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Screening for HIV in Pregnant Women: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation

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Structured Abstract

Background: A 2005 U.S. Preventive Services Task Force (USPSTF) review found good evidence that prenatal HIV screening is accurate and can lead to interventions that reduce the risk of mother-to-child transmission.

Purpose: To systematically update the 2005 USPSTF review on benefits and harms of prenatal HIV screening, focusing on research gaps previously identified and new evidence on treatments.

Data Sources: We searched MEDLINE (2004 to June 2012) and the Cochrane Library Database (2005 to the second quarter of 2012) and manually reviewed reference lists.

Study Selection: We selected randomized trials and cohort studies of pregnant women that reported risk of mother-to-child transmission or maternal or infant harms associated with prenatal HIV screening or antiretroviral therapy during pregnancy. We also selected studies that reported the yield of repeat prenatal screening or the positive predictive values and harms associated with rapid versus standard HIV testing during pregnancy.

Data Extraction: Two reviewers abstracted and confirmed study details and quality using predefined criteria, based on methods developed by the USPSTF.

Data Synthesis (Results): No study directly evaluated effects of prenatal screening for HIV infection versus no screening on risk of mother-to-child transmission or maternal or infant clinical outcomes. One fair-quality, large cohort study (0.7% HIV prevalence) found rapid testing during labor associated with a positive predictive value of 90 percent. New cohort studies of nonbreastfeeding women in the United States and Europe confirm that full-course combination antiretroviral therapy reduces risk of mother-to-child transmission (<1% to 2.4% vs. 9% to 22% with no antiretroviral therapy). New cohort studies found antiretroviral therapy during pregnancy associated with increased risk of preterm (prior to 37 weeks' gestation) delivery, with no clear association with low birth weight, congenital abnormalities, or infant neurodevelopment.

Although some studies found an association between in utero exposure to antiretroviral therapy and subsequent echocardiographic abnormalities, hematologic abnormalities, and markers of mitochondrial dysfunction, the clinical significance of these findings remains unclear. Evidence on long-term maternal harms associated with short-term exposure to antiretroviral therapy during pregnancy, or antiretroviral therapy started during pregnancy and continued after pregnancy, remains sparse.

Limitations: Only English-language articles were included. Due to limited evidence from randomized trials, we included cohort studies of treatments. Studies conducted in resource-poor settings may be of limited applicability to screening in the United States.

Conclusions: Antiretroviral therapy in combination with avoidance of breastfeeding and elective Cesarean delivery in women with viremia reduces risk of mother-to-child transmission. Use of certain antiretroviral therapy regimens during pregnancy may increase risk of preterm delivery, but more evidence is needed to fully understand short- and long-term maternal and infant effects.

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CHAPTER 1. INTRODUCTION

Purpose of Review and Prior USPSTF Recommendation

The purpose of this report is to update a previous evidence review[1, 2] commissioned by the U.S. Preventive Services Task Force (USPSTF) on screening for asymptomatic HIV infection in pregnant women, including adolescents. In 2005, based on the earlier review, the USPSTF recommended that clinicians screen all pregnant women for HIV (grade A recommendation).[3] Although the USPSTF found no studies that directly evaluated prenatal HIV screening versus no screening on risk of mother-to-child transmission or other clinical outcomes, it found good evidence that prenatal testing is accurate and acceptable to women and that treatment with recommended interventions (combination antiretrovirals, elective Cesarean delivery in women with viral loads >1,000 copies/mL near the time of delivery, and avoidance of breastfeeding) is associated with major reductions in risk of mother-to-child transmission (from 14% to 25% in untreated women to 1% to 2% with treatment). The USPSTF concluded that benefits of treatments in reducing perinatal transmission substantially outweighed short-term harms, though evidence on long-term maternal or infant harms associated with screening and subsequent interventions was limited.[1, 2] The current report will be used by the USPSTF to update its 2005 recommendation on prenatal HIV screening.

This update focuses on newer evidence on the accuracy and acceptability of rapid versus standard testing, the effectiveness of newer antiretroviral regimens for reducing mother-to-child transmission, long-term maternal outcomes following use of antiretroviral regimens during pregnancy, and maternal and infant harms associated with use of antiretroviral medications. Because perinatal practices and interventions related to prevention of HIV infection are substantially impacted by the availability of resources, the report will emphasize evidence applicable to typical practice in the United States.

Condition Definition

HIV is a ribonucleic acid (RNA) retrovirus that infects the immune cells of its human hosts, in particular, CD4 helper T cells. HIV infection leads to acquired immune deficiency syndrome (AIDS) in most patients if left untreated. HIV is a communicable disease with two types: HIV-1 and HIV-2. HIV-2 infection is very uncommon in the United States, primarily affects persons from West Africa, and is less likely to progress to AIDS.[4] AIDS is a life threatening disease defined by severe immune dysfunction (CD4 T cell count $\leq 0.200 \times 10^9$ cells/L) or one or more AIDS-defining opportunistic infections or neoplastic conditions.[5]

Prevalence and Burden of Disease

In 2009, women represented 24 percent of all diagnoses of HIV infection among adults and adolescents in the United States.[6] About 300,000 U.S. women were living with HIV infection in 2008,[7] with 11,200 new cases in 2009.[6] The prevalence of HIV infection increases from 0.03 percent in women ages 15 to 19 years to 0.7 percent in women ages 40 to 44 years, though estimates vary depending on geographic area, demographic characteristics, and presence of risk factors.[8] The

prevalence of HIV infection is higher in black and Latina women compared with women of other races/ethnicities. An estimated 18 percent of women with HIV infection are unaware of their status.[6, 7]

Between 6,000 and 7,000 HIV-positive women give birth each year in the United States,[9] with approximately 30 percent of women unaware of their HIV-positive status prior to pregnancy.[10] From 2001 to 2004, approximately 7 percent of HIV-infected women in the United States were undiagnosed at the time of delivery.[10] Mother-to-child transmission is responsible for more than 90 percent of pediatric HIV infections in the United States.[8, 11] Through 2008, there have been nearly 5,000 cumulative deaths of individuals with perinatally acquired HIV infection, with recent estimates of 60 to 70 deaths per year.[12] The number of cases of perinatal HIV infections in the United States peaked at about 1,650 in 1992, but has declined dramatically with the widespread adoption of routine prenatal screening coupled with the use of more effective therapies for preventing mother-to-child transmission, and was estimated at between 215 to 370 cases in 2005.[13]

Etiology and Natural History

Peripartum transmission of HIV infection can occur during pregnancy (intrauterine), during labor and delivery (intrapartum), and following delivery (postpartum). In the absence of breastfeeding, intrauterine transmission is thought to account for 25 to 40 percent of vertically infected infants, with the remainder occurring during labor and delivery.[14] A high proportion of intrauterine transmission is thought to occur shortly before delivery.[15] HIV is present in and transmitted through breast milk,[16] and breastfeeding is thought to be the only important mode for postpartum transmission to newborns and infants.[17, 18] In resource-poor settings in which women breastfeed for prolonged periods, postpartum transmission accounts for about 44 percent of infant cases.[19] Antiretroviral treatment of the mother and infant does not completely eliminate breastfeeding transmission risk.[20] In the United States, HIV-infected women are advised against breastfeeding, given the risk of transmission and the availability of affordable and safe alternatives.[15]

Risk Factors

About 50 percent of HIV-infected pregnant women are exposed to HIV through heterosexual contact, 8 percent through injection drug use, and 8 percent through some other exposure category (such as blood transfusion or perinatal exposure).[10] In about one third of women, exposure is unknown.

Well-established risk factors for perinatal transmission include high viral load, immunologically or clinically advanced disease in the mother, prolonged rupture of membranes, maternal infection with other sexually transmitted diseases, and labor and delivery procedures and events (such as abruptio placentae, fetal scalp electrode use, episiotomy, and second degree or greater perineal laceration) associated with an increased probability of bodily fluid contact between mother and infant.[21]

Risk factors for clinical progression of HIV infection (in particular, high viral load and low CD4 count) appear to be similar for pregnant and nonpregnant women. In developed countries, pregnancy itself does not appear to be an important independent predictor of clinical progression in

chronically infected HIV-positive women.[22, 23]

Rationale for Screening

A major goal of prenatal screening for HIV is to reduce the risk of mother-to-child transmission through subsequent interventions. Other important goals are to improve long-term clinical outcomes in HIV-infected women, facilitate early identification of infected newborns, help women to make more informed future reproductive choices, and reduce risk of horizontal transmission through effects on risky behaviors.

Interventions/Treatment

The current standard of care to prevent perinatal transmission of HIV infection in the United States is a three-drug antiretroviral regimen started at the beginning of the second trimester of pregnancy or earlier (followed by treatment of the infant in the postnatal period) in all HIV-infected women (regardless of viral load or CD4 count), elective Cesarean delivery before labor or rupture of membranes in women with HIV RNA levels >1,000 copies/mL near the time of delivery, and avoidance of breastfeeding in all women.[14, 24] The choice of antiretroviral drugs is based on evidence regarding effectiveness for reducing perinatal transmission, risks to the fetus, side effect profile, and other factors, such as the potential for drug interactions or the possibility of inducing antiretroviral drug resistance.

HIV-positive women identified during pregnancy may also benefit from other interventions that would be considered in nonpregnant persons with HIV infection, including long-term antiretroviral therapy, prophylaxis for opportunistic infections, immunizations, and counseling to reduce high-risk behaviors for horizontal transmission.

Current Clinical Practice

The use of repeatedly reactive enzyme immunoassay (EIA) for an office-based venipuncture specimen followed by confirmatory Western blot or immunofluorescent assay for positive tests is associated with a sensitivity and specificity >99 percent, and is the standard test for diagnosing HIV infection.[25] The diagnostic accuracy of standard HIV testing is thought to be similar for pregnant and nonpregnant persons, though indeterminate results may occur slightly more frequently among parous and pregnant women.[26] A revised Centers for Disease Control and Prevention (CDC) HIV testing algorithm is expected in 2012. The algorithm, which will utilize combination immunoassays that screen simultaneously for both the p24 antigen and HIV antibody and test for HIV RNA without requiring Western blot confirmation, is intended to detect acute HIV infection earlier and to differentiate HIV-2 from HIV-1 infection.[27]

Rapid HIV antibody tests on blood or oral fluid specimens provide results in 5 to 40 minutes compared with 1 to 2 weeks for standard testing, and are associated with diagnostic accuracy comparable with standard testing.[28-30] A large, prospective cohort study of 5,744 pregnant women presenting in labor in six U.S. cities between 2001 and 2003 (HIV prevalence, 0.59%) found rapid

testing (prior to confirmation) associated with a sensitivity of 100 percent, specificity of 99.9 percent, positive predictive value of 90 percent, and negative predictive value of 100 percent.[28] Point-of-care rapid tests are recommended for women presenting in labor who received no prenatal care or who were not tested earlier in pregnancy for other reasons.[31] Basing therapeutic decisions on a positive rapid test result prior to confirmation is only recommended in situations in which decisions to initiate treatments cannot wait, such as in women presenting in active labor. Otherwise, confirmation of positive rapid test results prior to initiating interventions is recommended due to the possibility of false-positive results,[28] which could result in unnecessary exposure to antiretroviral or other therapies.

Current U.S. practice for HIV screening in pregnant women includes "opt-out" HIV screening at the initial prenatal visit as part of the standard prenatal test panel. Opt-out screening refers to screening that is performed after informing the women about the test, unless the woman specifically declines. The CDC recommends that clinicians consider repeat testing in all women in the third trimester for those who test negative initially, and recommends repeat testing for women who continue to practice high-risk behaviors or are in a high-incidence setting.[31]

In the United States, antiretroviral therapy is received during the prenatal and intrapartum period in about 85 percent of HIV-infected women, with about 40 percent undergoing elective Cesarean delivery.[10] Over 95 percent of infants born to HIV-infected women receive antiretroviral therapy during the postnatal period.

Recommendations of Other Groups

Many groups, including the American Congress of Obstetricians and Gynecologists,[14, 32] the American Academy of Family Physicians,[33] the American Academy of Pediatrics,[34, 35] the American College of Physicians,[36] and the CDC[31] recommend voluntary opt-out testing for HIV in all pregnant women as part of routine prenatal care. Although the CDC recommends that clinicians consider repeat testing for all women who are negative early in pregnancy and recommends repeat testing in women with risk factors and who are in high-incidence settings,[31] the USPSTF did not address repeat testing in its 2005 recommendation.[3]

CHAPTER 2. METHODS

Key Questions and Analytic Framework

Using the methods developed by the USPSTF,[37] the USPSTF and the Agency for Healthcare Research and Quality (AHRQ) determined the scope and key questions for this review. Investigators created an analytic framework with the key questions and patient populations, interventions, and outcomes reviewed (**Figure**). The target population for HIV screening was pregnant women without signs or symptoms of HIV infection.

Key Questions

Key Question 1. What are the benefits of HIV screening versus no screening in asymptomatic pregnant women on maternal or child morbidity, mortality, or quality of life or rates of mother-to-child transmission?

Key Question 2a. What is the yield (number of new diagnoses) of repeat HIV screening in asymptomatic pregnant women?

Key Question 2b. What are the adverse effects (including false-positive results and anxiety) of rapid versus standard HIV testing in asymptomatic pregnant women?

Key Question 3a. What is the effectiveness of newer antiretroviral regimens for reducing mother-to-child transmission?

Key Question 3b. What are the effects of antiretroviral regimens in pregnant, HIV-positive women on long-term maternal morbidity, mortality, or quality of life?

Key Question 3c. What are the harms (including longer-term harms) to the mother or child associated with antiretroviral therapy during pregnancy?

Key question 1 focuses on direct evidence that prenatal screening for HIV infection improves important health outcomes compared with not screening. Such direct evidence on the effectiveness of screening interventions may not be available. Therefore, the remainder of the analytic framework (key questions 2a through 3c) evaluates the chain of indirect evidence needed to link screening for HIV infection with improvement in important health outcomes. Links in the chain of indirect evidence include the performance, yield, and acceptability of the screening test for identifying HIV infection, the effectiveness of interventions for reducing perinatal transmission as well as effects on other clinical outcomes (such as long-term maternal outcomes), and any harms associated with screening and subsequent interventions. The general diagnostic accuracy of standard HIV testing was not re-reviewed for this update, since it is well established as highly accurate.[1, 2] Rather, the update focuses on research gaps identified in the prior review, such as harms (including false-positive results and anxiety) of alternative testing methods (rapid vs. standard testing) and the yield of repeat screening. This update also does not re-review effects of avoidance of breastfeeding and elective Cesarean delivery in women with viremia on risk of perinatal transmission, as the

effectiveness of these interventions is well established[1, 2] and part of standard U.S. practice. Rather, the update focuses on new evidence on effectiveness of combination antiretroviral regimens on perinatal transmission, as well as evidence on long-term clinical outcomes in the mother and harms to either the mother or infant.

Search Strategies

We searched Ovid MEDLINE from 2004 to June 2012 and the Cochrane Library Database from 2005 through the second quarter of 2012 and reviewed reference lists to identify relevant articles published in English. Search strategies are shown in **Appendix A1**.

Study Selection

At least two reviewers independently evaluated each study to determine eligibility for inclusion. We selected studies on the basis of inclusion and exclusion criteria developed for each key question (**Appendix A2**). Articles were selected for full review if they were about HIV infection in pregnancy, were relevant to a key question, and met the predefined inclusion criteria. We restricted inclusion to English-language articles and excluded studies only published as abstracts. Studies of nonhuman subjects were also excluded, and studies had to include original data.

For all key questions, we included studies of pregnant women without signs or symptoms of HIV infection or HIV-positive pregnant women receiving treatment. For key question 3c, we also included infants exposed to antiretroviral drugs in utero or postnatally. The screening interventions were standard or rapid HIV antibody testing. For treatment interventions, we focused on antiretroviral drug therapy. Outcomes were mother-to-child transmission, morbidity, mortality, quality of life, and harms from antiretroviral therapy (such as adverse pregnancy outcomes; adverse congenital, neurodevelopmental, cardiovascular, metabolic, or hematologic outcomes in exposed children; and adverse clinical outcomes in mothers), including long-term (defined as 1 or more years after birth for women and 2 or more years after birth for children) outcomes. We included randomized, controlled trials and cohort studies for all key questions. For key questions related to harms and other long-term maternal and infant outcomes, we also included case-control studies and intervention series if randomized trials and cohort studies were unavailable or lacking. Although the target intervention was full-course combination antiretroviral regimens (started by the second trimester and continued through delivery, with postnatal treatment of the infant) and the target population was nonbreastfeeding women, we included studies from resource-poor settings that evaluated short-course antiretroviral regimens or breastfeeding populations, as these may provide some information about the effectiveness of antiretroviral therapies in women who present late in pregnancy or about the general effectiveness of combination antiretroviral therapy. **Appendix A3** shows the results of our literature search and selection process and **Appendix A4** lists excluded studies with reasons for exclusion.

Data Abstraction and Quality Rating

One investigator abstracted details about the study design, patient population, setting, screening

method, treatment regimen, analysis, followup, and results. A second investigator reviewed data abstraction for accuracy. Two investigators independently applied criteria developed by the USPSTF[37] to rate the quality of each study as good, fair, or poor (**Appendix A5**). Discrepancies were resolved through a consensus process.

Data Synthesis

We assessed the aggregate internal validity (quality) of the body of evidence for each key question (good, fair, poor) using methods developed by the USPSTF, based on the number, quality, and size of studies, consistency of results between studies, and directness of evidence.[37] Meta-analysis was not attempted as the data could not be pooled, due to differences across studies in design, interventions, populations, and other factors.

External Review

The draft report was reviewed by content experts, USPSTF members, AHRQ Project Officers, and collaborative partners prior to finalization (**Appendix A6**).

CHAPTER 3. RESULTS

Key Question 1. What Are the Benefits of HIV Screening Versus No Screening in Asymptomatic Pregnant Women on Maternal or Child Morbidity, Mortality, or Quality of Life or Rates of Mother-to-Child Transmission?

No randomized trial or observational study compared clinical outcomes (including risk of perinatal transmission) between pregnant women screened and not screened for HIV infection. Given what is established about HIV screening and transmission, a randomized trial would not be considered ethical at this point. Although the number of infants with perinatally acquired HIV transmission has markedly declined in the United States, this is likely due to a combination of increased screening during pregnancy and increased effectiveness and use of interventions to prevent transmission. Some HIV-positive women may also have been identified before pregnancy. We identified no studies estimating the relative impact of these factors on transmission risk.

