine when conclusive evidence of ARV efficacy was available, if there was any.²⁶

We used the Q and I^2 statistics to assess heterogeneity of effect estimates.²⁷ We also ran an analysis using each study group, as opposed to the trial arm, as the data point. For this we combined the different ARV arms in each study first, and then ran the analysis with one data point for each study. This allowed an assessment of heterogeneity across the studies.

We assessed publication bias by plotting a precision funnel plot²⁸ and using Duval and Tweedie's trim and fill procedure to assess the number of small studies missing if there is publication bias.²⁹ We also calculated Orwin's fail safe number of studies required to raise the total transmission rate to 20% (assumed as the transmission rate without using ARVs) if each missing study has a transmission rate of 25%.³⁰ We also used Begg and Mazumdar's rank correlation method³¹ and Egger's regression test for publication bias.³²

Results

The search results are summarized in Fig. 1. The search strategy yielded 378 articles from Medline searched via PubMed, 467 articles from combined Medline and EMBASE databases searched from EMBASE, and 156 trials from the Cochrane Library. After screening titles and abstracts from each database separately, and excluding irrelevant papers and articles with no primary data, 64 papers were selected for full-text article review, from which 10 clinical trials met the inclusion criteria. Using the trial names and authors, multiple publications on each trial were retrieved and analyzed to provide as complete a picture of the studies as possible. Trial data not included in this analysis are the pooled 24 month analysis of the RETRO-CI and DITRAME studies^{33,34} because the trial data were already included separately for each study, the component of the Malawi postexposure prophylaxis study for which there was no nevirapine given to the mother,³⁵ the component of the MASHI study that focused on feeding strategies,³⁶ and the South Africa postexposure prophylaxis because it had no ARV exposure to the mother.³⁷

The characteristics of the selected studies are summarized in Table 1. The studies were conducted in West Africa (Côte d'Ivoire and Burkina Faso), East Africa (Uganda, Tanzania, and Kenya) and Southern Africa (South Africa, Malawi, Botswana, and Zimbabwe). Eight of the studies were designed to assess the efficacy of ARV regimens to reduce MTCT, one was designed to test nucleoside analogue antiviral activity during short course mono or dual therapy in

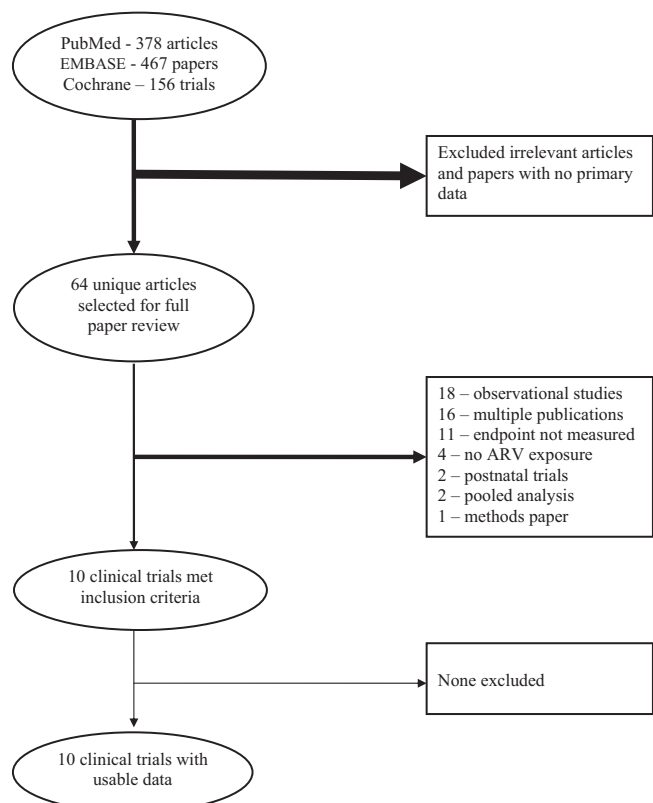


FIG. 1. Search results.