Key Question 2a. What Is the Yield (Number of New Diagnoses) of Repeat Screening in Asymptomatic Pregnant Women?

No randomized trial or observational study evaluated the yield of repeat prenatal HIV screening compared with one-time screening, or compared the yield of different strategies for repeat screening (e.g., risk-based repeat screening vs. a routine repeat test). Repeat testing of women who screen HIV-negative during early pregnancy could identify those who are infected after initial testing but before delivery. Repeat screening and the optimal timing of repeat testing during pregnancy would depend, in part, on the frequency of new HIV infections. One modeling study discussed in the 2005 USPSTF review[1, 2] estimated that repeat testing in the third trimester after a negative test in the first trimester would detect 5.3 new infections per 100,000 average-risk women tested and 192 infections per 100,000 high-risk women tested.[38]

Key Question 2b. What Are the Adverse Effects (Including False-Positive Results and Anxiety) of Rapid Versus Standard HIV Testing in Asymptomatic Pregnant Women?

Summary

One large (n=7,753), prospective study of women presenting in labor with unknown HIV status (HIV prevalence, 0.7%) found the OraQuick rapid HIV test (OraSure Technologies, Inc., Bethlehem, PA) associated with a positive predictive value of 90 percent and the standard EIA test associated with a positive predictive value of 74 percent when each was compared with Western blot as the reference standard. One other, smaller study (n=910) of pregnant women at any gestational age also found rapid testing associated with a higher positive predictive value compared

with standard testing, but only five HIV-positive women were identified. No study compared psychological or other harms associated with rapid versus standard testing or adverse clinical consequences of interventions given as a result of false-positive results.

Evidence

The large (n=7,753), prospective, fair-quality Mother-Infant Rapid Intervention at Delivery (MIRIAD) study provides the strongest evidence on the diagnostic accuracy of the rapid OraQuick test compared with standard EIA HIV testing.[28, 39] MIRIAD specifically enrolled women in labor with unknown HIV status (HIV prevalence, 0.7% [52/7,753]) for whom immediate test results were needed to help guide treatment decisions. Initial (2-year) results from MIRIAD[28] were included in the prior USPSTF review (**Table 1**, **Appendix B1**).[39] Final (40-month) results[39] found that compared with Western blot as the reference standard, sensitivity was 100 percent for both tests, and specificity was 99.9 and 99.8 percent for rapid and standard testing, respectively. The positive predictive value for the rapid test was higher (90% [52/58]) than for the standard test (74% [52/70]). In clinical practice, a positive standard test result would not be available in time to inform interventions during labor and delivery, and positive standard test results are typically confirmed with Western blot prior to patient notification.

One other study (n=910) of pregnant, predominantly Hispanic (about 90%) women at any gestational age (HIV prevalence, 0.5%) found the OraQuick test associated with a positive predictive value of 100 percent (5/5) and EIA associated with a positive predictive value of 36 percent (5/14).[40]

No study compared psychological or other harms associated with rapid versus standard tests or adverse clinical consequences of interventions given as a result of initial false-positive rapid test results.

Key Question 3a. What Is the Effectiveness of Newer Antiretroviral Regimens for Reducing Mother-to-Child Transmission?

Summary

Consistent with the prior USPSTF review, three new U.S. and European cohort studies published since 2005 found perinatal full-course triple antiretroviral therapy associated with a risk of mother-to-child transmission that ranged from <1 to 2.4 percent compared with 9 to 22 percent with no antiretroviral therapy. Two randomized trials of breastfeeding women in Africa found triple antiretroviral therapy started at 26 to 28 weeks associated with mother-to-child transmission rates of 1 to 5 percent. Other African trials found shorter courses of perinatal antiretroviral therapy and regimens using fewer than three drugs associated with a lower risk of mother-to-child transmission of HIV infection compared with the expected transmission rate without therapy, but were generally associated with higher transmission rates than full-course, three-drug regimens.

Evidence

The landmark Pediatric AIDS Clinical Trials Group (PACTG) protocol 076 study found that a three-phase maternal and infant zidovudine regimen starting at 14 to 34 weeks' gestation through 6 weeks postpartum decreased the risk of mother-to-child transmission from about 25 percent with placebo to 8 percent in nonbreastfeeding women.[41] The 2005 USPSTF review[1, 2] identified no completed trials of full-course combination antiretroviral therapy during pregnancy. It included four large U.S. or European cohort studies that all found full-course antiretroviral regimens with more drugs superior to regimens with fewer antiretroviral drugs for preventing mother-to-child transmission.[42-45] The only study that specifically evaluated the effectiveness of three-or-more-drug regimens compared with no antiretrovirals reported an odds ratio (OR) of 0.13 (95% confidence interval [CI], 0.06 to 0.27) for prevention of mother-to-child transmission.[44] Another study reported an adjusted OR of 0.07 (95% CI, 0.02 to 0.23) for two-or-more-drug regimens compared with no antiretrovirals.[43] In all of the studies, transmission rates were 1 to 2 percent with combination regimens.[42-45] The 2005 USPSTF review also included several randomized trials that found that shorter courses of antiretroviral prophylaxis were effective at reducing risk of mother-to-child transmission of HIV infection, though they were not as effective as full-course regimens.[46-55]

We identified no new randomized trials on full-course combination antiretroviral therapy during pregnancy in nonresource poor, nonbreastfeeding settings. Four fair-quality U.S. or European cohort studies published since the 2005 USPSTF review evaluated the effectiveness of combination antiretroviral regimens during pregnancy (**Table 2**, **Appendix B2**).[56-58] Sample sizes ranged from 489 to 7,344. Methodological shortcomings in the studies included inadequate reporting of baseline characteristics[56-58] or failure to report adjusted risk estimates[58] (**Appendix B3**). The proportion of women who had a Cesarean delivery in these cohorts ranged from 51 to 78 percent.

One large (n=7,344) cohort study was based on U.S. surveillance data from 1999 to 2001.[57] It found full-course single- or multi-drug antiretroviral therapy associated with lower risk of mother-to-child transmission compared with no antiretroviral therapy (2.4% vs. 22%; adjusted OR, 0.09 [95% CI, 0.06 to 0.12]). In women who received antiretroviral therapy, combination regimens with zidovudine plus other drugs were about twice as effective as zidovudine monotherapy for reducing risk of mother-to-child transmission (adjusted OR range, 0.4 to 0.5). Two smaller European cohort studies also reported lower mother-to-child transmission rates with combination antiretroviral therapy (0.6% and 1.0%) compared with no therapy (9% and 18%).[56, 58] A fourth study, which analyzed European surveillance data (n=7,573) over a 9-year period and included one of these cohorts,[56] found transmission rates of <1 percent with either zidovudine-sparing or zidovudine-containing three-or-more-drug regimens.[59]

One good-quality[60] and five fair-quality[61-65] randomized trials published since the 2005 USPSTF review evaluated shorter-course prenatal antiretroviral regimens in primarily breastfeeding African women (**Table 3**, **Appendixes B4** and **B5**).[60-65] Sample sizes ranged from 355 to 805 infants. The studies are most applicable in the United States to HIV-infected women identified later in pregnancy, who cannot receive full-course regimens. In general, these studies reported lower transmission rates with antiretroviral therapy than expected without treatment. Studies that evaluated longer courses of treatment and regimens that included at least three drugs reported the lowest transmission rates. One trial of breastfeeding women (n=709) found various three-drug

antiretroviral regimens started at 18 to 34 weeks' gestation (median, 26 to 27 weeks) associated with an overall infant HIV infection rate of 1.1 percent at 6 months.[63] Another trial of breastfeeding women (n=805) found zidovudine, lamivudine, and ritonavir-boosted-lopinavir started at 28 weeks' gestation and continued through weaning from breastfeeding associated with lower risk of infant HIV infection at 12 months compared with zidovudine plus single-dose nevirapine (5.4% vs. 9.5%; p=0.03).[60] Three trials, including one of nonbreastfeeding women,[62] found shorter-course (starting at 32 to 34 weeks' gestation) perinatal antiretroviral therapy with one or two drugs (with or without the addition of a single maternal dose of an antiretroviral during labor) associated with mother-to-child transmission rates that ranged from 4 to 12 percent.[61, 62, 64] One other trial (n=609) found high rates of mother-to-child transmission with ultra-short-course zidovudine (during labor and given to the infant for 72 hours after birth) plus single-dose maternal and infant nevirapine versus single-dose nevirapine alone (14% vs. 17%), as well as a high rate of infant mortality (7% at 6 weeks).[65]

Key Question 3b. What Are the Effects of Antiretroviral Regimens in Pregnant, HIV-Positive Women on Long-Term Maternal Morbidity, Mortality, or Quality of Life?

Summary

No study published since the prior USPSTF review evaluated effects of prenatal antiretroviral therapy on long-term maternal clinical outcomes. The prior USPSTF review included one study (n=226) of U.S. women that found no difference in risk of AIDS-defining events or death after a mean of 4.1 years between women randomized to zidovudine during pregnancy versus placebo in risk of AIDS or death, death alone, or AIDS-defining CDC clinical category C events after a mean of 4.1 years.

Evidence

No study published since the prior USPSTF review evaluated effects of prenatal antiretroviral therapy on long-term maternal clinical outcomes. One good-quality study included in the prior USPSTF review of U.S. women (n=226) originally enrolled in a randomized trial of zidovudine monotherapy for reducing mother-to-child transmission (PACTG 076) found no difference between women randomized to zidovudine versus placebo in risk of AIDS or death (19% vs. 25%; relative risk [RR], 0.73 [90% CI, 0.46 to 1.2]), death alone (3% vs. 2%; RR, 1.5 [90% CI, 0.34 to 6.7]), or AIDS-defining CDC clinical category C events (7% vs. 10%; RR, 0.70 [90% CI, 0.34 to 1.4]) after a mean of 4.1 years.[68] At the time of enrollment, women were not receiving or eligible (based on criteria at the time) for antiretroviral therapy, and zidovudine was discontinued after delivery. Although only about 50 percent of eligible women enrolled in the randomized trial participated in this study, there were few differences in demographic and clinical characteristics between participants and nonparticipants, and baseline characteristic similarity between the zidovudine and placebo groups was preserved during the study. The prior USPSTF review also included a study that found women still benefit from antiretroviral therapy after receiving antiretroviral treatment during pregnancy.[69]

Key Question 3c. What Are the Harms (Including Longer-Term Harms) to the Mother or Child Associated With Antiretroviral Therapy During Pregnancy?

Summary

New evidence (27 studies) on infant and maternal harms associated with perinatal exposure to antiretroviral therapy was generally consistent with the evidence included in the 2005 USPSTF review.[1, 2] Of one randomized trial and 10 cohort studies reporting on the association between perinatal antiretroviral therapy and risk of preterm delivery or low birth weight, the trial and six cohort studies found perinatal antiretroviral therapy associated with increased risk of preterm delivery, but no clear association with low birth weight. Although studies found an association between exposure to perinatal antiretroviral therapy and increased risk during infancy of laboratory markers of mitochondrial dysfunction, hematological abnormalities, and echocardiographic markers of impaired myocardial growth, the clinical significance of these findings remains unclear. Four studies showed no association between perinatal exposure to antiretroviral drugs and risk of congenital abnormalities, and two studies showed no clear association between perinatal exposure to antiretroviral drugs and infant neurodevelopment. A large cohort study found exposure to antiretroviral drugs during pregnancy associated with increased risk of maternal anemia. No study evaluated long-term maternal harms associated with short-term exposure to antiretroviral therapy during pregnancy, or antiretroviral therapy started during pregnancy and continued after pregnancy.

Evidence

Infant harms.

Preterm birth and other birth outcomes. The 2005 USPSTF review[1, 2] identified one good-quality U.S. meta-analysis of five prospective cohort studies and one good-quality, large European prospective cohort study that found no association between exposure to combination antiretroviral therapy and low birth weight.[70, 71] Evidence regarding the association between combination antiretroviral therapy and increased rates of premature delivery was mixed. The meta-analysis found no increase in risk of premature delivery for infants exposed to combination therapy with (adjusted OR, 1.5 [95% CI, 0.72 to 3.0]) or without a protease inhibitor (OR, 0.95 [95% CI, 0.51 to 1.7]) compared with no treatment,[70] but the large, prospective European Collaborative Study reported an increased risk of premature delivery (before 37 weeks' gestation) associated with combination antiretroviral therapy initiated during pregnancy (RR, 1.9 [95% CI, 1.3 to 2.7]) or prior to pregnancy (RR, 2.0 [95% CI, 1.4 to 3.0]) versus no treatment.[71] Use of monotherapy or dual therapy during pregnancy was not associated with increased risk of premature delivery.

One randomized trial[72] and 10 cohort studies[73-82] published since the prior USPSTF review reported risk of prematurity, low birth weight, and other birth outcomes following in utero exposure to antiretroviral therapy (**Appendix B6**). Sample sizes ranged from 57 to 8,793. Eight studies, including the randomized trial, were rated fair-quality[72, 73, 75, 77, 78, 80-82] and three were rated poor-quality[74, 76, 79] (**Appendixes B7** and **B8**). Methodological shortcomings included differences in

baseline characteristics between groups and poor reporting of attrition. Six studies reported risk estimates adjusted for important confounders such as maternal age, CD4 count, and viral load.[73, 75, 77, 79, 81, 82]

The randomized trial (n=530) found protease inhibitor-based antiretroviral therapy associated with greater risk of preterm delivery than nonnucleoside reverse transcriptor-based antiretroviral therapy (OR, 2.0 [95% CI, 1.3 to 3.3]).[72] Three prospective cohort studies (n=183 to 8,793) also found maternal exposure to combination antiretroviral therapy with a protease inhibitor associated with increased risk of preterm delivery (<37 weeks) compared with combination antiretroviral therapy without a protease inhibitor (adjusted OR, 1.8 [95% CI, 1.1 to 3.0]),[75] dual therapy (adjusted OR, 1.2 [95% CI, 1.0 to 1.4]),[81] or monotherapy (adjusted OR, 3.4 [95% CI, 1.1 to 10]),[77] after adjustment for potential confounders (**Table 4**). None found exposure to combination therapy without a protease inhibitor associated with increased risk of preterm delivery. However, a fourth large (n=4,939) cohort study found combination therapy associated with increased risk of preterm delivery (<37 weeks) (adjusted OR, 1.4 [95% CI, 1.1 to 1.8]; p=0.02) and very preterm delivery (<32 weeks) (OR, 2.6 [95% CI, 1.3 to 5.3]; p=0.007) compared with monotherapy or dual therapy, with no difference in risk according to whether the antiretroviral regimen included a protease inhibitor or not.[82] Among four studies that did not adjust for confounders, one found an association between prenatal antiretroviral therapy and preterm delivery,[80] but three other studies found no clear association.[74, 76, 78]

Seven cohort studies (n=352 to 8,192) published since the 2005 USPSTF review found no clear association between maternal use of antiretroviral therapy and low birth weight or intrauterine growth restriction.[73-76, 78, 81, 82]

Mitochondrial dysfunction. Although molecular evidence of mitochondrial dysfunction has been reported in infants exposed in utero to antiretroviral therapy,[83, 84] the clinical significance of such dysfunction remains unclear. The 2005 USPSTF review[1, 2] included three prospective cohort studies that found no clear evidence of clinical mitochondrial dysfunction in infants exposed to antiretroviral therapy in utero, despite evidence of high rates of elevated lactic acid levels.[71, 85, 86] Population-based studies included in the 2005 USPSTF review reported no deaths due to mitochondrial dysfunction among antiretroviral-exposed, HIV-negative infants.[87-89]

Three studies published since the 2005 USPSTF review evaluated risk of mitochondrial dysfunction based on laboratory findings following in utero exposure to antiretroviral therapy, but none evaluated clinical outcomes associated with findings of mitochondrial dysfunction.[90-92]

Congenital abnormalities. The 2005 USPSTF review[1, 2] identified one large, good-quality European prospective cohort study that found no association between exposure to any combination of antiretroviral drugs and risk of congenital anomalies.[71]

Three fair-quality European cohort studies (n=1,414 to 8,576) published since the 2005 USPSTF review each found no association between perinatal exposure to antiretroviral therapy and congenital abnormalities[93-95] (**Appendixes B6** and **B8**). Followup ranged from 6 months to 17 years. One large study (n=7,573) of European surveillance data over a 9-year period found no difference in the risk of infant congenital abnormalities with maternal use of zidovudine-sparing versus

zidovudine-containing three-or-more-drug regimens.[59]

Neurodevelopmental outcomes. The 2005 USPSTF review[1, 2] included one good-quality prospective cohort study that found no association between in utero and postnatal zidovudine exposure and long-term adverse effects on growth or development in exposed infants through age 4 years.[71]

We identified two cohort studies published since the 2005 USPSTF review[1, 2] that evaluated neurodevelopmental outcomes following in utero and postnatal exposure to antiretroviral therapy[96, 97] (**Appendixes B6** and **B8**). Both utilized the Bayley Scales of Infant Development-II, which includes a Mental Development Index (MDI) and Psychomotor Development Index (PDI). One good-quality prospective study (n=63) found no statistically significant difference in MDI scores in antiretroviral-exposed children compared with unexposed control groups at ages 18 to 36 months, after adjustment for maternal substance abuse.[96] A second, larger (n=1,840), fair-quality prospective study found slightly higher (better) MDI and PDI scores in antiretroviral-exposed children compared with unexposed children at age 2 years after adjustment for confounders, but the differences were small (<3 points on a 100-point scale) and did not reach statistical significance.[97]

Other infant harms. The 2005 USPSTF review[1, 2] identified one prospective cohort study that found no association between in utero exposure to zidovudine and acute or chronic abnormalities in left ventricular structure or functioning based on serial echocardiography through ages10 to 14 months.[98]

One prospective cohort study published since the 2005 USPSTF review found in utero exposure to antiretroviral therapy associated with echocardiographic findings of impaired myocardial growth (decreased left ventricular mass and septal wall thickness) but improved left ventricular contractility compared with no exposure through age 2 years, though the clinical significance of these findings was not evaluated[99] (**Appendixes B6** and **B8**). There were no differences between exposed and unexposed infants in these echocardiographic parameters through ages 2 to 5 years. Three observational studies each found in utero exposure to antiretroviral drugs associated with increased risk of neutropenia or anemia through age 24 months[100-102] (**Appendixes B6** and **B8**). Average difference in neutrophil count for exposed versus unexposed children ranged from about 0.150 to 0.550 x 10^9 cells/L.[100, 102] No study evaluated the association between lower neutrophil counts following in utero exposure to antiretroviral drugs and adverse clinical outcomes. One study found no difference in incidence of cancer in uninfected infants exposed to perinatal antiretroviral therapy at 5.4 years (10/9,127 children [0.1%]) compared with the general population, though among exposed infants the combination of didanosine and lamivudine was associated with higher risk compared with zidovudine monotherapy (hazard ratio [HR], 14 [95% CI, 2.5 to 74])[103] (**Appendixes B6** and **B8**).