TABLE 1. CHARACTERISTICS OF THE STUDIES^a

<i>Study, country</i>	<i>References</i>	<i>Dates performed</i>	<i>Design</i>	<i>Number</i>	<i>Population</i>	<i>Study quality</i>	<i>Test</i>
RETRO-CI; Abidjan, Côte d'Ivoire	48	April 1996–Feb 1998; stopped after Thai results	RCT; oral ZDV vs. placebo	280	HIV, women > 18 years, before 36 weeks, ARV naive, 100% BF	Block randomization; placebo; binding; compliance measured; observed administration of drug in labor; LOF reduced	DNA PCR
DITRAME ARNS 049a; Côte d'Ivoire and Burkina Faso	49, 50	Sept 1995–Feb 1998; stopped after Thai results	RCT; oral ZDV vs. placebo	421	HIV, women > 18 years, before 32 weeks, BF	Block randomization; sealed packages with placebo or drug; compliance assessed; LOF recorded	DNA RNA PCR
HIVNET 012; Uganda	51, 52	Nov 1997–April 1999; no placebo from 1998	RCT; oral NVP vs. ZDV	626	HIV, women > 18 years, after 32 weeks, ARV naive, 96% BF	Individual randomization into blocks; open label after randomization; adherence assessed by interview; LOF recorded	RNA PCR
PETRA; South Africa, Uganda and Tanzania	53	June 1996–Jan 2000; no placebo from 1998	RCT; four arms ZDV/3TC vs. placebo	1797	HIV, women > 18 years, before 36 weeks; 53–97% BF	Block randomization by site; placebo; double blinding; adherence assessed by pill packs; LOF recorded	DNA RNA PCR
Kenya	54	Nov 1999–Jan 2001	RCT for compliance.	139	HIV, women, from 35 weeks, 66% BF	Block randomization; sealed envelopes; compliance measured; LOF recorded	DNA PCR
SAINT; South Africa	55	May 1999–Feb 2000	RCT; ZDV vs. NVP vs. ZDV/3TC	1317	HIV, women > 16 years, 38 weeks, ARV naive, 47% BF	Computer-generated scratch card randomization; open label; drugs administered by nurses; compliance assessed by interview	DNA PCR + NSens
NVAZ; Malawi	56	April 2000–Mar 2003	RCT; NVP/NVP vs. NVP/ZDV	894	HIV, women > 4 hours before delivery; ARV naive, 99% BF	Block randomization for each of six clinics; open label; NVP directly administered by nurse but ZVD taken home; adherence assessed by interview; LOF recorded	RNA NSens
South Africa	57	May 1999–May 2000	RCT; four arms; no placebo	373	HIV, women > 18 years, 34 weeks, naive, formula × 6 months	Method of randomization not given; open label; adherence not recorded; LOF recorded	DNA PCR
Mashi; Botswana	58	June 2002–Oct 2003	2 × 2 factorial RCT; ZDV vs. ZDV/NVP	709	HIV, women > 18 years, from 33–35 weeks gestation, BF randomized	Centralized randomization by site; blinding for NVP vs. placebo; LOF recorded; adherence assessed	DNA PCR
Zimbabwe	59	Dec 2002–Aug 2004; stopped; no superiority trend	RCT; NVP vs. NVP/ZDV	609	HIV, women first antenatal visit; ARV naive, BF	Computer-generated block randomization; placebo for mother but not baby; LOF recorded	RNA NSens

^aRCT, randomized clinical trial; ZDV, zidovudine; ARV, antiretroviral drug; BF, breast feeding; LOF, loss of follow-up; NVP, nevirapine; 3TC, lamivudine.