Maternal harms.

Receipt of antiretroviral therapy during pregnancy is associated with the nonobstetric adverse events typically associated with the specific drugs and regimens, but these often resolve after stopping the offending drug or drug combination, and effective alternatives are usually available.[24] Regularly updated guidelines summarizing adverse events associated with specific antiretroviral drugs, classes, and combinations are available, and specific antiretroviral combinations associated

with serious complications are not recommended.[24]

The 2005 USPSTF review[1, 2] included one good-quality meta-analysis that found no association between perinatal zidovudine monotherapy and maternal death or long-term harms.[104] A large observational study found gestational diabetes mellitus the only complication associated with antiretroviral therapy, and was most likely with combination therapy that included a protease inhibitor initiated early in the pregnancy.[105] The 2005 USPSTF review also included one clinical trial that was discontinued early due to a high rate (29%) of treatment-limiting hepatic or cutaneous toxicity with continuous use of nevirapine with zidovudine during pregnancy, including one death and one case of Stevens-Johnson syndrome.[106] These events occurred most frequently in women with CD4 counts >0.250 x 10^9 cells/L. However, three randomized trials found no difference between a single maternal intrapartum dose of nevirapine with or without antiretroviral therapy and no nevirapine in risk of liver function test abnormalities or hepatitis.[51, 53, 107]

We identified one large (n=2,543), fair-quality U.S. cohort study published since the 2005 USPSTF review that found antiretroviral use associated with increased risk of maternal anemia compared with nonuse (adjusted OR, 1.6 [95% CI, 1.1 to 2.4])[108] (**Appendixes B6** and **B8**). It also found late use of antiretroviral therapy (started between 25 and 32 weeks' gestation) associated with increased risk of gestational diabetes compared with nonuse (adjusted OR, 3.5 [95% CI, 1.2 to 10]), but causality was unclear since screening for gestational diabetes is typically performed at 24 to 28 weeks' gestation and women may have been diagnosed prior to initiation of antiretroviral therapy. Another, smaller (n=167) fair-quality cohort study found exposure to combination therapy associated with a trend toward increased risk of gestational diabetes compared with exposure to monotherapy with zidovudine or no antiretroviral therapy, but the difference was not statistically significant (12% vs. 0%; unadjusted RR, 0.11 [95% CI, 0.01 to 1.7])[109] (**Appendixes B6** and **B8**).

CHAPTER 4. DISCUSSION

Summary of Review Findings

As in the 2005 USPSTF review,[1, 2] we found no direct evidence on effects of prenatal screening for HIV infection versus no screening on risk of mother-to-child transmission or maternal or infant clinical outcomes. Other evidence reviewed in this update is summarized in **Table 5**.

The 2005 USPSTF review[1, 2] found that HIV tests are accurate. The strongest evidence on potential harms associated with rapid testing is from the large MIRIAD study, which found a lower positive predictive value with standard EIA than for a rapid test (74% and 90%, respectively) in a population of women presenting in labor with 0.7 percent prevalence of undiagnosed HIV infection. This could result in unnecessary maternal and fetal exposure to antiretroviral therapy.[39] The positive predictive value would be expected to be lower in lower-prevalence populations, potentially resulting in more unnecessary antiretroviral exposure. No study has evaluated the clinical consequences of unnecessary exposure to antiretroviral therapy as a result of an initially false-positive rapid HIV test result, though any such harms would have to be weighed against the potential benefits of prenatal identification and treatment of undiagnosed HIV infection. As in the 2005 USPSTF review, no study has evaluated the yield of repeated HIV screening during pregnancy, which depends on the incidence of new HIV infection.

New cohort studies of antiretroviral therapy conducted in nonbreastfeeding women in the United States and Europe confirm the findings from the 2005 USPSTF review that full-course combination antiretroviral therapy is highly effective at reducing risk of mother-to-child transmission (<1% to 2.4% with combination antiretroviral therapy vs. 9% to 22% with no antiretroviral therapy).[56-58] Randomized trials also found low risk of transmission with combination therapy regimens started around the end of the second trimester in breastfeeding African women.[60, 63] Shorter courses of antiretroviral therapy are not as effective as full-course regimens, but also reduce risk of mother-to-child transmission compared with historical transmission rates without antiretroviral therapy, and are relevant for women who might be started on therapy late due to delayed diagnosis or treatment.[61, 62, 64]

Evidence on harms of antiretroviral therapy was also largely consistent with the 2005 USPSTF review. Current evidence continues to suggest that the long-term harms associated with antiretroviral therapy are relatively small. New, primarily observational studies found perinatal antiretroviral therapy associated with increased risk of preterm delivery,[72, 74-82] with no clear association with low birth weight,[73, 75, 76, 78, 81, 82] congenital abnormalities,[59, 93-95] or impaired infant neurodevelopment.[96, 97] Although other studies found an association between in utero exposure to antiretroviral therapy and echocardiographic abnormalities,[99] hematologic abnormalities,[100-102] or markers of mitochondrial dysfunction,[90-92] the clinical significance of these findings remains unclear. Evidence on long-term maternal harms associated with short-term exposure to antiretroviral therapy during pregnancy, or antiretroviral therapy started during pregnancy and continued after pregnancy, remains sparse.

Limitations

We excluded nonEnglish-language articles, which could result in language bias, though we identified no nonEnglish-language studies that would have met inclusion criteria. We could not formally assess for publication bias with graphical or statistical methods because of small numbers of studies and differences in study designs, populations, and outcomes assessed. We included observational studies, which are more susceptible to bias and confounding than well-conducted randomized trials, though we focused on results from studies that performed statistical adjustment for potential confounding. Randomized trials of combination antiretroviral therapy have only been conducted in Africa. The applicability of studies conducted in resource-poor and high-prevalence settings to U.S. practice is likely to be limited due to differences in the antiretroviral drugs evaluated, evaluation of shorter regimens, reliance on breastfeeding, and other factors.

Emerging Issues

Antiretroviral therapy regimens for use during pregnancy and indications for initiating long-term antiretroviral therapy continue to evolve. Regularly updated guidelines on selection of antiretroviral therapy in pregnant women are available.[24]

Future Research

More research is needed on the long-term maternal effects of transient exposure to antiretroviral therapy during pregnancy or use of less-intense antiretroviral regimens during pregnancy. Integrase inhibitors may be a potential option for antiretroviral therapy in women who present late in pregnancy due to potent and rapid virological suppression, but require additional study to determine effects on transmission and safety in pregnancy.[110] Children exposed to antiretroviral therapy in utero should continue to be followed to help identify unexpected or emerging long-term harms from combination regimens. More research is also needed to understand the clinical significance of the hematologic abnormalities, echocardiographic abnormalities, and markers of mitochondrial dysfunction observed in some children exposed to antiretroviral therapy.

Conclusions

In summary, prenatal HIV screening is accurate, and antiretroviral therapy in combination with avoidance of breastfeeding and Cesarean delivery in women with HIV RNA levels >1,000 copies/mL near the time of delivery is effective at reducing risk of mother-to-child transmission. Use of certain antiretroviral therapy regimens during pregnancy may be associated with increased risk of preterm delivery, but more evidence is needed to fully understand short- and long-term maternal and infant effects.

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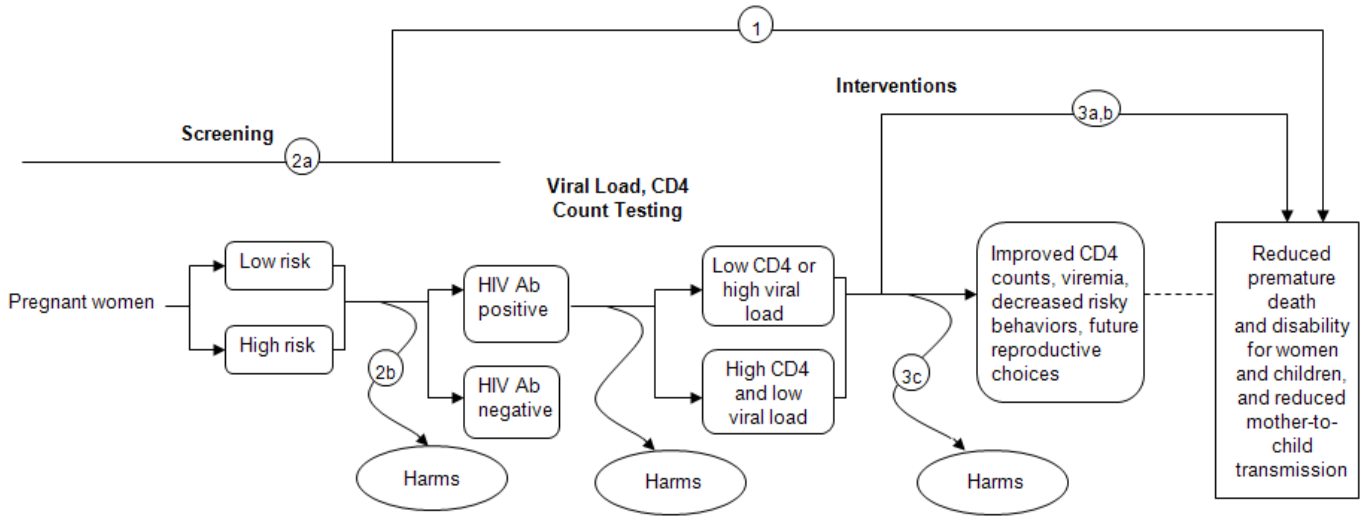
Figure. Analytic Framework for Screening for HIV in Pregnant Women



Key Questions

1. What are the benefits of HIV screening versus no screening in asymptomatic pregnant women on maternal or child morbidity, mortality, or quality of life or rates of mother-to-child transmission?

2a. What is the yield (number of new diagnoses) of repeat HIV screening in asymptomatic pregnant women?

2b. What are the adverse effects (including false-positive results and anxiety) of rapid versus standard HIV testing in asymptomatic pregnant women?

3a. What is the effectiveness of newer antiretroviral regimens for reducing mother-to-child transmission?

3b. What are the effects of antiretroviral regimens in pregnant, HIV-positive women on long-term maternal morbidity, mortality, or quality of life?

3c. What are the harms (including longer-term harms) to the mother or child associated with antiretroviral therapy during pregnancy?

Table 1. Diagnostic Accuracy and Acceptability of Rapid Versus Standard HIV Testing in Pregnant Women

Author, year *Quality rating*	Rapid vs. standard testing						
	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	False positives	False negatives	Acceptability
Bulterys et al, 2004[28] *Fair*	100% (90 to 100%) vs. 100% (89 to 100%)	99.9% (99.8 to 99.9%) vs. 99.8% (99.6 to 99.9%)	90% (75 to 97%) vs. 76% (61 to 87%)	100% (99.9-100%) vs. 100% (99.9-100%)	4 vs. 11	0 vs. 0	84% accepted and consented
Jamieson et al, 2007[39] *Fair*	100% (93 to 100%) vs. 100% (93 to 100%)	99.9% (99.8 to 100%) vs. 99.8% (99.6 to 99.9%)	89.7% (78.8 to 96.1%) vs. 74.3% (62.4 to 84%)	100% (99.9-100%) vs. 100% (99.9-100%)	6 vs. 18	0 vs. 0	85% overall
Tung et al, 2010[40] *Fair*	NR	NR	OraQuick vs. EIA* 100% vs. 35.7% (90% CI)	NR	OraQuick vs. EIA* 0/5 (0%) vs. 7/14 (50%)	NR	NR

*Confirmed by Western blot.
CI = confidence interval; EIA = enzyme immunoassay; NR = not reported.

Table 2. Cohort Studies of Mother-to-Child HIV Transmission While Using Antiretroviral Therapy

Author, Year	Setting	Intervention	Sample	Mother-to-child transmission rates by treatment group	Quality rating
Garcia-Tejedor et al, 2009[58]	Spain Maternity hospitals	ART A: No treatment B: Mono/dual therapy C: ART	489 mother-infant pairs analyzed Rate of Cesarean section 51% No infants breastfed Followup NR	A: 18% (39/214) B: 8.6% (10/116) C: 0.6% (1/159) p<0.001	Fair
Harris et al, 2007[57]	United States Population surveillance data from areas reporting ≥60 HIV-positive women giving birth per year	ART A: No treatment B: Prenatal, intrapartum and neonatal ART*	7,344 HIV-exposed infants with ART data Rate of Cesarean section 53% Breastfeeding rate NR Followup by health department every 6 months until HIV status determined Analyses of data over 3 year study period	A: 22% (59/265), OR referent B: 2.4% (139/5757), AOR 0.09 (95% CI 0.06 to 0.12) Prenatal ART regimen and infant infection status among those on 3 arms of treatment: ZDV: OR referent ZDV & other drugs with PI: AOR 0.4, 95% CI 0.3 to 0.7 ZDV & other drugs no PI: AOR 0.5, 95% CI 0.3 to 0.8 Other drugs with PI, no ZDV: AOR 0.6, 95% CI 0.2 to 1.4 Other drugs no PI, no ZDV: AOR 0.3, 95% CI 0.1 to 1.5 n=5,602 due to exclusions	Fair
Townsend et al, 2008[56]	Ireland, United Kingdom Population surveillance data from National Study of HIV in Pregnancy and Childhood	Antepartum treatment A: ART therapy B: Dual therapy C: Monotherapy D: No therapy	5,027 mother-infant pairs with ART data Rate of Cesarean section 78% 0.6% of infants breastfed Followup NR Analyses of data over 6 year study period	A: 1.0% (40/4120) B: 0.8% (1/126) C: 0.5% (3/638) D: 9.1% (13/143) A: AOR 1.0 B: AOR 1.7 (95% CI 0.2 to 13), p=0.61 C: AOR 0.6 (95% CI 0.2 to 1.9), p=0.37 D: AOR 3.2 (95% CI 1.2 to 8.6), p=0.02 n=4,084 due to exclusions	Fair
Tariq et al, 2011[59]	United Kingdom, Ireland, Belgium, Denmark, Germany, Italy, the Netherlands, Poland, Spain, Sweden/Population surveillance data from the European Collaborative Study and the National Study of HIV in Pregnancy and Childhood	ART A: ZDV-containing B: ZDV-sparing	7,573 mother-child pairs analyzed Rate of Cesarean section 74% Breastfeeding rate NR Followup NR Analyses of data over 9 year study period	0.9% (56/6130; 95% CI 0.7 to 1.0) of infants were infected (infection status available for 80% [6130/7645] of infants at analysis) A: 0.9% (n=5214); AOR 1 B: 0.8% (n=897); AOR 1.8 (95% CI 0.8 to 4.3) p=0.18	Fair

*Not all study interventions shown.
AOR = adjusted odds ratio; ART = antiretroviral therapy; CI = confidence interval; NR = not reported; OR = odds ratio; PI = protease inhibitor; ZDV = zidovudine.

Table 3. African-Based Trials of Mother-to-Child HIV Transmission While Using Antiretroviral Therapy

Author, year	Setting	Prenatal intervention	Peripartum intervention	Postpartum intervention	Sample	Mother-to-child transmission rates by treatment group	Quality rating
Chi et al, 2008[61] Other publication: Chi, 2007[66]	Zambia	From 32 weeks: ZDV to all groups	A: TDF/FTC + NVP B: NVP	All neonates: NVP dose in hospital + ZDV for one week	355 mother-infant pairs analyzed 92% of infants breastfed in both groups	6 weeks postpartum A: 6% B: 8% p=0.4	Fair
de Vincenzi et al, 2011[60] Other publication: Kesho Bora Study Group, 2010[67]	Burkina Faso, Kenya, South Africa	From 28 weeks: A: ZDV + 3TC + ABT-378 + RTV B: ZDV	A: ZDV, 3TC, ABT-378, RTV B: ZDV + sdNVP	A: Maternal ZDV, 3TC, ABT-378, RTV until cessation of breastfeeding (maximum 6.5 months postpartum) B: Maternal 3TC and ZDV for one week postpartum* All neonates: ZDV for one week*, NVP dose within 72 hours of birth, co-trimaxozole from age 6 weeks to 12 months unless not HIV infected after cessation of breastfeeding	805 live born infants 77% of infants in group A and 78% in group B were ever breastfed	12 months of age A: 5.4% (21/333), 95% CI 3.6 to 8.1 B: 9.5% (37/305), 95% CI 7.0 to 13 RR reduction 0.43 p=0.03	Good
Gray et al, 2006[62]	South Africa	From 34 weeks gestation: A: d4T B: ddI C: d4T + ddI D: ZDV	A: d4T B: ddI C: d4T + ddI D: ZDV	Infants received same ART regimen as mother until 6 weeks of age	362 mother-infant pairs analyzed No infants breastfed	24 weeks postpartum A: 12% (11/91), 95% CI 6.2 to 21 B: 11% (10/94), 95% CI 5.2 to 19 C: 4.6% (4/88), 95% CI 1.3 to 11 D: 5.6% (5/89), 95% CI 1.9 to 13 All groups: 8.3% (30/362), 95% CI 5.7 to 12	Fair
Shapiro et al, 2010[63]	Botswana	Randomization groups† From 26 weeks: A: ABC + ZDV + 3TC B: ABT-378 + RTV + ZDV + 3TC Observational group‡ From 18 weeks: C: NVP + ZDV + 3TC	A: ABC + ZDV + 3TC B: ABT-378 + RTV + ZDV + 3TC C: NVP + ZDV + 3TC	A: ABC + ZDV + 3TC B: ABT-378 + RTV + ZDV + 3TC Above to continue until weaning or 6 months postpartum, whichever came first C: NVP + ZDV + 3TC to continue indefinitely All neonates: sdNVP at birth + ZDV from birth to 4 weeks	709 live born infants (including n=156 in the observational group) 97% of live born infants breastfed and 71% continued for >5 months	6 months of age A: 2.1% (6/283) B: 0.4% (1/270) percentage point difference, 1.7, 95% CI -2.0 to 7.1§ All groups: 1.1% (8/709), 95% CI 0.5 to 2.2	Fair
Shapiro et al, 2006[64]	Botswana	From 34 weeks: ZDV to all groups‖	A: sdNVP B: placebo	All neonates: NVP at birth and ZDV from birth to one month of age¶	694 live first born infants 50% of infants in both groups were breastfed Infant followup until one month of age	1 month of age A: 4.3%+/-2.3 (2 SD), 15/345 B: 3.7%+/-2.2 (2 SD), 13/346 95% CI for difference, -2.4 to 3.8% (met equivalence)	Fair
Thistle et al, 2007[65]	Zimbabwe	None	A: ZDV/sdNVP B: sdNVP	A: Infant ZDV for 72 hours after delivery and NVP dose within 72 hours of delivery B: Infant NVP dose within 72 hours of delivery	Study terminated secondary to futility 609 infants with data 89% of infants in group A and 91% of infants in group B were breastfed at 6 weeks (one infant in group A was breast and formula fed)	6 weeks of age A:14% (45/312) HIV+, 7.4% (23/312) mortality, 22% (68/312) met primary outcome (death or HIV infection) B:17% (49/297) HIV+, 7.1% (21/297) mortality, 24% (70/297) met primary outcome	Fair

*Began after protocol change in December 2006 (enrollment commenced June 2005).