TABLE 2. STUDY EXPOSURES AND ENDPOINTS^a

Study	Group, n	Antepartum	Intrapartum	Postpartum mother	Postpartum baby	Results	Safety
RETRO-CI	Arm 1: 140	ZDV 300 mg bd from 36 weeks	ZDV 300 mg/3 h	No ARVs	No ARVs	15/22 cases at 4 weeks (KM)	Well tolerated
	Arm 2: 140	Placebo	Placebo	No ARVs	No ARVs	26/119	
DITRAME 049a	Arm 1: 209	ZDV 300 mg bd from 36–38 weeks	ZDV 600 mg stat	ZDV 300 mg bd × 7 days	No ARVs	28/183 cases at 45 days (KM)	Well tolerated
	Arm 2: 212	Placebo	Placebo	Placebo	No ARVs	42/187	
HIVNET 012	Arm 1: 313	No ARVs	NVP 200 mg once	No ARVs	NVP 2 mg/kg once	37 cases 13.1% (9.1–17.1) at 14–16 weeks (KM)	Well tolerated
	Arm 2: 313	No ARVs	ZDV 600 mg stat + 300 mg/3 h	No ARVs	ZDV 4 mg/kg bd × 7 days	65 cases 25.1% (19.5–30.8)	
PETRA	Arm 3: 19	No ARVs	Placebo	No ARVs	Placebo	6 cases 36.7% (13.2–60.1)	
	Arm A: 475	36 weeks ZDV 300 mg + 3TC 150 mg bd	ZDV 300 mg/3 h + 3TC 150 mg bd	ZDV 300 mg + 3TC 150 mg bd × 7 days	ZDV 4 mg/kg + 3TC 2 mg/kg bd × 7 days	16 (5.7%) at 6 weeks (KM)	Well tolerated
Kenya	Arm B: 474	Placebo	ZDV 300 mg/3 h + 3TC 150 mg bd	ZDV 300 mg + 3TC 150 mg bd × 7 days	ZDV 4 mg/kg + 3TC 2 mg/kg bd × 7 days	24 (8.9%)	
	Arm C: 471	Placebo	ZDV 300 mg every 3 h	Placebo	Placebo	40 (14.2%)	
SAINT	Arm D: 377	Placebo	Placebo	Placebo	Placebo	40 (15.3%)	Not reported
	Arm 1: 70	ZDV 300 mg bd from 36 weeks	ZDV 300 mg	No ARVs	No ARVs	5/55 infections at 6 weeks (raw data)	
Malawi	Arm 2: 69	No ARVs	NVP 200 mg stat	No ARVs	NVP 6 mg	12/55 at 6 weeks	Well tolerated
	Arm 1: 655	No ARVs	NVP 200 mg	NVP 200 mg	NVP 6 mg	63 cases 10.4% (7.9–12.8) at 4 weeks (KM)	
South Africa	Arm 2: 662	No ARVs	ZDV 300 mg/3 h + 3TC 150 mg bd	ZDV 300 mg + 3TC 150 mg bd × 7 days	ZDV 12 mg + 3TC 6 mg bd × 7 days	49 cases 7.9% (5.8–10.1)	
	Arm 1: 448	No ARVs	NVP 200 mg	No ARVs	NVP 2 mg/kg	59 cases 14.1% (10.7–17.4) at 6–8 weeks (life table method)	Well tolerated
Mashi	Arm 2: 446	No ARVs	NVP 200 mg	No ARVs	NVP 2 mg/kg once + ZDV 4 mg/kg bd × 7 days	70 cases 16.3% (12.7–19.8)	
	Arm 1: 93	D4T 40 mg bd from 34–36 weeks	D4T 40 mg stat	No ARVs	ZDV 1 mg/kg bd × 6 weeks	9/91 infections at 6 weeks (raw data)	Well tolerated
Zimbabwe	Arm 2: 95	DDI 200 mg bd	DDI 200 mg stat	No ARVs	DDI 120 mg/sqm bd	6/94	
	Arm 3: 93	D4T 40 mg bd + DDI 200 mg bd	D4T 40 mg + DDI 200 mg stat	No ARVs	D4T 1 mg/kg bd + DDI 120 mg/sqm bd	3/88	
Zimbabwe	Arm 4: 92	ZDV 300 mg bd	ZDV 300 mg	No ARVs	ZDV 4 mg/kg bd	4/89	
	Arm 1: 354	ZDV 300 mg bd from 34 weeks	NVP 200 mg stat	No ARVs	ZDV 4 mg/kg bd × 1 month + NVP 6 mg	15/345 infections at 45 days (raw data)	Well tolerated
Zimbabwe	Arm 2: 355	ZDV 300 mg bd from 34 weeks	ZDV 300 mg/3 h + placebo	No ARVs	ZDV 4 mg/kg bd × 1 month + NVP 6 mg	13/349	
	Arm 1: 312	No ARVs	ZDV 300 mg/3 h + NVP 200 mg	No ARVs	ZDV 2 mg/kg qid × 3 days + NVP 2 mg/kg	45/312 infections at 6 weeks (raw data)	Well tolerated
Arm 2: 297	No ARVs	NVP 200 mg + stat placebo	NVP 200 mg + stat placebo	No ARVs	NVP 2 mg/kg	49/297	

^aZDV, zidovudine; ARV, antiretroviral drug; KM, Kaplan–Meier method; NVP, nevirapine; 3TC, lamivudine; D4T, stavudine; DDI, didanosine.

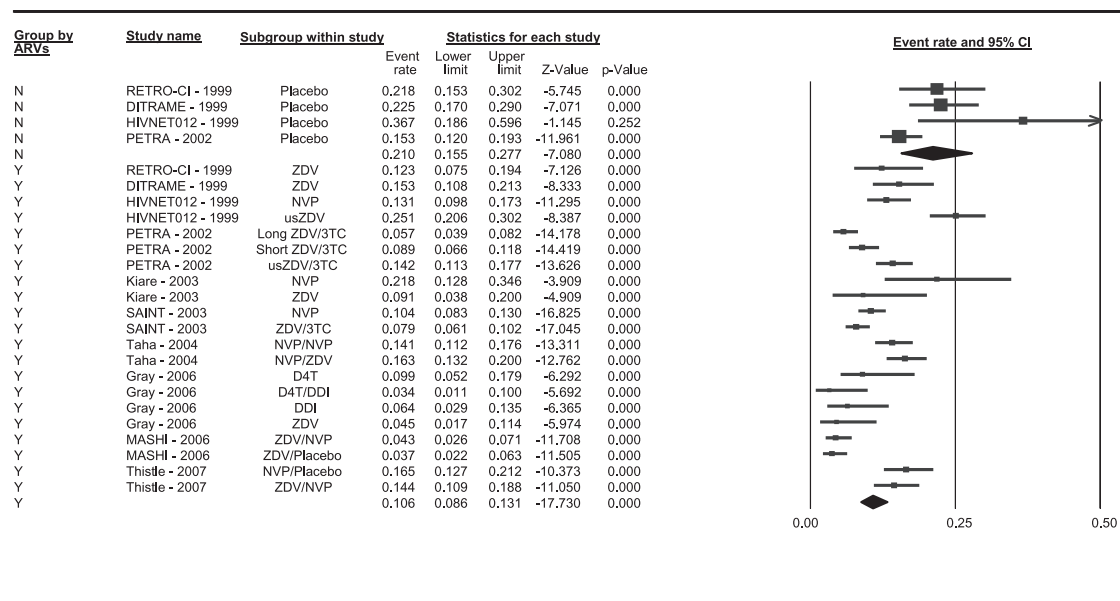


FIG. 2. Combined effect estimate for ARVs and combined effect estimate for placebo arms.

pregnant women, and one study was designed to measure compliance of two regimens used to reduce MTCT. The studies were conducted from as early as 1995, although the first publications appeared in 1999. Studies ranged in sample size from 139 to 1797, and they recruited confirmed HIV-positive pregnant women in the third trimester with exclusions for young age, abnormal blood counts, and abnormal liver function tests. All studies were randomized controlled trials and used a nucleic acid assay to determine infection in babies; the Jadad quality of most studies was high.

The drug regimens used and trial endpoints are summarized in Table 2. The studies differed in whether ARV drugs were given antepartum, intrapartum, postpartum to the mother, and postpartum to the baby; the drug or combination used; the dose, frequency, and duration of drug administration; and whether there was a placebo arm. Eight of

the 10 studies had the HIV transmission measured at 4–6 weeks, while one was measured at 6–8 weeks, and for one we selected 14–16 weeks because that is when the placebo arm had an HIV transmission estimate. Four studies published the endpoint as raw data of infections/sample size, five as an estimate from the Kaplan–Meier method, and one as an estimate from the life table method. Although most of the trials were designed primarily to assess efficacy, they reported good toleration of the drugs by women and their babies. One trial did not report tolerance or toxicity.