Table 3. African-Based Trials of Mother-to-Child HIV Transmission While Using Antiretroviral Therapy

†Women with CD4 count >0.200 x 10^9 cells/L.
‡Women with CD4 count <0.200 x 10^9 cells/L or with AIDS-defining illness.
§Study not powered for between-group comparisons of transmission rates.
‖ART was offered to women with CD4 counts <0.200 x 10^9 cells/L or AIDS-defining illness at any point in study participation. If women started ART before delivery, they did not receive peripartum nevirapine or placebo.
¶Infants confirmed HIV-infected were also given ART.

3TC = lamivudine; ABC = abacavir; ABT-378 = lopinavir; ART = antiretroviral therapy; CI = confidence interval; d4T = stavudine; ddI = didanosine; FTC = emtricitabine; NVP = nevirapine; RR = relative risk; RTV = ritonavir; sdNVP = single-dose nevirapine; TDF = tenofovir; usZDV = ultra-short zidovudine; ZDV = zidovudine.

Table 4. Preterm Birth Outcomes*

Study, year	ART regimen (N; %)	Preterm Definition	Gestational age distribution	Magnitude of risk: Adjusted OR (95% CI), p-value
Cotter et al, 2006[75]	A: None (n=338; 25%) B: Monotherapy (n=492; 37%) C: Combination therapy with PIs (n=134; 10%) D: Combination therapy without PIs (n=373; 28%) Total N=1,337	<37 weeks; "Very preterm" <32 weeks	Median at delivery 39 weeks	Combination with vs. without PI: <37 weeks: 1.8 (1.1 to 3.0), p=0.03 Combination + PI: <37 weeks: 36.6% of women (p<0.05) <32 weeks: 2.2% of women (NS)
Schulte et al, 2007[81]	A: None (n=2565; 29%) B: Monotherapy (n=2621; 30%) C: Dual therapy (n=1044; 12%) D: Triple therapy: ART, non-PI (n=1781; 20%) E: Triple therapy: ART, PI (n=782; 9%) Total N=8,793	<37 weeks	Mean 37 weeks (range 26-42)	1.21 (1.04 to1.48), p-value NR
Townsend et al, 2007[82]	A: ART (n=3384; 69%) B: Mono/dual therapy (n= 1061; 21%) C: Untreated; not included in analyses (n= 494; 10%) Total N=4,939	<37 weeks	<37 weeks 14.1%† <35 weeks 7.8% <32 weeks 1.4%	<37 weeks: 1.39 (1.05 to1.83), p=0.02 <35 weeks: 2.02 (1.35 to 3.04), p=0.001 <32 weeks: 2.63 (1.3 to 5.33), p=0.007
Grosch-Warner et al, 2008[77]	A: Monotherapy (n=76; 42%) B: Dual therapy (n=32; 17%) C: ART without PI (n=54; 30%) D: ART with PI (n=21; 11%) Total N=183	<36 weeks	<36 weeks 34%† (crude rate)	ART (-) PI: 0.89 (0.38 to 2.12), p=0.8 ART (+) PI: 3.40 (1.13 to 10.2), p=0.03
Powis et al, 2011[72]	A: PI group, KAL/CBV (lopinavir/ ritonavir/ zidovudine/ lamudivine) (n=275; 49%) B: NRTI group, TZV (abacavir/zidovudine/lamidvudine)(n=285; 51%) Total N=560	<37 weeks	<37 weeks 11.8%† Triple NRTI; 21.4% PI based <32 weeks 2.6% (n=12); 8/12 associated with ART + PI; 4/12 triple NRTI	ART (-) PI (NRTI-based): 1.0 ART (+) PI: 2.02 (1.25 to 3.27), p=0.004

*Studies that adjusted for confounders.
†Percent of study population.

ART = antiretroviral therpy; GA = gestational age; NR = not reported; NRTI = nucleoside/nucleotide reverse transcriptase inhibitors; NS = not significant; PI = protease inhibitor.

Table 5. Summary of Evidence

Main findings from 2005 USPSTF review	Number and type of studies identified for update *Overall quality**	Limitations	Consistency	Applicability	Updated findings
Key Question 1. What are the benefits of HIV screening vs. no screening in asymptomatic pregnant women on maternal or child morbidity, mortality, or quality of life or rates of mother-to-child transmission?					
No studies	No studies	No studies	No studies	No studies	No study directly compared clinical outcomes (including risk of perinatal transmission) between pregnant women screened and not screened for HIV infection.
Key Question 2a. What is the yield of repeat HIV screening in asymptomatic pregnant women?					
No studies	No studies	No studies	No studies	No studies	No study evaluated the yield of repeat prenatal HIV screening compared to one-time screening, or compared the yield of different strategies for repeat screening.
Key Question 2b. What are the adverse effects (including false-positive results and anxiety) of rapid vs. standard HIV testing in asymptomatic pregnant women?					
1 observational study reported false-alarm rate of 10% with rapid testing during labor	2 observational studies† *Overall quality: Fair*	Few studies; small numbers of HIV-infected women	Consistent	No issues	One large (n=7,753), fair-quality prospective study of women presenting in labor with unknown HIV status (prevalence 0.7%) found the positive predictive value for the rapid test was higher (90% [52/58]) than for the standard test (74% [52/70]). One other, smaller study reported consistent results, but only five HIV cases were identified. No study evaluated adverse clinical consequences of interventions given as a result of false-positive results.
Key Question 3a. What is the effectiveness of newer antiretroviral regimens for reducing mother-to-child transmission?					
4 cohort studies found full-course combination antiretroviral therapy associated with substantially lower risk of transmission compared to no antiretrovirals or regimens with fewer drugs (absolute risk 1%-2%)	4 cohort studies and 6 RCTs *Overall quality: Fair*	No RCTs of full-course combination antiretroviral therapy in nonresource-poor settings	Consistent	RCTs evaluated shorter-course antiretroviral regimens in primarily breastfeeding women in resource-poor countries	Three cohort studies of antiretroviral therapy conducted in nonbreastfeeding women in the U.S. and Europe confirm the findings from the 2005 USPSTF review that full-course combination antiretroviral therapy is highly effective at reducing risk of mother-to-child transmission (<1% to 2.4% with combination antiretroviral therapy compared to 9% to 22% with no antiretroviral therapy). Shorter courses of antiretroviral therapy are not as effective as full-course regimens, but also reduce risk of mother-to-child transmission.
Key Question 3b. What are the effects of antiretroviral regimens in pregnant, HIV-positive women on long-term maternal morbidity, mortality, or quality of life?					
1 study of women originally enrolled in an RCT of zidovudine monotherapy found no adverse maternal outcomes after 4 years	No studies	No studies	No studies	No studies	No new studies evaluated effects of prenatal antiretroviral therapy on long-term maternal clinical outcomes.
Key Question 3c. What are the effects of antiretroviral regimens in pregnant, HIV-positive women on long-term maternal morbidity, mortality, or quality of life?					
Pregnancy outcomes					
1 meta-analysis and one large cohort study found no clear association between combination antiretroviral therapy use and low birth weight, and mixed evidence on premature delivery	1 RCT and 10 cohort studies *Overall quality: Fair*	No RCTs of full-course combination antiretroviral therapy	Some inconsistency	No issues	One RCT and four prospective cohort studies that adjusted for confounders found some antiretroviral regimens associated with increased risk of preterm delivery. Four studies that did not adjust for confounders reported inconsistent results. Cohort studies found no association between antiretroviral therapy use and low birth weight.

Table 5. Summary of Evidence

Main findings from 2005 USPSTF review	Number and type of studies identified for update *Overall quality**	Limitations	Consistency	Applicability	Updated findings
Mitochondrial dysfunction					
3 cohort studies found in utero antiretroviral exposure associated with laboratory mitochondrial dysfunction, but did not assess clinical effects	3 cohort studies *Overall quality: Fair*	No RCTs of full-course combination antiretroviral therapy; studies did not assess clinical outcomes	Consistent	No issues	Three studies evaluated risk of mitochondrial dysfunction following in utero exposure to antiretroviral therapy, but none evaluated clinical outcomes associated with mitochondrial dysfunction.
Congenital abnormalities					
1 prospective cohort study found no association between in utero antiretroviral exposure and congenital abnormalities	4 cohort studies *Overall quality: Fair*	No RCTs of full-course combination antiretroviral therapy	Consistent	No issues	Four studies found no association between in utero exposure to antiretroviral drugs and risk of congenital abnormalities
Neurodevelopment					
1 prospective cohort study found no effect of in utero antiretroviral exposure on neurodevelopment	2 cohort studies *Overall quality: Fair*	No RCTs of full-course combination antiretroviral therapy	Consistent	No issues	Two studies found no association between in utero exposure to antiretroviral drugs and neurodevelopment through ages 2 to 3 years.
Other harms of in utero exposure					
1 cohort study found no association between in utero exposure to zidovudine and echocardiographic abnormalities	5 cohort studies *Overall quality: Fair*	No RCTs of full-course combination antiretroviral therapy; studies of mitochondrial dysfunction and echocardiography abnormalities did not assess clinical outcomes	Consistent	No issues	Four cohort studies found an association between exposure to perinatal antiretroviral therapy and increased risk during infancy of hematological abnormalities and echocardiographic markers of impaired myocardial growth, but the clinical significance of these findings was unclear. One cohort study found no association between exposure to perinatal antiretroviral therapy and increased risk of childhood cancer.
Maternal harms					
1 meta-analysis found no association between perinatal zidovudine monotherapy and maternal deaths or long-term harms. 1 study found antiretroviral therapy associated with gestational diabetes. 1 trial found continuous nevirapine associated with serious hepatic or cutaneous toxicity in women with CD4 counts >0.250 x 10^9 cells/L	2 cohort studies *Overall quality: Fair*	No RCTs of full-course combination antiretroviral therapy; not clear if gestational diabetes diagnosed prior to initiation of antiretroviral therapy	Consistent	No issues	2 cohort studies found an association between antiretroviral therapy during pregnancy and gestational diabetes, but causality was unclear or estimates were not statistically significant.

* "Overall quality" is based on new evidence identified for this update plus previously reviewed evidence.
† One of the observational studies reports longer-term followup from a study included in the prior review.

All Key Questions

Database: EBM Reviews - Cochrane Database of Systematic Reviews

1 hiv.ti.
2 limit 1 to full systematic reviews
3 antiretroviral.mp. [mp=title, short title, abstract, full text, keywords, caption text]
4 haart.mp. [mp=title, short title, abstract, full text, keywords, caption text]
5 3 or 4
6 2 and 5
7 screen$.mp. [mp=title, short title, abstract, full text, keywords, caption text]
8 2 and 7
9 test$.mp. [mp=title, short title, abstract, full text, keywords, caption text]
10 2 and 9
11 6 or 8 or 10
12 limit 11 to last 8 years
13 pregnan$.mp. [mp=title, short title, abstract, full text, keywords, caption text]
14 12 and 13

Key Questions 1, 2a, and 2b

Database: Ovid MEDLINE(R) without Revisions

1 exp AIDS Serodiagnosis/
2 exp HIV Seronegativity/
3 exp HIV Antigens/
4 exp HIV/
5 exp HIV Seroprevalence/
6 exp HIV Seropositivity/
7 exp HIV Antibodies/
8 or/2-7
9 exp Mass Screening/
10 8 and 9
11 1 or 10
12 (hiv adj1 screen$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
13 11 or 12
14 13 and (200406$ or 200407$ or 200408$ or 200409$ or 20041$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$).ed.
15 limit 14 to English language
16 limit 14 to abstracts
17 15 or 16
18 limit 17 to humans
19 Pregnancy/
20 pregnan$.mp.
21 19 or 20
22 18 and 21

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

1 exp AIDS Serodiagnosis/

2 exp HIV Seronegativity/
3 exp HIV Antigens/
4 exp HIV/
5 exp HIV Seroprevalence/
6 exp HIV Seropositivity/
7 exp HIV Antibodies/
8 or/2-7
9 exp Mass Screening/
10 8 and 9
11 1 or 10
12 (hiv adj1 screen$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
13 11 or 12
14 limit 13 to yr="2004 -Current"
15 Pregnancy/
16 14 and 15

Key Question 3a

Database: Ovid MEDLINE(R) without Revisions

1 Antiretroviral Therapy, Highly Active/
2 haart.mp.
3 1 or 2
4 Anti-HIV Agents/
5 3 or 4
6 Infectious Disease Transmission, Vertical/
7 HIV Infections/tm [Transmission]
8 6 or 7
9 5 and 8
10 Pregnancy/
11 9 and 10
12 limit 11 to English language
13 limit 11 to abstracts
14 12 or 13
15 limit 14 to yr="2004 -Current"

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

1 Antiretroviral Therapy, Highly Active/
2 haart.mp.
3 1 or 2
4 Anti-HIV Agents/
5 3 or 4
6 Infectious Disease Transmission, Vertical/
7 HIV Infections/tm [Transmission]
8 6 or 7
9 5 and 8
10 Pregnancy/
11 9 and 10

12 limit 11 to yr="2004 -Current"

Key Question 3b and 3c

Database: Ovid MEDLINE(R) without Revisions

1 Antiretroviral Therapy, Highly Active/
2 Anti-HIV Agents/
3 haart.mp.
4 or/1-3
5 Pregnancy/
6 4 and 5
7 limit 6 to yr="2004 - Current"
8 limit 7 to English language
9 limit 7 to abstracts
10 8 or 9
11 10 not (letter or editorial or comment or case reports).pt.

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

1 Antiretroviral Therapy, Highly Active/
2 Anti-HIV Agents/
3 haart.mp.
4 or/1-3
5 Pregnancy/
6 4 and 5
7 limit 6 to yr="2004 -Current"

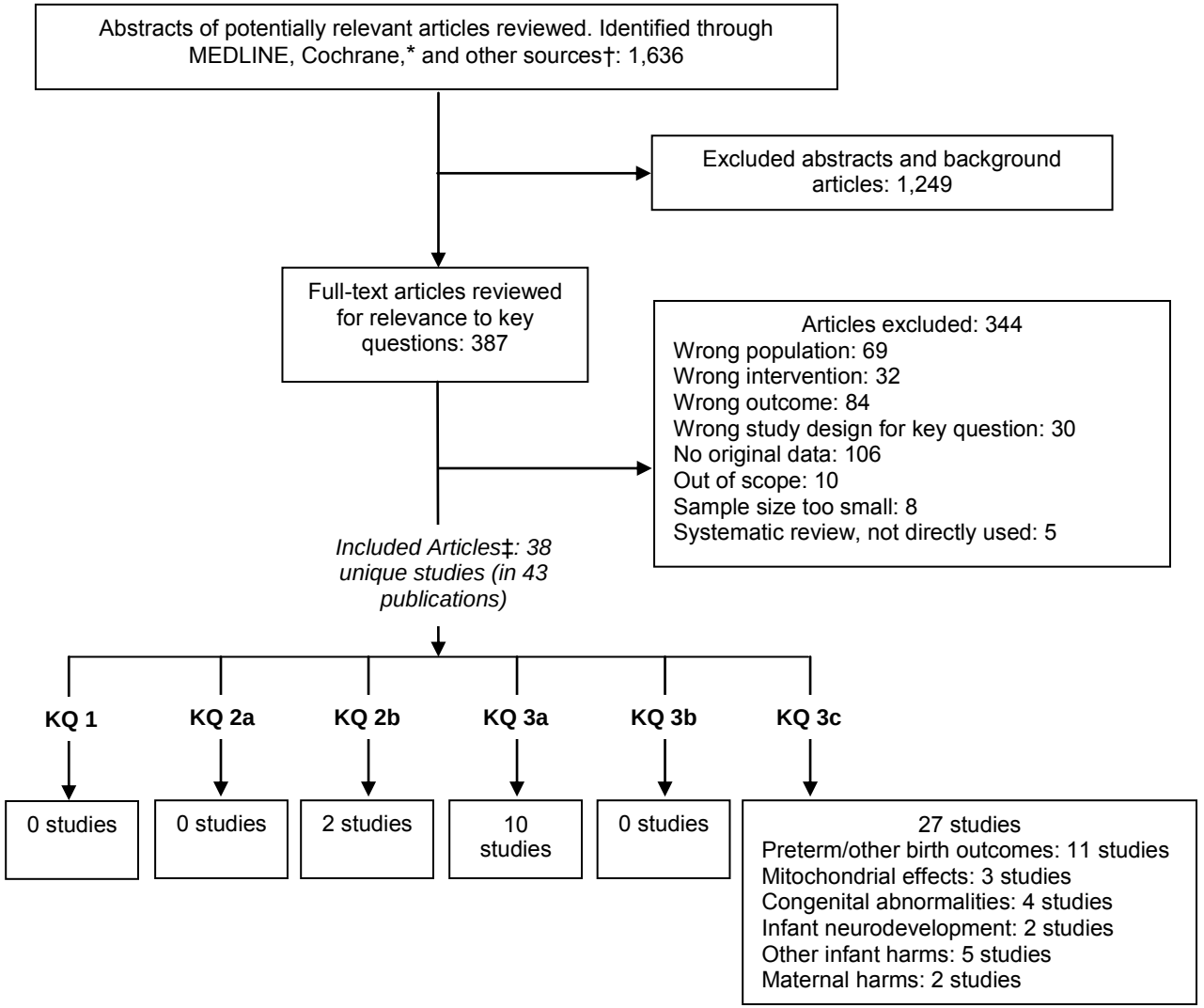
Appendix A2. Inclusion and Exclusion Criteria per Key Question