The random effects meta-analysis with study arm as the unit of analysis is shown in Fig. 2. The combined transmission rate for arms that used ARVs is 10.6% (95% CI: 8.6–13.1), while the combined transmission rate for arms that used placebo is 21.0% (95% CI: 15.5–27.7). Using the combined transmission rates above, the efficacy of using ARVs to re-

TABLE 3. FIXED AND RANDOM EFFECTS MODELS WITH STUDY SUBGROUP AS UNIT OF ANALYSIS

Group	Number of studies	Point estimate	Lower limit	Upper limit (95% CI)
Fixed effect analysis				
No ARVs	4	0.192	0.165	0.224
Yes ARVs	21	0.124	0.116	0.133
Random effects analysis				
No ARVs	4	0.210	0.155	0.277
Yes ARVs	21	0.106	0.086	0.131
<i>Heterogeneity statistics</i>				
Q-value	df (Q)	p-value	I-squared	
8.998	3	0.029	66.658	
156.212	20	0.000	87.197	

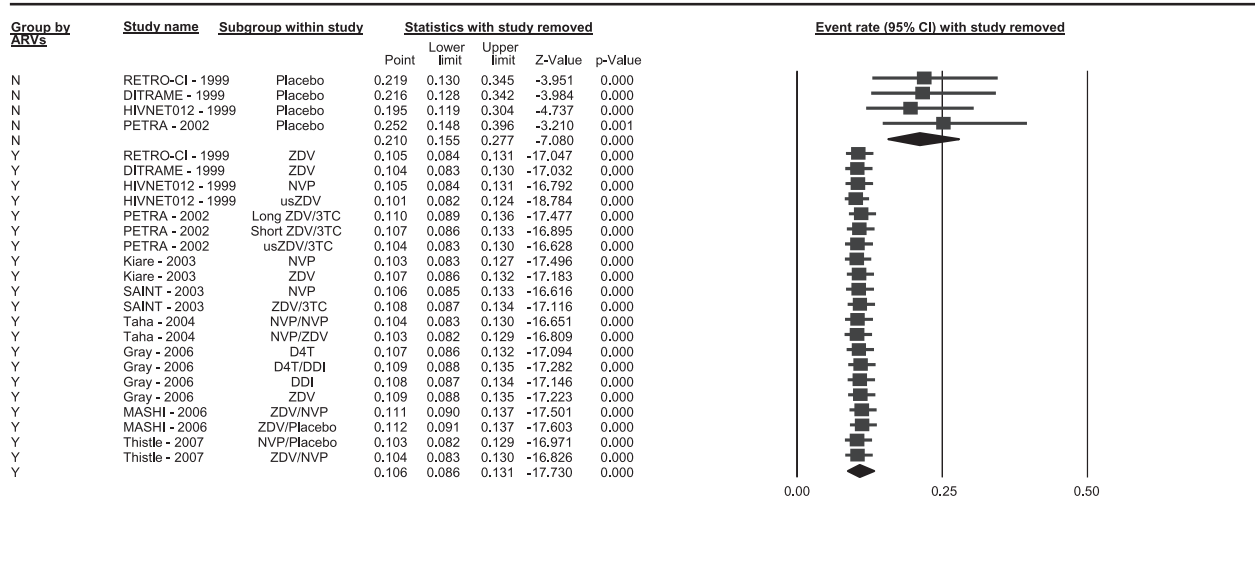


FIG. 3. One study removed meta-analysis, grouped by ARVs and placebo.

duce MTCT is approximately 50% (1–10.6/21.0). The result does not change qualitatively depending on the model used. Table 3 shows that using a Mantel–Hanszel fixed effects analysis, the combined transmission rate for ARVs is 12.4% (95% CI: 11.6–13.3) and the combined transmission rate for placebo is 19.2% (95% CI: 16.5–22.4). The combined transmission estimate is not disproportionately driven by one single study or a few studies. Figure 3 shows the one-study-removed meta-analysis and the effect estimate for transmission using ARVs varies slightly between 10.1% and 11.2%. Similarly, the estimate for transmission for the placebo group varies from 19.5% to 25.2%. The cumulative meta-analysis, ordered by year of publication, is shown in Fig. 4. It shows that the de-

creased transmission rate by using ARVs was clear right from 1999 when the first studies were published, and later studies have confirmed this efficacy and increased the precision of the estimate. Taken together, the results are robust in showing the efficacy of using ARVs to reduce MTCT. Using a vote count of trials that recorded toxicity, ARV use was tolerated by both the mothers and babies in all trial arms.

We assessed publication bias using the funnel plot. Figure 5 shows the funnel plot of precision by logit event rate with each study arm as a data point. Using Duval and Tweedie’s trim and fill method and the random effects model, one study was added to the right of the mean to enhance symmetry. The one-tail *p*-values (since publication bias refers

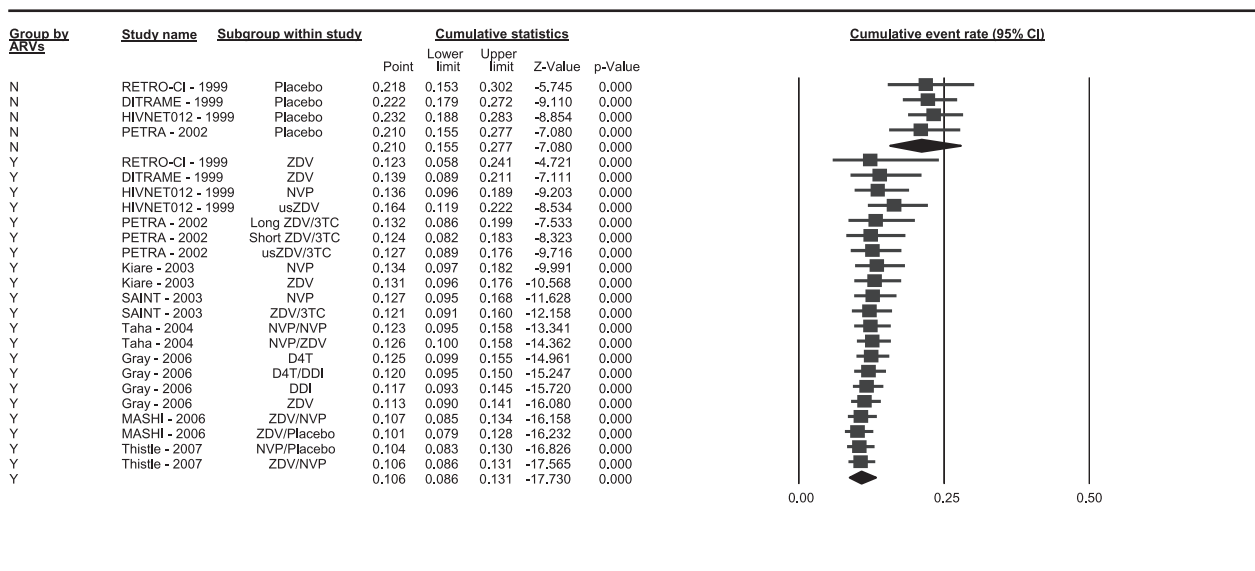


FIG. 4. Cumulative meta-analysis ordered by publication date.

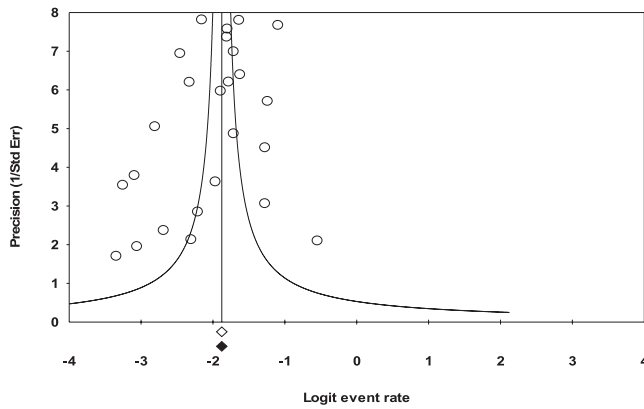


FIG. 5. Publication bias. Funnel plot of precision by logit event rate.

only to small nonsignificant studies) for Egger’s regression intercept (0.07) and Begg and Mazumdar’s rank correlation with (0.08) or without (0.08) continuity correction are all nonsignificant. Using Orwin’s method and setting 20% as the trivial transmission rate, we calculated that the number of studies with a 25% transmission that are needed to bring the transmission rate to 20% is 43. It seems unlikely that 43 nonsignificant clinical trials exist and have just not been published. We conclude that there is no statistical evidence of publication bias.