	Include	Exclude
All Key Questions		
Settings	Primary care or other settings generalizable to primary care (e.g., family planning clinics, school-based health clinics), other health care settings in which screening is commonly performed (e.g., emergency room or urgent care). Focus on studies conducted in the United States and other developed countries, except for randomized trials of antiretroviral therapies (Africa).	Developing countries, unless fair- or good-quality trials and studies in the United States are lacking
Key Question 1: What are the benefits of HIV screening vs. no screening in asymptomatic pregnant women on maternal or child morbidity, mortality, or quality of life or rates of mother-to-child transmission?		
Populations	Asymptomatic pregnant women; neonates, infants, and children who were exposed to ART in utero	Known HIV infection, on dialysis, post-transplant, occupational exposure
Interventions	Rapid or standard HIV testing	
Comparisons	HIV screening versus no screening	
Outcomes	Mother-to-child transmission rates of HIV, mortality related to HIV infection, and quality of life for mothers and their newborns	Pharmacokinetics
Study designs	Randomized, controlled trials and controlled observational studies	Modeling studies
Key Question 2a: What is the yield of repeat HIV screening in asymptomatic pregnant women?		
Populations	Asymptomatic pregnant women	Known HIV infection, on dialysis, post-transplant, occupational exposure
Interventions	Rapid or standard HIV testing	
Comparisons	Repeat HIV screening during pregnancy versus one-time screening, or screening at one interval versus another interval	
Outcomes	Number of positive test results	
Study designs	Randomized, controlled trials and controlled observational studies	Modeling studies
Key Question 2b: What are the adverse effects (including false-positive results and anxiety) of rapid vs. standard HIV testing in asymptomatic pregnant women?		
Populations	Asymptomatic pregnant women	Known HIV infection, on dialysis, post-transplant, occupational exposure
Interventions	Rapid or standard HIV testing	
Comparisons	Rapid versus standard HIV testing	
Outcomes	False-positive results, anxiety, and effects of labeling; partner discord, abuse, or violence	
Study designs	Randomized, controlled trials and comparative observational studies	Modeling studies
Key Question 3a: What is the effectiveness of newer antiretroviral regimens for reducing mother-to-child transmission?		
Populations	Pregnant women with HIV; neonates and infants who were exposed to antiretroviral regimens in utero	Women already or previously on ART prior to pregnancy; acute HIV or HIV subtypes
Interventions	Newer antiretroviral regimens	Discontinuing ART during pregnancy; treatment interruption
Comparisons	Newer antiretroviral regimens versus placebo, older antiretroviral regimens, or one another	
Outcomes	Mother-to-child transmission rates of HIV	
Study designs	Randomized, controlled trials and controlled observational studies	Modeling studies
Key Question 3b: What are the effects of antiretroviral regimens in pregnant, HIV-positive women on long-term maternal morbidity, mortality, or quality of life?		
Populations	Women who were on antiretroviral regimens while pregnant	Women already or previously on ART prior to pregnancy; acute HIV or HIV subtypes
Interventions	Newer antiretroviral regimens	Discontinuing ART during pregnancy; treatment interruption
Comparisons	Newer antiretroviral regimens versus placebo, older antiretroviral regimens, or one another	
Outcomes	Long-term maternal morbidity, mortality, or quality of life	Pharmacokinetics
Study designs	Any	
Timing	One or more years after giving birth	Less than 1 year after giving birth

Appendix A2. Inclusion and Exclusion Criteria per Key Question

	Include	Exclude
Key Question 3c: What are the harms (including longer-term harms) to the mother or child associated with antiretroviral therapy during pregnancy?		
Populations	Women who were on antiretroviral regimens while pregnant; neonates, infants, and children who were exposed to antiretroviral therapy in utero	Women already or previously on antiretroviral therapy prior to pregnancy; acute HIV or HIV subtypes
Interventions	Newer antiretroviral regimens	Discontinuing antiretroviral therapy during pregnancy; treatment interruption
Comparisons	Newer antiretroviral regimens versus placebo, older antiretroviral regimens, or one another	
Outcomes	Harmful effects on pregnancy outcomes, neonatal outcomes, or effects on exposed children; long-term cardiovascular and metabolic maternal outcomes	Pharmacokinetics
Study designs	Any	
Timing	Any	

Appendix A3. Literature Flow Diagram



*Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
†Other sources include reference lists, suggestions from peer reviewers.
‡ Some articles are included for more than one key question.

Wrong Population

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Diagnostic Accuracy Studies

Criteria:

- Screening test relevant, available for primary care, adequately described
- Study uses a credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Handles indeterminate results in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Administration of reliable screening test
- Random or consecutive selection of patients
- Screening cutoff pre-determined
- All patients undergo the reference standard

Definition of ratings based on above criteria:

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (more than 100) broad-spectrum patients with and without disease; study attempts to enroll a random or consecutive sample of patients who meet inclusion criteria screening cutoffs pre-stated.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients (i.e. applicable to most screening settings).

Poor: Has important limitation such as: uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size of very narrow selected spectrum of patients.

Randomized Controlled Trials (RCTs) and Cohort Studies

Criteria:

- Initial assembly of comparable groups: RCTs—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs; for cluster RCTs, correction for correlation coefficient

Definition of ratings based on above criteria:

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.

Poor: Studies will be graded "poor" if any of the following major limitations exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

Source: Harris R, Helfand M, Woolf SH, et al. Current methods of the U.S. Preventive Services Task Force: a review of the process. *Am J Prev Med*. 2001;20(3S):21-35.

Appendix A6. Expert Reviewers of the Draft Report

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Appendix B1. Key Question 2b: Quality Ratings of Diagnostic Accuracy Studies

Study, year	Representative spectrum	Random or consecutive sample	Screening test adequately described	Screening cutoffs predefined	Credible reference standard	Reference standard applied to all screened patients	Same reference standard applied to all patients	Reference standard and screening examination interpreted independently	High rate of uninterpretable results or noncompliance with screening test	Analysis includes patients with uninterpretable results or noncompliance	Quality rating
Jamieson, 2007[39] See also Bulterys, 2004[28]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	No	No	Fair
Tung, 2010[40]	Limited	Yes	Yes	Yes	Yes	No; only those testing positive	Yes	Yes	No	No	Fair

Appendix B2. Key Question 3a: Evidence Table of Cohort Studies of Mother-to-Child HIV Transmission While Using Antiretroviral Therapy

Author, Year	Type of study/location/setting/ high or low prevalence population (based on 0.1% prevalence rate)	Study dates/ duration of followup	Comparison groups	Baseline population characteristics for mother/baby	Eligibility criteria
Garcia-Tejedor, 2009[58]	Cohort Maternity hospital Spain Prevalence not reported	1984-2006 Details not reported	ART during pregnancy: A: no treatment n=214 B: mono/dual therapy n=116 C: ART n=159	Age, race, CD4 count, HIV stage not reported Before 1997, 27% of women received ART (mono/dual therapy) After 1997, 91% of women received ART (77% with ART, 23% with mono/dual therapy) After 2002, ART was only therapy administered; 96% of women receiving treatment during pregnancy also received ART during delivery	HIV-infected pregnant women with attendance for prenatal care at least once at study obstetric clinic and/or delivery in maternity department between Jan 1984-Dec 2006
Harris, 2007[57]	Cohort United States surveillance data from areas that reported ≥60 HIV-positive women giving birth per year but prevalence not reported (sites represented 89% of all perinatal AIDS cases reported in 2003)	Births from 1999-2001 Infants followed up by health department every 6 months until HIV status determined Analysis of surveillance data over study period	Prenatal ART regimes: A: no treatment n=292 B: neonatal ART only n=359 C: intrapartum ART and neonatal ART n=322 D: prenatal ART and neonatal ART n=316 E: prenatal ART and intrapartum ART and neonatal ART n=6029	Age at delivery (years): 13-19: n=509 20-29; n=3641 30-39: n=2652 >40; n=195 Race: White n=826 Black n=4887 Hispanic n=1224 Other n=60 CD4 count and HIV stage not reported	HIV-infected mothers and HIV-exposed infants born in 1999, 2000, 2001. Women known to be HIV-infected in pregnancy (tested before or at delivery), women not known to be HIV-infected in pregnancy but whose child tested positive for HIVAll infants born in or receiving care in project site
Tariq, 2011[59] See also Townsend, 2008[56]; European Collaborative Study, 2005[93]	Cohort Population surveillance data from the European Collaborative Study and the National Study of HIV in Pregnancy and Childhood United Kingdom, Ireland, Belgium, Denmark, Germany, Italy, the Netherlands, Poland, Spain, Sweden Prevalence not reported (rates of mother to child transmission in Europe and the UK declined from 20% in 1990s to <2% in "recent" years)	2000-2009 Followup testing schedule not reported Analyses of data over study period	Only antepartum treatment considered: A: ZDV-containing ART n=6374 B: ZDV-sparing ART n=1199 About 30% of women were on ART at conception	Maternal age at delivery, years (n=7547); A vs. B, p<0.001: <25; n=1072 (16.9%) vs. n=110 (9.2%) 25-29; n=1979 (31.2%) vs. n=257 (21.6%) 30-34; n=2006 (31.6%) vs. n=738 (61.7%) ≥35; n=1293 (20.4%) vs. n=92 (7.7%) Ethnicity (n=7550); A vs. B, p<0.001: Black n=4974 (78.3%) vs. n=882 (73.8%) White n=1086 (17.1%) vs. n=269 (22.5%) Asian/other n=294 (4.6%) vs. n=45 (3.8%) Baseline CD4 count, cells/mm^3 (n=6993); A vs. B, p=0.14: ≥500; n=1520 (25.9%) vs. n=316 (28.4%) 200-499; n=3427 (58.3%) vs. n=636 (57.2%) <200; n=934 (15.9%) vs. n=160 (14.4%) HIV stage: Not reported	All reported live singleton births to women who received ART for at least 14 days before delivery between 2000-2009
Townsend, 2008[56]	Cohort Population surveillance data from the NSHPC UK, Ireland Prevalence not reported (mother to child transmission rates in UK, Ireland fell from 20% to 2% between 1993 and 1998)	Births from 2000-2006 to women diagnosed before delivery and reported by June 2007 Followup testing schedule not reported Analyses of data over study period	Only antepartum treatment considered: Number at baseline/number in analysis A: ART therapy n=4726/4120 B: Dual therapy n=136/126 C: Monotherapy n=712/638 D: None n=186/14324 1% (1075/4469) started ART before pregnancy	Age at delivery, median (years): 29.8 (IQR 26.2-33.6) Race: White n=775 (13.2%) Black African n=4630 (78.8%) Other n=470 (8.0%) CD4 count:At least 0.500 x 10^9 cells/L n=1595 (35.1%) 350-499 cells/mL n=1158 (25.5%) 0.200-0.349 x 10^9 cells/L n=1241 (27.3%) <0.200 x 10^9 cells/L n=545 (12.0%) Clinical status: Asymptomatic n=4606 (89.7%) AIDS or HIV-related symptoms n=528 (10.3%)	Singleton births between 2000 and 2006 to women diagnosed with HIV infection before delivery and reported to the NSHPC by June 2007

Appendix B2. Key Question 3a: Evidence Table of Cohort Studies of Mother-to-Child HIV Transmission While Using Antiretroviral Therapy

Author, Year	Exclusion criteria	Number screened/ eligible/enrolled/ withdrawals/% analyzed	Breastfeeding rate/duration	Cesarean rate	Adjusted variables for statistical analysis
Garcia-Tejedor, 2009[58]	Children with unknown serological status	500 HIV-infected women (495 singleton births, five twins); 505 children delivered; 489 mother-child pairs analyzed (1 miscarriage, 11 stillborns, 2 perinatal deaths, 2 lost to followup)	Breastfeeding suppressed in all cases	Elective; n = 139/489 Emergency; n = 109/489	Clinical outcomes of interest not adjusted
Harris, 2007[57]	None reported a priori for population Inadequate ART data excluded from analysis, missing data for other variables of interest excluded cases as appropriate for logistic regression models of interest	8530 eligible; 7344 births with ART data (further excluded as per logistic regression models and outcomes of interest resulting in n=6997 and n=6974 for analyses)	Not reported	n=3678/6997 (elective or emergency not reported)	AOR=maternal age, race, prenatal care, timing of maternal HIV test, delivery type, site AOR2=year of birth, maternal age, race, delivery type, site
Tariq, 2011[59] See also Townsend, 2008[56]; European Collaborative Study, 2005[93]	Mother-child pairs lacking information on all 3 outcomes of interest ECS excluded data from centers in the Ukraine (limited antenatal ART) and UK (to avoid duplication of cases reported to the NSHPC)	7573 mother-child pairs analyzed (n=1263 from ECS, n=6310 from NSHPC)	Not reported	n=7488 with data Elective; A vs B: n=3564 (56.5%) vs n=634 (54.0%) Emergency; A vs B: n=1151 (18.2%) vs n=243 (20.7%)	AOR=OR adjusted for duration of ART, study, mode of delivery
Townsend, 2008[56]	Multiple births excluded Children with unreported infection status excluded from analysis. Analysis performed using likely infection status to check for potential bias from excluding this group Only antepartum treatment considered in analysis	5930 singleton births; 5151 mother-child pairs with infection status reported; 5027 with ART data for analysis	Breastfeeding reported in 0.6% (29/4399) of infants (although not recommended in UK or Ireland). 3 infants infected, all born to untreated women	Elective; n=3368/5901 (57.1%) Emergency; n=1223/5901 (20.7%)	AOR=OR adjusted for ART, mode of delivery, sex (gestational age was not a significant risk factor for transmission in women on ART and was excluded from analyses) AOR2=OR adjusted for mode of delivery, gestational age, sex, viral load

AIDS = acquired immune deficiency syndrome; AOR = adjusted odds ratio; ART = antiretroviral therapy; CD4 = cluster of differentiation 4; CDC = Centers for Disease Control and Prevention; CI = confidence interval; ECS = European Collaborative Study; IQR = interquartile range; MTCT = mother-to-child transmission; NNRTI = nonnucleoside reverse transcriptase inhibitor; NSHPC = National Study of HIV in Pregnancy and Childhood; OR = odds ratio; PI = protease inhibitor; ZDV = Zidovudine.

Appendix B3. Key Question 3a: Quality Ratings of Cohort Studies of Mother-to-Child HIV Transmission While Using Antiretroviral Therapy

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study maintain comparable groups through the study period?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to followup or overall high loss to followup?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Quality rating
Garcia-Tejedor, 2009[58]	Yes	Unclear; baseline characteristics are not reported	Unclear	Unclear	Unclear	Yes	No; only univariate results available for outcome of interest	No	Yes	Fair
Harris, 2007[57]	Yes; included study sites meeting prespecified criteria (represented 89% of all perinatal AIDS cases reported in 2003)	Unclear; not reported by ART groups	Yes	Yes	Unclear	Yes	Yes	No	Yes	Fair
Tariq, 2011[59]	Yes	No; significant between ART group differences on several variables	Unclear	Yes	Unclear	Yes	Yes	No/Yes	Yes	Fair
Townsend, 2008[56]	Yes	Unclear; not reported by ART groups	Unclear	Yes	Unclear	Yes	Yes	No	Yes	Fair

Appendix B4. Key Question 3a: Evidence Table of African-Based Randomized, Controlled Trials of Mother-to-Child HIV Transmission While Using Antiretroviral Therapy

Author, Year	Location/setting/high or low prevalence population (based on 0.1% prevalence rate)	Study dates/ duration of followup	Treatment groups	Baseline population characteristics for mother/baby
Chi, 2008[61] See also Chi, 2007[66]	Zambia; public health clinics; prevalence not reported	Women randomized between March 16 2005 and February 13 2007; followup until infant is 6 weeks old	A: maternal TDF 300mg/FTC 200mg at delivery B: maternal ZDV 300mg BD starting at 32 weeks, NVP 200mg in labor, infant NVP 2mg/kg at birth, and discharged with 7 day course of ZDV 4mg/kg (standard of care)	Original cohort (as per Chi 2007): Intervention vs. Control Median age (interquartile range): 26 y (22-29) vs. 24 y (22-29) Race: Not reported Mean CD4 (SD): 464 (208) vs. 490 (200) cells/mL WHO stage III: 3 (2%) vs. 3 (2%)
de Vincenzi, 2011[60] See also Kesho Bora Study Group, 2010[67]	Burkina Faso, Kenya, South Africa; antenatal clinics; prevalence not reported	June 2005 to August 2008; followup until infant is 12 months old	From 34-36 weeks gestation: A: Maternal ZDV + 3TC + ABT-378 + RTV until cessation of breastfeeding (maximum 6.5 months postpartum) B: Maternal ZDV until delivery, ZDV + sdNVP at labor onset (protocol change from December 2006, prophylaxis started at 28 weeks gestation and women given 3TC + ZDV for 1 week postpartum) Infants received NVP within 72 hours of birth, co-trimaxozole from age 6 weeks to 12 months, unless not HIV infected after cessation of breastfeeding (protocol change from December 2006, infants received 1 week of ZDV from birth)	A: median age (IQR) 27 years (24-31), median CD4 count (IQR) at enrollment 0.336 x 10^9 cells/L (0.282-0.408 x 10^9 cells/L), median maternal viral load (IQR) at enrollment 4.23 $\log_{10}$ copies/mL (3.66-4.75) B: median age (IQR) 27 years (23-31), median CD4 count (IQR) at enrollment 339 cells/mL (267-408), median maternal viral load (IQR) at enrollment 4.21 $\log_{10}$ copies/mL (3.58-4.74)
Gray, 2006[62]	South Africa; prevalence not reported	Open label, randomized 4-arm single-center study from May 1999 to May 2000; maternal followup until 6 weeks postpartum. Infant followup until 24 weeks of age.	From 34 weeks gestation: A: d4T 40mg BD B: ddI 200mg BD C: d4T 40 mg + ddI 200mg BD D: ZDV 300mg BD Infants received same ART regime as mother within 36 hours of birth until 6 weeks of age.	ALL groups, n = 373 Age, mean (SD): 28.3 (5.8) Race: Black = 372/373 (100) Est. week of gestation: mean: 34.7 (0.8), median: 34.7, range: 31-39 CD4 count (cells/L): mean: 0.4308 x 10^9 cells/L (225), median: 0.3920 x 10^9 cells/L, range: 0.027-1.286 x 10^9 cells/L
Shapiro, 2010[63]	Botswana; study clinics; 27% of pregnant women screened at antenatal clinics had HIV	Enrolled July 2006 to May 2008; followup until 6 months postpartum	Randomization groups (women with CD4 count ≥200 cells/mm^3): From 26-34 weeks gestation through weaning or 6 months postpartum, whichever first: A: maternal ABC + ZDV + 3TC B: maternal ABT-378 + RTV + ZDV + 3TC Observational group (women with CD4 count <200 cells/mm^3 or with AIDS defining illness): From 18-34 weeks to continue indefinitely: C: maternal NVP, ZDV, 3TC Infants received sdNVP at birth and ZDV from birth to 4 weeks.	A: median age at enrollment 26 years, median CD4 count (IQR) 0.393 x 10^9 cells/L (0.305-0.514 x 10^9 cells/L), median HIV-1 RNA (IQR) 13,300 copies/mL (2,340-50,900), median (IQR) gestational age at delivery 39.3 years (37.9-40.3), median (IQR) infant birthweight 3.0 kg (2.7-3.3) B: median age at enrollment 25 years, median CD4 count (IQR) 403 (297-514), median HIV-1 RNA (IQR) 9,100 copies/mL (2,210-39,900), median (IQR) gestational age at delivery 39.0 years (37.4-40.0), median (IQR) infant birthweight 2.9 kg (2.6-3.2) C: median age at enrollment 29 years, median CD4 count (IQR) 147 (115-183), median HIV-1 RNA (IQR) 51,700 copies/mL (14,400-179,000), median (IQR) gestational age at delivery 39.4 years (38.4-40.3), median (IQR) infant birthweight 2.9 kg (2.6-3.2) Median duration of ART before delivery was 11 weeks in randomized groups, 13 weeks in observational group

Appendix B4. Key Question 3a: Evidence Table of African-Based Randomized, Controlled Trials of Mother-to-Child HIV Transmission While Using Antiretroviral Therapy

Author, Year	Location/setting/high or low prevalence population (based on 0.1% prevalence rate)	Study dates/ duration of followup	Treatment groups	Baseline population characteristics for mother/baby
Shapiro, 2006[64]	Botswana; study sites at district hospitals; 37% of pregnant women test HIV positive at surveillance sites in Botswana	Enrolled June 2002 to October 2003; followup until infant is 1 month old	A: maternal sdNVP during labor B: maternal placebo during labor All mothers received ZDV from 34 weeks gestation until delivery and all infants received sdNVP and ZDV from birth to 1 month of age ART was offered to women with CD4 counts <200 or AIDS defining illness at any point in study participation. If women started ART before delivery, they did not receive NVP or placebo at labor onset. Infants confirmed HIV infected were also given ART.	A: median age 27.6 years, median CD4 count (IQR) 0.356 x 10^9 cells/L (0.218-0.519 x 10^9 cells/L), median length of gestation at delivery (IQR) 40 weeks (38-40), median infant birthweight (IQR) 3.0 kg (2.8-3.4) B: median age 27.1 years, median CD4 count (IQR) 363 (250-536) cells/µl, median length of gestation at delivery (IQR) 40 weeks (39-40), median infant birthweight (IQR) 3.1 kg (2.9-3.4) Race: Not reported HIV stage: Not reported
Thistle, 2007[65]	Zimbabwe; hospital; 21.6% at study site	2002 to2004 (terminated secondary to futility)	A: maternal ultra short course ZDV (given during labor), sdNVP in labor, infant ZDV for 72 hours after delivery and NVP therapy within 72 hours of delivery B: maternal sdNVP therapy in labor, infant NVP therapy within 72 hours of delivery	Age, mean years $\pm$ SD: A: 25.7 $\pm$ 5.6 B: 25.6 $\pm$ 5.7

Author, Year	Eligibility criteria	Exclusion criteria	Number screened/ eligible/enrolled/ withdrawals/% analyzed	Breastfeeding rate/duration
Chi, 2008[61] See also Chi, 2007[66]	HIV-infected women seeking care at 2 public sector primary health facilities who tested positive for HIV and who were between 28 and 38 weeks gestation. All women were offered short course ZDV from 32 weeks onward and intrapartum NVP for perinatal prophylaxis prior to recruitment as part of routine care. All HIV-exposed infants were given NVP syrup before discharge and week long supply of ZDV.	Women who qualified for ART based on WHO criteria for health, and women with any previous use of ART. Enrolled women who had given consent and who presented to study facility in labour were assessed by staff. Only women who reported self-administration of single-dose NVP before arrival or who were seen to ingest the dose after admission, who were in active labor, and had no clinical indications for transfer to tertiary care facility, were randomized.	627 enrolled; 397 randomized; 355 (89%) mother-infant pairs analyzed (n=3 [1%] stillbirths, n=9 [2%] infant deaths before 6 weeks of age, n=30 [8%] mother-child pairs lost to followup) A: n=180 (51%) B: n=175 (49%)	Intervention vs. Control Infant breastfeeding at 6 weeks n = 166 (92%) vs. 161 (92%) (as per Chi 2007 Table 1)
de Vincenzi, 2011[60] See also Kesho Bora Study Group, 2010[67]	ART naive pregnant women infected with HIV-1 visiting antenatal clinics at 5 study sites, less than 32 weeks gestation, WHO stage 1, 2, or 3 HIV infection, CD4 count 0.200-0.500 x 10^9 cells/L	Women with contraindications to rapid initation of ART (i.e., allergy to ART or benzodiazepines), those on drugs that interact with ART, or those with severe anemia, neutropenia, liver or renal failure First, liveborn infants used for analysis	882 enrolled; 824 randomized (412 to group A, 412 to group B); 401 livebirths in group A, 404 livebirths in group B	A: 307/401 (77%) ever breastfed, median duration of breastfeeding (IQR) 21.4 weeks (8.6-25.4), exclusive breastfeeding up to last available visit before 3 months 135/298 (45%) B: 317/404 (78%) ever breastfed, median duration of breastfeeding (IQR) 19.0 weeks (9.0-25.7), exclusive breastfeeding up to last available visit before 3 months 134/304 (44%) P values = 0.55, 0.95, 0.80

Appendix B4. Key Question 3a: Evidence Table of African-Based Randomized, Controlled Trials of Mother-to-Child HIV Transmission While Using Antiretroviral Therapy

Author, Year	Eligibility criteria	Exclusion criteria	Number screened/ eligible/enrolled/ withdrawals/% analyzed	Breastfeeding rate/duration
Gray, 2006[62]	HIV-1 infected, antiretroviral-naive pregnant women >18 years old, 34-36 weeks of gestation; prepared to formula feed infants; willing to have infants followed for 6 months	Presence of severe fetal abnormalities, presence of 3 or more fetuses, occurrence of a newly diagnosed HIV-related opportunistic infection, malignancy, condition requiring acute therapy, active drug abuse, history of pancreatitis, past or present symptoms of grade 2 or greater bilateral peripheral neuropathy	373 women randomized: A: 93 to d4T B: 95 to ddI C: 95 to d4T + ddI D: 92 to ZDV 13 women began study treatment ealier or later than 34-36 weeks gestation 372 infants born to 369 women (3 sets of twins) 11 mother-infant pairs unevaluable	None
Shapiro, 2010[63]	Pregnancy of 26-34 weeks gestation for randomized groups or 18-34 weeks gestation for observational group, had positive HIV-1 ELISA on 2 separate samples, were ≥18 years old, had hemoglobin ≥8 g/dL, absolute neutrophil count ≥1000 cells/mm^3, alanine amino transferase and aspartate amino transferase no more than 2.5 times upper limit of normal range	Women who preferred to exclusively formula feed their infants	15,414 screened; 4209 tested positive; 1248 referred to study clinics; 730 enrolled; 560 randomized and 170 observed (709 liveborn infants) A: n=285 assigned, 274 had live born infants (n=283 liveborn infants) B: n=275 assigned, 269 had live born infants (n=270 liveborn infants) C: n=170 assigned, 156 had live born infants (n=156 liveborn infants)	All women asked to exclusively breast-feed and wean 3 days before 6 month study visit; 97% of all women with live-born infants breastfed and 71% continued for at least 5 months (70% in group A, 73% in group B, 71% in group C) A: n=264 (96%) initiated breastfeeding while receiving ART, n=71 (27%) weaned ≤5 months before stopping ART, n=2 (1%) weaned ≤5 months after stopping ART, n=5 (2%) lost to followup but breastfed to last contact, n=186 (70%) breastfed for >5 months while receiving ART B: n=263 (98%) initiated breastfeeding while receiving ART, n=66 (25%) weaned <5 months before stopping ART, n=4 (2%) weaned <5 months after stopping ART, n=3 (1%) stopped ART before weaning >5 months, n=5 (2%) lost to followup but breastfed to last contact, n=185 (70%) breastfed for >5 months while receiving ART C: n=150 (96%) initiated breastfeeding while receiving ART, n=39 (26%) weaned <5 months while continuing ART, n=1 (1%) lost to followup but breastfed to last contact, n=1 (1%) died <5 months, n=109 (72%) breastfed for >5 months while receiving ART

Appendix B4. Key Question 3a: Evidence Table of African-Based Randomized, Controlled Trials of Mother-to-Child HIV Transmission While Using Antiretroviral Therapy

Author, Year	Eligibility criteria	Exclusion criteria	Number screened/ eligible/enrolled/ withdrawals/% analyzed	Breastfeeding rate/duration
Shapiro, 2006[64]	HIV positive pregnant women who were between 33 and 35 weeks gestation, had positive HIV-1 ELISA on 2 separate samples, were ≥18 years old, had hemoglobin ≥8 g/dL, absolute neutrophil count ≥1000 cells/µl, alanine amino transferase and aspartate amino transferase ≤10 times the upper limit of normal, creatinine ≤1.5 mg/dL, did not have intolerance to zidovudine or nevirapine and provided written informed consent	Did not plan to remain in study area, presented after 34 weeks gestation, laboratory ineligibility Only first born, liveborn infants included in analysis	9031 screened; 709 enrolled A: n=354 randomized, n=345 live births, n=40 started ART prior to delivery, n=327 infants with HIV status known at 1 month B: n=355 randomized, n=349 live births, n=31 started ART prior to delivery, n=329 infants with HIV status known at 1 month	C: n=150 (96%) initiated breastfeeding while receiving ART, n=39 (26%) weaned <5 months while continuing ART, n=1 (1%) lost to followup but breastfed to last contact, n=1 (1%) died <5 months, n=109 (72%) breastfed for >5 months while receiving ART
Thistle, 2007[65]	HIV positive pregnant women with positive test results on both dipstick HIV 1, 2 and recombigen test kit, able to give informed consent, willing to have infants involved	Inability to give or refusal to give informed consent, clinical evidence of significant hepatic disease, receipt of previous ART Only data from firstborn infant included if multiple birth	Overall: 7467 screened; 1610 eligible; 1140 randomized A: n = 569 randomized B: n = 571 randmomized A: n=440 births B: n=434 births n=609 infants with data at 6 weeks A: n=312 B: n=297	A: 89.4% breastfeeding at 6 weeks, 0.4% mixed feeding at 6 weeks B: 91.1% breastfeeding at 6 weeks, 0 mixed feeding at 6 weeks

Author, Year	Cesarean rate	Transmission rates
Chi, 2008[61] See also Chi, 2007[66]	Not reported	Transmission according to actual use ART regimens for perinatal HIV prevention: Intrauterine With antenatal ZDV NVP+TDF/FTC: 3/126 (2.4%) NVP alone: 8/117 (6.8%) Without antenatal ZDV NVP+TDF/FTC: 3/22 (13.6%) NVP alone: 1/27 (3.7%) Other ZDV + TDF/FTC: 1/23 (4.3%) ZDV only: 0/22 TDF/FTC only: 1/5 (20.0%) No drug: 0/6 Missing NVP cord plasma: 1/7 (14.3%) Total: 18/355 (5.1%) Intrapartum/Early transmission With antenatal ZDV NVP+TDF/FTC: 2/123 (1.6%) NVP alone: 3/109 (2.8%) p=0.67 Without antenatal ZDV NVP+TDF/FTC: 0/19 NVP alone: 1/26 (3.4%) Other ZDV + TDF/FTC: 0/22

Appendix B4. Key Question 3a: Evidence Table of African-Based Randomized, Controlled Trials of Mother-to-Child HIV Transmission While Using Antiretroviral Therapy

Author, Year	Cesarean rate	Transmission rates
		ZDV only: 0/22 TDF/FTC only: 0/4 No drug: 0/6 Missing NVP cord plasma: 0/6 Total: 6/337 (1.8%) Overall With antenatal ZDV NVP+TDF/FTC: 5/126 (4.0%) NVP alone: 11/117 (9.4%) p=0.12 Without antenatal ZDV NVP+TDF/FTC: 3/22 (13.6%) NVP alone: 2/27 (7.4%)p=0.65 Other ZDV + TDF/FTC: 1/23 (4.3%) ZDV only: 0/22 TDF/FTC only: 1/5 (20.0%) No drug: 0/6 Missing NVP cord plasma: 1/7 (14.3%) Total: 24/355 (6.8%) **Intrapartum/early transmission = baby tested negative at birth but positive at 6 weeks (IMP: these women are breastfeeding), so this transmission rate seems not applicable to nonbreastfeeding groups Overall, 24/355 (7%) infants were infected with HIV by 6 weeks. Most transmissions occurred during intrauterine period (n=18) compared to intrapartum/early postpartum (n=6). Transmission rates were similar between intervention and control arms for intrauterine (4% vs. 6%, p=0.63), intrapartum/early postpartum (1% vs. 2%, p=0.44), or overall (6% vs. 8%, p=0.40) transmission. Mother-to-child HIV transmission according to drug regimen: ZDV use during antenatal period None: AOR=1.0 <30 days: AOR=0.7 (95% CI 0.3-2.1) >30 days: AOR=0.4 (95% CI 0.1-1.3)
de Vincenzi, 2011[60] See also Kesho Bora Study Group, 2010[67]	A: Cesarean before labor, rupture of membranes, or both n=19 (5%), Cesarean after labor, rupture of membranes, or both n=25 (6%) B: Cesarean before labor, rupture of membranes, or both n=13 (3%), Cesarean after labor, rupture of membranes, or both n=38 (9%)	Comparing infection rates and events among infants: Birth A: 7/394, 1.8%, 95% CI 0.9-3.7% B: 10/402, 25%, 95% CI 1.3-4.6% RR reduction 28% p=0.52 6 weeks A: 13/375, 3.3%, 95% CI 1.9-5.6% B: 20/374, 5.0%, 95% CI 3.3-7.7% RR reduction 34% p=0.24 6 months A: 19/349, 4/9%, 95% CI 3.1-7.6% B: 33/339, 8.4%, 95% CI 6.0-11.6% RR reduction 42% 12 months A: 21/333, 5.4%, 95% CI 3.6-8.1% B: 37/305, 9.5%. 95% CI 7.0-12.9% RR reduction 43% p=0.029 *p value stratified by center, intention to breastfeed

Appendix B4. Key Question 3a: Evidence Table of African-Based Randomized, Controlled Trials of Mother-to-Child HIV Transmission While Using Antiretroviral Therapy

Author, Year	Cesarean rate	Transmission rates
Gray, 2006[62]	37% (137/372) 5 stillbirths	Mother to child transmission rates by treatment group: Cumulative positive HIV-1 DNA (MTCT rate*) Birth A: 3/91 (3.3%) B: 2/94 (2.1%) C: 2/88 (2.3%) D: 4/89 (4.5%) All groups: 11/362 (3.0%) Week 6 A: 9/91 (9.9%) B: 6/94 (6.4%) C: 3/88 (3.4%) D: 4/89 (4.5%) All groups: 22/362 (6.1%) Week 12 A: 10/91 (11.0%) B: 9/94 (9.6%) C: 4/88 (4.6%) D: 4/89 (4.5%) All groups: 27/362 (7.5%) Week 24 A: 11/91 (12.1%, 95% CI 6.2-20.6) B: 10/94 (10.6%, 95% CI 5.2-18.7) C: 4/88 (4.6%, 95% CI 1.3-11.2) D: 5/89 (5.6%, 95% CI 1.9-12.6) All groups: 30/362 (8.3%, 95% CI 5.7-11.6) * number with positive HIV-1 DNA divided by the number of evaluable mother-infant pairs
Shapiro, 2010[63]	Not reported	Overall 8/709 (1.1%, 95% CI 0.5-2.2) infants were infected by 6 months of age: 6 infants infected in utero; A: n=4, B: n=1, C: n=1 (includes one infant that died without confirmed AIDS defining cause after positive PCR result at birth) 2 infants in group A infected through late breastfeeding transmission Infections between randomized groups (study not powered for between randomized group comparisons of transmission rates): A: 6/283 (2.1%) liveborn infants infected B: 1/270 (0.4%) liveborn infants infected percentage point difference, 1.7, 95% CI -2.0 to 7.1 In utero transmission = confirmed positive HIV PCR assay of DNA from blood sample obtained from infants less than 4 days old Late breastfeeding transmission = negative test at one month and first confirmed positive test thereafter Intrapartum/early breastfeeding transmission = negative result at birth and first confirmed positive test at one month of age
Shapiro, 2006[64]	Emergency or elective A: Median 8.8% B: Median 9.9%	A: n=345 live births, n=345 delivieries with HIV PCR test results, n=13 (3.8%) HIV+ at birth, n=15 [4.3%±2.3 (2SD)] HIV+ at one month of age B: n=349 live births, n=346 delivieries with HIV PCR test results, n=8 (2.3%) HIV+ at birth, n=13 [3.7%±2.2 (2SD)] HIV+ at one month of age 95% CI for difference between infant groups at one month with HIV infection, -2.4 to 3.8%, met equivalence Rate of HIV infection at birth is number of first positive HIV PCR results by 15 days of age divided by number of live births Rate of HIV infection by one month is number of first positive HIV PCR results by 45 days divided by number of live births Excluding liveborn infants whose mothers received ART before delivery, 14/305 (4.6%) in maternal NVP arms were