We assessed heterogeneity of effect estimates using the Q and I^2 statistics shown in Table 3. The p -value for the Q statistic is 0.000 and the I^2 statistic is 87 for ARV arms. We conclude that there is significant heterogeneity of effect estimates between the study arms. For the placebo arms, the Q statistic has a p -value of 0.029 and the I^2 statistic is 67. We conclude that there is some heterogeneity between the placebo arms. This is also shown by doing the analysis with study (not study arm) as the unit of analysis. Figure 6 shows the forest plot and Table 4 shows the heterogeneity statistics; both show significant heterogeneity across the studies. We a priori expected heterogeneity; the statistics thus confirm this heterogeneity.

Discussion

The key result of this meta-analysis is that ARVs reduce MTCT of HIV from 21% (combined placebo estimate) to 10.6% at 4–6 weeks after birth in Africa. From a unanimous vote of the studies that reported toxicity, ARV regimens for PMTCT are well tolerated by both the mothers and babies. The quantity of this evidence is 10 clinical trials with a combined sample size of over 7000 HIV-infected pregnant women and over 800 transmission endpoints. The type of this evidence is high grade, that is, randomized clinical trials rather than observational, cross-sectional or case reports.^{38,39} The quality of the individual clinical trials is high. The efficacy of using ARVs versus placebo is 50%. Using the Institutes of Medicine categories of assessing evidence,^{40,41} we may conclude that the evidence establishes that ARVs are efficacious in reducing MTCT in Africa, and the evidence favors rejection of the hypothesis that ARVs, in the doses used, are toxic to the mothers or babies.

This study is different from the other systematic reviews that have been published on the topic in that it is restricted to studies conducted in Africa, and it produces a summary statistic of the efficacy of using ARVs. The efficacy estimate is important, especially for modeling policy implications of using or not using ARVs for PMTCT in Africa. Other published reviews^{42–44} do not have a summary efficacy estimate for two reasons: first, there is much heterogeneity across the studies, and second, it is not meaningful to summarize efficacy estimates (as published) from trials with different head-to-head comparisons. Regarding heterogeneity, we were aware before the analysis that the PMTCT studies compared different drugs or combinations, different permutations of whether the drugs were administered ante-, intra-, or postpartum to mother or baby, absence of a placebo comparison for all recruitment done after February 1998, the slightly different times when the endpoints were measured, and other differences in breastfeeding and C-section rates. This is significant heterogeneity and the Q and I^2 statistics confirmed this. However, heterogeneity is as much a foe as it is a friend. The strength is that when there is this much heterogeneity, but virtually all arms that used ARVs show reduction in MTCT, the result is robust.⁴⁵ This is the consistency, following Sir Bradford Hill’s criteria,⁴⁶ that makes it possible to move toward generalizing that ARVs are efficacious in reducing MTCT.

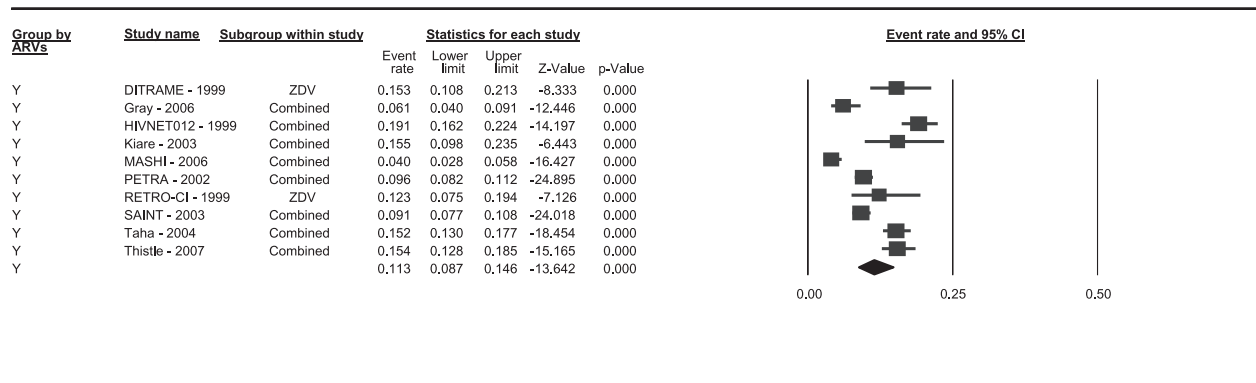


FIG. 6. Meta-analysis with study as unit of analysis.