Appendix B4. Key Question 3a: Evidence Table of African-Based Randomized, Controlled Trials of Mother-to-Child HIV Transmission While Using Antiretroviral Therapy

Author, Year	Cesarean rate	Transmission rates
		HIV infected by one month vs. 12/319 (3.8%) in maternal placebo arm (p=0.69, 95% CI for difference -2.4 to 4.2%, met equivalence) No transmission difference in infants who became infected between birth and one month between groups (2 infections in maternal NVP arm vs. 5 in placebo arm, p=0.45)
Thistle, 2007[65]	A: 8.2% B: 6.1%	Outcomes at 6 weeks postpartum in infants whose mothers were randomized: A: n=312 infants with data at 6 weeks postpartum; n=45 (14.4%) of infants positive for HIV, n=23 (7.4%) of infants were dead, n=68 (21.8%) of infants met primary outcome (death or HIV infection) B: n=297 infants with data at 6 weeks postpartum; n=49 (16.5%) of infants positive for HIV, n=21 (7.1%) of infants were dead, n=70 (23.6%) of infants met primary outcome p=0.06, percentage difference 1.8%, 95% CI -4.9 to 8.4% for primary outcome, AOR = 1.28 (95% CI 0.75-2.19) *AOR = age, gestational age, marital status, premature rupture of membranes, mode of delivery, maternal opportunistic infection, sexually transmitted infection

3TC = lamivudine; ABC = abacavir; ABT-378 = lopinavir; AIDS = acquired immunodeficiency syndrome; AOR = adjusted odds ratio; ART = antiretroviral therapy; BD = twice daily; CD4 = cluster of differentiation 4; CDC = Centers for Disease Control and Prevention; CI = confidence interval; CIDA = Canadian International Development Agency; D4T = stavudine; DDL = didanosine; DNA = deoxyribonucleic acid; ELISA = enzyme-linked immunosorbent assay; FTC = emtricitabine; IQR = interquartile range; MTCT = mother-to-child transmission; NVP = nevirapine; PCR = polymerase chain reaction; PROM = premature rupture of membranes; RNA = ribonucleic acid; RR = relative risk; RTV = ritonavir; SD = standard deviation; sdNVP = single-dose nevirapine; TDF = tenofovir; UNDP = United Nations Development Programme; UNFPA = United Nations Population Fund; WHO = World Health Organization; ZDV = zidovudine.

Appendix B5. Key Question 3a: Quality Ratings of African-Based Randomized, Controlled Trials of Mother-to-Child HIV Transmission While Using Antiretroviral Therapy

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup differential/high?	Intention-to-treat analysis?	Quality rating	Funding
Chi 2008[61]	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	No	Fair	Elizabeth Glaser Pediatric AIDS Foundation
de Vincenzi, 2011[60]	Yes	Yes	Yes	Yes	Unclear	No	No	Yes	No	Yes	Good	Agence Nationale de Recherches sur le SIDA et les Hepatites Virales, Department of Int'l Development, European and Developing Countries Clinical Trials Partnership, Thrasher Research Fund, Belgian Directorate General for Int'l Cooperation, CDC, Eunice Kennedy Shriver National Insititue of Child Health and Human Development, UNDP/ NFPA/World Bank/WHO Special Programme of Research, Development and Research Training in Human Reproduction
Gray, 2006[62]	Unclear	No; open trial	Yes	Yes	No	No	No	Yes	No	No	Fair	Not reported
Shapiro, 2010[63]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Unclear	Fair	National Institute of Allergy and Infectious Diseases, Fogarty International Center, GlaxoSmithKline, Abbott Pharmaceuticals
Shapiro, 2006[64]	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair	National Institutes of Health , Boehringer Ingelheim, GlaxoSmithKline, Fogarty International Center
Thistle, 2007[65]	Yes	Unclear	Yes	Yes	Unclear	Unclear; physician blinded to study allocation determined infant admiss-ion to at-risk nursery but no comment on other providers	Yes	Yes	No/Yes	Unclear	Fair	Ministry of Health and Child Welfare, Zimbabwe; CIDA; Ve'ahavta: Canadian Jewish Humanitarian and Relief Committee; Salvation Army of Zimbabwe; MAC AIDS; GlaxoSmithKlein Canada, Rotary club of Whitby, Canada; Department of Family and Community Medicine, St.Michaels' Hospital, Toronto, Canada

Appendix B6. Key Question 3c: Studies of Adverse Outcomes Associated With Antiretroviral Therapy

Author, Year	Type of harm	Type of study/location/setting/high or low prevalence population (based on 0.1% prevalence rate)	Study dates/duration of followup	Comparison groups
Aldrovandi, 2009[90]	PBMC mtDNA	Retrospective cohort US Samples from WITS and p1009 observational cross-sectional study	Study dates unclear Followup: up to 5 years post-delivery	Uninfected infants born to HIV-infected women who received: A. No ARV therapy n=71 B. ZDV monotherapy n=71 C. ZDV/Lamivudine cARV therapy n=71 D. Healthy children aged birth to 18 years born to HIV-uninfected women n=411
Alimenti, 2006[96]	Neuro-development	Prospective, cross-sectional British Columbia, Canada Hospital based	June 2003 to December 2004	A: ART exposed group of HIV-uninfected children born to HIV positive women, n=39 B: Unexposed children, n=24 BSID-I (Bayley Scales of Infant Development) used to assess cognitive, language, psychomotor functioning to identify developmental delay); results provide MDI and PDI scores (Mental Development and Psychomotor Development Index)
Benhammou, 2008[103]	Other harms	Cohort France Multicenter NR French Perinatal Cohort	September 24, 1984 to May 1, 2007 Followup 24 months	A: Peri or postpartum exposure only (n=274) B: Zidovudine monotherapy (n=2147) C: zidovudine + lamivudine + other NRTIs except didanosine (n=4752) D: didanosine = lamivudine + other NRTIs (n=365) Other NRTI combinations (n=715) Prospective multicenter study following HIV infected pregnant women and their children
Briand, 2009[73]	Low birth weight, INGR	Prospective cohort France	Infants born from January 1990 through 2006	A. Monotherapy 1999-2004 n=4270, ART widespread B. ART 2005-2006 n=1239 C. 1990-1993, n=846, no ART during pregnancy D. 1994-1996, n=906, ZDV monotherapy as standard E. 1997-1998, n=931, dual nucleoside therapy trial and 1st availability of ART
Brogly, 2007[91]	Mitochodrial toxicity	Cohort US, Puerto Rico NR PACTG 219, 219C Study Group	May 1993 to August 2000	A: Cases (n=20) B: Noncases (n=1017)
Bunders, 2005[100]	Hematologic	Observational Single center Europe NR European Collaborative Study	February 1997 to October 2002	75 children matched for gestational age, gender, ethnicity, prematurity, race
Carceller, 2009[74]	Premature birth	Retrospective cohort Canada	1997 through 2005 Infant followup: 2 year minimum 5 year median, range 2-10 years	A. ART with protease inhibitors n=176 B. ART without protease inhibitors n=30 C. Control: infants born to non-HIV infected mothers (not exposed to ART) n=206
Cote, 2008[92]	Mitochodrial toxicity	Prospective cohort Canada	July 2003 to June 2006 Infants followed birth to 8 months	A: ART exposed infants; majority exposed to ADV + 3TC, with a protease inhibitor (n=41), a non-NRT (n=20) or both (n=4) All infants born to HIV+ mothers recived ZDV prophylaxis B: Infants born to HIV uninfected mothers
Cotter, 2006[75]	Premature birth	Prospective cohort US	Women who gave birth 1990 through 2002	Antiretroviral therapy A. None n=338 (25%) B. Monotherapy n=492 (37%) C. Combination therapy with PIs n=373 (28%) D. Combination therapy without PIs n=134 (10%)

Appendix B6. Key Question 3c: Studies of Adverse Outcomes Associated With Antiretroviral Therapy

Author, Year	Type of harm	Type of study/location/setting/high or low prevalence population (based on 0.1% prevalence rate)	Study dates/duration of followup	Comparison groups
El Beitune, 2005[76]	Premature birth	Prospective cohort Brazil	September 2001 to March 2003	A. HIV infected pregnant women taking zidovudine (CD4>500 and viral load <1,000 copies/mL) n=20 B. HIV infected pregnant women taking triple ARV (zidovudine + lamivudine + nelfinavir), (CD4 <500) n=25 C. Non-HIV infected pregnant women with normal clinical and lab data n=12
Grosch-Woerner, 2008[77]	Birth outcomes (prematurity, LBW)	Observational Germany, Austria	1995-2001 18 month followup	A: Monotherapy B: Dual therapy C: ART without PID: ART with PI
Lipschultz, 2011[99]	Infant harms: cardiac	Cohort US NR	June 2003 to January 2006	A: CHAART-1 infants exposed to ART; n = 166 B: P^2 C^2 HIV infants not exposed to ART n = 216 CHAART = cardiovascular status of HAART therapy in HIV exposed infants and children P^2C^2 = pediatric pulmonary and cardiac complications of vertically transmitted HIV
Marti, 2007[109]	Maternal toxicity	Prospective cohort Spain	Women who delivered between January 1, 1997 and December 31, 2003 Infants were followed for at least 2 years after delivery	A: Women who did not receive ART during pregnancy n=15 (9%) B: Monotherapy with zidovudine n=23 (14%) C: Dual NRTIs were used with or without a 3rd NRTI or NNRTI n=35 (21%) D: Triple ART used along with a protease inhibitor n=94 (56%)
Morris, 2005[78]	Premature birth	Retrospective cohort US, Puerto Rico	Women treated between December 1997 and December 2001	Treatment with single PIs: 96.5% Ritonavir-boosted regimen: 3.4% Nelfinavir as part of the regimen: 92% Regimen included dual nucleoside combination of zidovudine and lamivudine: 93%
Mussi-Pinhata, 2007[101]	Hepatotoxicity	Observational Latin America, Carribean Hospital NR	September 2002 to March 1, 2005 6 month followup	A: 1 or 2 NRTIs B: 2 NRTIs + NNRTI (ART/NNRTI) C: 2 NRTIs + 1 PI (ART/PI) D: other
Pacheco, 2006[102]	Hematologic	Observational Multicenter US, Puerto Rico	1989-2004	2171 infants: A: No ARV drugs, n=351 B: Any ARV drugs, n=1820 C: Monotherapy, n=803 (91% zidovudine) D: Combination therapy, n=1017
Patel, 2005[93]	Congenital/birth defects	Cohort European Collaborative Study Includes low and high prevalance areas	Enrolled 1986 to December 2003	A: NRTI only B: NRTI + protease inhibitor C: NRTI + NNRTID: NRTI + NNRTI + PI
Paul, 2005[79]	Low birth weight, INGR	Prospective and retrospective cohort US, Puerto Rico	Children born to women enrolled in WITS January 1990 to October 1999 Children followed through age 2	A. HIV-infected children n=163 A-1. No maternal ARV n=78 (49%) A-2. Maternal monotherapy n=72 (46%) A-3. Maternal ART/combo n=8 (5%) B. HIV-uninfected children n=955 B-1. No maternal ARV n=139 (15%) B-2. Maternal monotherapy n=487 (51%) B-3. Maternal ART/combo n=328 (34%)
Powis, 2011[72]	Premature birth	Randomized, controlled trial Botswana NR	July 2006 and May 2008 Women evaluated before ART and monthly through postpartum	A: PI group (lopinavir/ritonavir/zidovudine/lamudivine) - KAL/CBV; n=275 B: NRTI group (abacavir/zidovudine/lamidvudine) - TZV; n=285

Appendix B6. Key Question 3c: Studies of Adverse Outcomes Associated With Antiretroviral Therapy

Author, Year	Type of harm	Type of study/location/setting/high or low prevalence population (based on 0.1% prevalence rate)	Study dates/duration of followup	Comparison groups
Rudin, 2011[80]	Premature birth	Cohort Switzerland Low MoCHiV = Swiss Mother & Child HIV Study SHCS = Swiss HIV Cohort Study	1990-1998	A: no ART, n=624 B: mono or dual ART, n=147 C: cART (combined) (84% PI based), n=409
Schulte, 2007[81]	Premature birth	Retrospective cohort US	Infants born in 1989 through 2004	Antiretroviral therapy A. None n=2565 (29%) B. 1 drug n=2621 (30%) C. 2 drugs n=1044 (12%) D. 3 drugs: ART, non-PI n=1781 (20%) E. 3 drugs: ART, PI n=782 (9%)
Tariq, 2011[59] See also Townsend, 2008[56]; European Collaborative Study, 2005[93]	Congenital	Cohort/ Population surveillance data from ECS and NSHPC/UK, Ireland, Belgium, Denmark, Germany, Italy, the Netherlands, Poland, Spain, Sweden Prevalence NR	2000-2009 Followup testing schedule not reported; analyses of data over study period	Only antepartum treatment considered: A: ZDV-containing ART n=6374 B: ZDV-sparing ART n=1199 Note: About 30% of women were on ART at conception
Townsend, 2007[82]	Birth outcomes (prematurity, LBW)	Cohort study UK, Ireland Low	1990-2005 N/A	A: ART therapy n = 3384 B: Mono/dual therapy n = 1061 C: Untreated n = 494 (this group not included in analyses)
Townsend, 2009[94]	Congenital/birth defects	Cohort UK, Ireland National Study of HIV in Pregancy and Childhood Low	January 1990 to December 2007 Median age of infants at last report was 6 months (interquartile range 3 to 15 months)	Timing of antiretroviral therapy exposure A: None B: Late (2nd, 3rd trimester) C: Early (1st trimester)
Tuomala, 2005[108]	Maternal toxicity	Prospective cohort US	Pregnancies that ended between January 1990 and February 2002 Followup duration: to delivery	A: Cohort 1, ART use before March 1994; n = 794 B: Cohort 2, ART use March 1994 through July 1996; n = 556 C: Cohort 3, ART use August 1996 through February 2002; n = 1190 Timing of ART use: Early: use recorded at enrollment and/or at 18- and/or 25-week visit Late: use recorded at 32-week visit and/or delivery visit Classes of ART: ZDV monotherapy and combination therapy including ZDV; NRTI other than ZDV; any PI; any NNRTI
Watts, 2011[95]	Congenital defects	Cohort of RCT participants US, Brazil, Bahamas, Europe Pediatric AIDS Clinical Trial Group 316 (PACTG 316) Prevalence NR	May 1997 to June 2000 Maternal followup until 6 weeks postpartum; infant followup until 6 months of age	A: First trimester ARV exposure (first 12 weeks of pregnancy) B: Second/third trimester ARV exposure (after 12 weeks gestation) PACTG 316 randomization groups Standard ART plus one of the following: A: maternal single dose NVP in active labor and single dose NVP to infant between 48 to 72 hours of birth B: maternal placebo in active labor and placebo to infant between 48 to 72 hours of birth
Williams, 2010[97]	Neuro-development	Prospective, multicenter cohort US	1993-2006	A: ARV exposed in utero B: non-ARV exposed in utero MDI = mental developmental index PDI = psychomotor developmental index

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Author, Year	Baseline population characteristics for mother/baby	Eligibility criteria	Exclusion criteria
Aldrovandi, 2009[90]	Mean age at delivery A: 28.02 B: 26.08 C. 29.18 Race White A. 6 (9%) B. 7 (10%) C. 8 (11%) Black A. 39 (55%) B. 30 (42%) C. 30 (42%) Hispanic A. 23 (32%) B. 30 (42%) C. 29 (41%) Other A. 3 (4%) B. 4 (6%) C. 4 (6%) Mean CD4 count at delivery A. 625.92 B. 479.47 C. 530.65 Mean HIV RNA at delivery A. 3.70 B. 3.69 C. 3.11 Infant birth weight <2.5 kg A. 8.95% B. 14.49% C. 7.14% Prematurity <37 week gestation A. 14.8% B. 8.45% C. 8.45%	HIV-positive women and their uninfected infants were selected from those who participated in WITS. Infection status was determined by WITS protocol and reflected differential use of ARVs during pregnancy. From among subject pairs who met the selection criteria and had sufficient stored material available, efforts were made to balance, within each time period, the degree of ARV exposure. Samples from healthy children born to HIV-uninfected women were obtained from an observational, cross-sectional study (P1009) of lymphocyte subsets at sites that included all of the WITS centers.	Not reported
Alimenti, 2006[96]	Maternal age at delivery: A:28.5 B:30.1 Maternal ethnicity: A, B White: 22 (56%), 21 (91); p=0.030 Aboriginal: 10 (26), 1 (4) Black: 4 (10), 0 other: 3 (8), 1 (4)	Cases: born to HIV positive mothers, exposed to at least 3 antiretroviral drugs in utero for a miminum of 1 week and to zidovudine during delivery and the neonatal period, HIV-uninfected at 18 and 36 weeks, at least 2 nonreactive HIV pcr tests between 1 and 6 months of age and seroreverted HIV-1 serologic testing. Controls: from a cohort of children followed in a hepatitis C vertical transmission study; born to HIV negative, HCV-infected mothers with a high proportion (49.5%) of IVDU history. Attempted to match the ART exposed group in terms of socioeconomic background and substance abuse during pregnancy	Sibling participation; non-English speaking, developmental delay due to other factor