TABLE 4. FIXED AND RANDOM EFFECTS MODELS WITH STUDY AS UNIT OF ANALYSIS

<i>Model</i>	<i>Number of studies</i>	<i>Point estimate</i>	<i>Lower limit</i>	<i>Upper limit</i>
Fixed effects	10	0.121	0.113	0.130
Random effects	10	0.113	0.087	0.146
<i>Heterogeneity statistics</i>				
<i>Q-value</i>	<i>df (Q)</i>	<i>p-value</i>	<i>I-squared</i>	
114.096	9	0.000	92.112	

To calculate the efficacy, we statistically combined all treatment arms, and, separately, all placebo arms, as a way of combining trials that performed different head-to-head comparisons. Although for each placebo arm there is at least one treatment arm, 6 of the 10 trials did not have placebo arms. This raises the possibility that the combined treatment arms (10 studies, 21 arms) and combined placebo arms (4 studies, 4 arms) may not be comparable. This method of analysis thus loses the comparability and exchangeability of arms that randomization brings to each trial. Accordingly, this study resembles a meta-analysis of different observational studies (with HIV transmission rate as the metamer), which is then subgrouped into studies that used ARVs versus those that did not. The efficacy is then *estimated* by comparing the two subgroups, without necessarily assuming that they are exchangeable. This means that there may be some bias in the efficacy estimate if the ARV and placebo groups are different. We did assess the characteristics of women in the trials that used placebo and compared them to the characteristics of women in trials that did not use placebo, and we are satisfied that they are broadly very similar in age and other demographic characteristics, clinical stage of HIV disease, CD4 count, and birth outcomes. Studies performed in South Africa had higher cesarean section rates than elsewhere, but both the placebo and ARV arms had such studies. Moreover, for results published by 2002, every trial had a placebo arm. The cumulative meta-analysis results to 2002 can therefore be taken as representing a comparison of ARVs versus placebo in comparable groups, and the results are very similar to results of the entire meta-analysis. A slight increase in efficacy after 2002 is explained by the MASHI and Gray studies, which administered ARVs for the longest durations both antepartum and postpartum.

We chose 4–6 weeks as the time when the endpoint was measured. Eight of the 10 studies had outcomes measured or estimated at 4–6 weeks, one study measured the endpoint at 6–8 weeks, and for one study we used 14–16 weeks because that is when the endpoint was estimated in the placebo arm. Since the study populations breastfed and HIV transmission occurs via breastfeeding, endpoints estimated at later time points do show a higher transmission rate. Accordingly, if we had chosen endpoints measured after 18 or 24 months, the transmission rates would be higher in both treatment and placebo arms.⁴⁷ We chose an early endpoint because (1) all studies have an early endpoint but few followed up babies to 24 months, and (2) we were interested in

combined antepartum and intrapartum transmission, without addressing the complex questions regarding breast or formula feeding, mortality, and HIV transmission.

We did address other general shortfalls of meta-analyses. First, although meta-analyses may summarize the findings of randomized clinical trials, the meta-analysis itself is a retrospective observational study that may suffer the biases common in other observational studies. We attempted to minimize bias in selection of studies by designing an a priori protocol that specified and justified the question to be asked, the inclusion and exclusion criteria for studies, the search methods and databases to be searched, the data to be extracted from each study, and methods for analysis. We assessed the possibility of publication bias using several methods including Orwin's fail-safe number. There is no statistical evidence of publication bias and it is highly unlikely that there are 43 unpublished studies to increase the combined MTCT rate to 20%. We therefore believe that this meta-analysis is an objective selection and analysis of the available data, rather than a study driven by a desired outcome.

Second, if the quality of the input studies is poor, the meta-analysis may report a very precise but wrong synthesis, what has been labeled "garbage in, garbage out." In this study, all studies were fully published articles in peer-reviewed journals (rather than abstracts or gray literature) so that we could assess several dimensions of quality. We did not assign a quantitative value to the quality for weighting in the analysis because we believe this confuses quality with sample size, the determinant of weight in analysis models. We were satisfied that all studies were of high Jadad quality; the Gray study *appeared* to be of good quality although the *reporting* could have been better by stating how randomization was generated and including a CONSORT flow diagram.^{48–59}

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