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Author, Year	Baseline population characteristics for mother/baby	Eligibility criteria	Exclusion criteria
Benhammou, 2008[103]	Risk factors for tumor in the subgroup of NRTI exposed children (n=8853) Mother's geographical origin Metropolitan France = 2556 Sub-Saharan Africa = 5051 Other =1158 Mmother's CD4 count, absolute number >0.350 x 10^9 cells/L n=5641 0.200-0.350 x 10^9 cells/L n=1850 <0.200 x 10^9 cells/L n=880	Uninfected children born to HIV infected mothers followed from birth until 2 years	541 HIV infected children, 521 questionnaires not completed or validated, 53 missing data for treatment exposure, 1852 not exposed to treatment, 274 exposed during only the peri and postpartum phases
Briand, 2009[73]	Maternal age <25 A: 736 (17%) B: 141 (11%) 25-34 A: 2640 (62%) B: 766 (62%) >35 A: 881 (21%) B: 331 (27%) Sub-Saharan African maternal geographic origin A. 2474 (60%) B: 914 (74%) Mean maternal CD4 at delivery A. 0.499 x 10^9 cells/L (SD 0.312 x 10^9 cells/L) B. 0.508 x 10^9 cells/L (SD 0.274 x 10^9 cells/L)	All live-born neonates born to HIV-infected mothers from January 1990 through 2006 enrolled in the French Perinatal Cohort (EPF CO-01) if they did not have the risk factors listed in exclusion criteria	Mothers who used illicit drugs during pregnancy, had no prenatal care before the 3rd trimester, twins and stillbirths. HIV-infected neonates diagnosed on site on 2 separate samples or if anti-HIV-1 antibodies persisted after 18 months of age
Brogly, 2007[91]	Characteristics of the 1037 children in the primary analysis: Cases, Noncases; n (%) Sex Male: 15 (75), 476 (47) Female: 5 (25), 541 (53) Race Black: 12 (63), 535 (54) Hispanic: 4 (21), 329 (33) White: 3 (15), 132 (13) Other/unknown: 1, 21 Premature birth Yes: 2 (24), 139 (18) No: 13 (77), 654 (83) Unknown: 3, 224	1220 HIV-uninfected children who enrolled in PACTG 219 or 219c prior to 2 years of age and had completed 1 year of followup as of 31 August 2003	512 not included: did not complete 1 year of followup Children whose presentation could be explained by an etiology other than mitochondrial dysfunction (MD) or who did not meet the case definition of possible MD; children whose only sign of MD was cognitive developmental delay
Bunders, 2005[100]	109 HIV-1/ART exposed infants: Gender (n, male/female) 64/45 Ethnicity (n, black, non) 78/31 Gestation, median week 38.4 (37-41) Delivery (n, vaginal/cesarean) 54/47	All neonates born to HIV-1 infected mothers enrolled (109)	17 children excluded because of HIV-infection, perinatal mortality, lack of ART exposure in utero, or insufficient data on in utero ART exposure

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Author, Year	Baseline population characteristics for mother/baby	Eligibility criteria	Exclusion criteria
Carceller, 2009[74]	Data not available for all mothers Age: <20 A: none reported B: 2/28 (7%) 21-30 A: 83/168 (49%) B: 12/28 (43%) 31-40 A: 76/168 (45%) B: 13/28 (46%) >40 A: 4/168 (2%) B: 1/28 (4%) Race: African A: 78/168 (46%) B: 11 (37%) Caucasian A: 49/168 (29%) B: 11 (37%) Haitian A:40/168 (24%) B: 8 (27%)	HIV-infected pregnant women treated with ART between 1997 and 2005 who were followed during pregnancy and delivered at CHU Sainte-Justine, Montreal, as well as their infants	Mothers infected with HIV and not treated, those who received antiretroviral monotherapy, or received only 2 antiretroviral agents during pregnancy or at the time of delivery.
Cote, 2008[92]	All infants: A: ART exposed, n=73 B: control, n=81 Gestation time, weeks: A: 38 (38-40) B: 39 (37-40) Birth Weight (kg) A: 3.1 (2.7-3.4) B: 3.2 (2.7-3.6) Maternal Ethnicity: A(%), B(%) Aboriginal: 8 (11), 0 (0) White: 18 (25), 44 (54) Black-African Canadian: 34 (47), 0 (0) Hispanic: 4 (5.5), 5 (6) Asian: 6 (8), 6 (7) South, East, West Asian: 6 (8), 6 (7) Other: 2 (3), 13 (16)	ART-exposed infants: 1) born to an HIV infected woman who received ART during pregnancy and intravenous ZDV during labor; 2) received oral ZDV prophylaxis during the first 6 weeks of life starting within ~12hrs of birth. Control infants: born to HIV uninfected mothers and enrolled from 3 sources: 1) 1 to 6 month old infants having bloodwork done prior to elective minor pediatric surgery, 2) neonates (0-3 days old) born at Children's and Women's Health Center of British Columbia, 3) infants 1 day to 8months old) having bloodwork done for various minor medical reasons	Known mitochondrial disorder or serious and/or febrile illness

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Author, Year	Baseline population characteristics for mother/baby	Eligibility criteria	Exclusion criteria
Cotter, 2006[75]	Age at delivery <34 A: 88% B: 86% C: 75% D: 84% ≥34 A: 12% B:18% C: 25% D: 16% Race Black A: 59% B: 44% C: 37% D: 47% White A: 6% B: 4% C: 6% D: 4% Hispanic A: 10% B:15% C: 26% D: 11% Haitian: A: 20% B: 30% C: 26% D:31% Lowest CD4 count >0.500 x 10^9 cells/L: A: 52% B: 33% C: 19% D:19%	Women determined to be HIV positive before or during pregnancy who sought care at the prenatal clinic and gave birth at the University of Miami/Jackson Memorial Medical Center from January 1990 to December 2002. Singleton pregnancy, attendance at >1 prenatal visit at obstetric clinic dedicated to the care of HIV positive patients	Not reported
El Beitune, 2005[76]	Median maternal age A: 24, interquartile variation of 7 years B: 27, interquartile variation of 6 years C: 22.5, interquartile variation of 6 years Race" Race distribution was uniform in the 3 groups, P=0.14, chi-square test = NR	Not clearly specified. Implied: pregnant women aged 16 to 43 with singleton gestations. 45 women infected with HIV; 12 were not. Only HIV-infected patients who had not been treated previously with antiretroviral drugs were selected for the study.	Renal and hepatic insufficiency, personal or 1st degree relative with history of diabetes, initial BMI >30 kg/m, predictors of recurrent gestational diabetes (spontaneous abortion, major congenital malformation, stillbirth or macrosomia in prior pregnancies), noncompliance with use of antiretroviral drugs, use of medication with known diabetogenic effect.

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Author, Year	Baseline population characteristics for mother/baby	Eligibility criteria	Exclusion criteria
Grosch-Woerner, 2008[77]	Maternal and delivery characteristics in mother-infant pairs exposed to antiretrovirals; A (%), B (%), C+D (%) Race White: 41 (54), 13 (41), 35 (57) Black: 28 (37), 11 (34), 27 (36) Other: 7 (9), 8 (25), 12 (16) Unknown: 0, 0, 1 Maternal age at delivery: <25: 20 (26), 13 (41), 26 (34) 26-34: 45 (59), 17 (53), 37 (49) >35: 11 (14), 2 (6), 12 (16) Median age: 28 (18-41), 27 (19-40), 28 (17-41) CD4 count at delivery >0.500 x 10^9 cells/L: 42 (56), 12 (39), 21 (29) 0.200-0.500 x 10^9 cells/L: 33 (44), 18 (58), 43 (59) <0.200 x 10^9 cells/L: 0, 1 (3), 9 (12)	All mother-child pairs with information on ART, exposure during pregnancy identified before or during pregnancy in one center in Berlin or 12 centers in Germany and Austria.	7 women: no information on ART exposure during pregnancy; 2 with late presentation; 1 refused to participate
Lipschultz, 2011[99]	Age at delivery: <30 A: 84 (62%) B: 153 (71%) >30 A: 52 (38%) B: 63 (39%) Race: Black A: 83 (61%) B:120 (56%) White A: 10 (7%) B: 29 (13%) Hispanic A: 43 (32%) B: 67 (31%) Birthweight: <2500 g A: 12 (9%) B: 32 (15%) >2500 g A: 124 (91%) B: 182 (84%) Unknown A: 0 B: 2 (1%) Maternal CD4 count during pregnancy: A: 0.5322 x 10^9 cells/L (0.491-0.572 x 10^9 cells/L) B: 0.5862 x 10^9 cells/L (0.517-0.655 x 10^9 cells/L)	Patients enrolled in Women and Infants Transmision Study (WITS), age 2 years or less, followed until loss to followup, child withdrew, December 2006, or whichever came first.	Maternal: diabetes, phenylketonuria, chromsomal or Mendelian defect, heart defect requiring medication or surgery, pregnancy exposures to chemotherapy, radiation, drugs associated with heart disease in offspring
Marti, 2007[109]	Maternal age: median 30.9, range 18-42 Nadir lymphocytes CD4 cell count <0.200 x 10^9 cells/L: n=40 (27%) CD4 cell count 1st trimester: mean 0.445 x 10^9 cells/L,SD: 0.214 x 10^9 cells/L	All HIV-infected women who delivered between January 1, 1997 and December 31, 2003 at a tertiary center hospital in Madrid.	Cases of prematurely interrupted pregnancy or early prenatal death of the fetus.

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Author, Year	Baseline population characteristics for mother/baby	Eligibility criteria	Exclusion criteria
Morris, 2005[78]	Median age: 27 years (1-43) Race: Latina: 47% African American: 31% White: 15% Other: 7% Asymptomatic HIV: 73% Symptomatic HIV but not AIDS: 7% AIDS based on CD4 cell counts <0.200 x 10^9 cells/L or history of AIDS indicator condition: 13%	Medical records of all women treated with PIs during pregnancy at 5 sites in the US and Puerto Rico between December 1997 and December 2001	Not reported
Mussi-Pinhata, 2007[101]	Maternal characteristics (n=503, 100%) Race: Hispanic/Latino: 197, 39.2% White: 163, 32.4% Black/ African: 102, 20.3% Other: 41, 8.2% CD4+ count at enrollment <0.200 x 10^9 cells/L: 80, 16% 0.200-0.499 x 10^9 cells/L: 297, 59% >0.500 x 10^9 cells/L: 53, 10.5%	Term, HIV-1 uninfected infants who were the products of the first pregnancy on study of HIV-1 infected women enrolled berore March 1, 2005 and were discharged from the hostpial within the first 6 days of life; followed through 6 months of life; mothers received ARVs for >28 days during the third trimester of pregnancy	Not reported
Pacheco, 2006[102]	Mothers: Age at delivery, mean A 27.8 (41.5-45.1) B: 27.6 (15.1-44.3) CD4 count at delivery A: 0.6709 x 10^9 cells/L (0.050-0.260 x 10^9 cells/L) B: 0.5114 x 10^9 cells/L (0-2.709 x 10^9 cells/L) <0.200 x 10^9 cells/L A: 13 (4.6%) B: 210 (14.2%) Race/ethnicity: A/B White/nonHispanic: 44 (12.7%)/190 (10.7%) Black/nonHispanic: 161 (46.5%)/885 (49.6%) Hispanic: 11 (3.2%)/80 (4.5%) Other: 5/37 Mode of delivery (%): A/B Scheduled Cesarean: 14 (4.2)/223 (15.6) Nonscheduled Cesarean: 41 (12.2)/193 (13.6) Vaginal: 280 (83.6)/1000 (70/6) NA: 16/404	2171 HIV infected mothers with singleton pregnancies and their HIV exposed, uninfected infants	Infants with no laboratory values obtained
Patel, 2005[93]	Age at delivery, mean = 28 (10-45) Race White: 72% (2700/3740) Black: 21% (781/3740; mainly from sub-saharan Africa) Other: 7% (493/3740) CD4 count at delivery, mean = 0.420 x 10^9 cells/L (0-2.350 x 10^9 cells/L) Median gestational age at delivery = 38 weeks (22-43)	HIV infected women identified during pregnancy	Reported elsewhere (see European Collaborative Study)

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Author, Year	Baseline population characteristics for mother/baby	Eligibility criteria	Exclusion criteria
Paul, 2005[79]	Child race/ethnicity White A: 23 (15%) B: 104 (11%) Black A: 66 (42%) B: 489 (52%) Hispanic A: 55 (35%) B: 309 (33%) Other A: 13 (8%) B: 39 (4%) Child ARV for perinatal prophylaxis None A: 104 (64%) B: 167 (18%) Monotherapy A: 52 (32%) B: 754 (79%) ART/combo A: 7 (4%) B: 34 (4%)	Children enrolled in WITS as of October 1999, born from 1st on-study pregnancy for a woman enrolled in WITS, HIV status was known, and complete clinical classification information was available	Not reported
Powis, 2011[72]	Median age: A: 25 B:26 CD4 count at enrollment A: 403 (297-514) B:393 (305-514) Gestational age at enrollment (weeks) A: 27.1 (26.4-29.0) B: 27.1 (26.4-29.9)	HIV infected women identified during pregnancy enrolled in the randomized aspect of the Mma Bana Study. Eligibility included pregnancy of 26-34 weeks gestation, HIV-1 infection confirmed by two blood samples poitive on ELISA, >8 years old, Hgb 8.0g/dL, an absolute neutrophil count of 1000 c/mm^3	Exclusively formula fed infants
Rudin, 2011[80]	Gestational age A: 39 (38-40) B: 39 (37-39) C: 39 (37-38) Birthweight (kg) A: 3.1 B: 2.9 C: 2.9 Premature birth A: 14.9% B: 20.4% C: 24.2%	HIV-1 positive women with a history of at least one pregnancy that was completed to live birth	Multiple (twin) pregnancies; elective Cesarean <37 weeks duration; not started cART before or during pregnancy; not under study followup; no viral load during pregnancy
Schulte, 2007[81]	Infants Race Black 62% Mean birth weight 2890 g Mean gestational age 37.3 weeks	White nonHispanic, black nonHispanic and Hispanic infants born in 1989 through 2004 for whom available data included birth weight and gestational age, and whose HIV testing was first conducted during the first 30 days of life.	Not reported

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Author, Year	Baseline population characteristics for mother/baby	Eligibility criteria	Exclusion criteria
Tariq, 2011[59] See also Townsend, 2008[56]; European Collaborative Study, 2005[93]	Maternal age at delivery, years (n=7547); A vs B: <25; n=1072 (16.9%) vs n=110 (9.2%) 25-29; n=1979 (31.2%) vs n=257 (21.6%) 30-34; n=2006 (31.6%) vs n=738 (61.7%) >35; n=1293 (20.4%) vs n=92 (7.7%) p<0.001 Ethnicity (n=7550); A vs B: Black n=4974 (78.3%) vs n=882 (73.8%) White n=1086 (17.1%) vs n=269 (22.5%) Asian/other n=294 (4.6%) vs n=45 (3.8%) p<0.001 Baseline CD4 count, cells/mm^3 (n=6993); A vs B: >500; n=1520 (25.9%) vs n=316 (28.4%) 200-499; n=3427 (58.3%) vs n=636 (57.2%) <200; n=934 (15.9%) vs n=160 (14.4%)p=0.14 HIV stage: not reported	All reported live singleton births to women who received ART for at least 14 days before delivery between 2000-2009	Mother-child pairs lacking information on all outcomes of interest, ECS excluded data from centers in the Ukraine (limited antenatal ART) and the UK (to avoid duplication of cases reported to the NSHPC)
Townsend, 2007[82]	Age at delivery; #, % (A, B, C) 14-24 yrs: 572, 17%; 239, 23%; 124, 25% 25-34: 2161, 36.9; 681, 64.2; 334, 67.7 35-46: 651, 19.2; 140, 13.2; 35, 7.1 Ethnic origin White: 439, 13; 211, 19.9; 164, 33.7 Black African: 2647, 78.2; 763, 72; 303, 62.3 Other: 297, 8.8; 86, 8.1; 19, 3.9 CD4 count >0.500 x 10^9 cells/L: 895, 30.1; 387, 47.9; 63, 30.9 0.200-0.499 x 10^9 cells/L: 1628. 54.7; 372, 46; 110, 53.9; <0.200 x 10^9 cells/L: 454, 15.3; 49, 6.1; 31, 15.2 HIV stage/AIDS defining illness Major differences in baseline characteristics	Pregnancies resulting in singleton livebirth, stillbirth; between 1990-2005;diagnosis of HIV before delivery; reported to National Study of HIV in Pregnancy and Childbirth by March 2006	Inadequate information on ART
Townsend, 2009[94]	Maternal ethnicity: n, % (n=8171) White: 1285, 15.7 Black African: 6244, 76.4 Black other: 326, 4.0 Other: 316, 3.9 Age at delivery (n=8184) <25: 1471, 18% 25-34: 5154, 63 >35: 1559, 19 Clinical status (n=7235) No HIV related symptoms: 6451, 89.2 HIV related symptoms/AIDS: 784, 10.8	All infants born between 1990-2007 in the UK and Ireland to women diagnosed with HIV before delivery, and reported by June 2008	Inadequate information on ART
Tuomala, 2005[108]	Early ART Age range: 27.34 to 28.82 Ethnicity: White 12% to 15% Black: 40% to 59% Latina: 29% to 46% CD4 mean: 24% to 29% Late ART Age range: 27.19 to 28.04	Enrollment in WITS study of HIV-infected pregnant women and their infants. For maternal toxicities: All singleton pregnancies that ended between January 1990 and February 2002. For obstetric outcomes: all singleton pregnancies resulting in delivery at more than 20 weeks of gestation.	Not reported in this publication

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Author, Year	Baseline population characteristics for mother/baby	Eligibility criteria	Exclusion criteria
	Ethnicity: White 10% to 15% Black 47% to 58% Latina 32% to 38% CD4 mean: 26% to 29%		
Watts, 2011[95]	Age, mean (years): 28.2 Race/ethnicity: Caucasian, nonHispanic n=317 (22%) Black, nonHispanic n=827 (58%) Hispanic n=253 (18%) Other n=17 (1%) CD4 count: >400 cells/µL n=790 (56%) 200-399 cells/µL n=450 (32%) <200 cells/µL n=173 (12%)	Women aged 13 years or older, receiving a stable ARV regimen not including a nonnucleoside reverse transcriptase inhibitor, able and willing to sign informed consent, enrolled after 20 weeks gestation	Women already enrolled in other treatment trials, women with elevated alanine aminotransferase levels, hypersensitivity to benzodiazepines, women who had received nonnucleoside ARV drugs in the past, or had a fetus with an anomaly incompatible with life in the current pregnancy
Williams, 2010[97]	Age at test, median = 1.8 (1-2) Race/ethnicity, n (%) White nonHispanic + other = 242 (13) Black nonHispanic = 1016 (55) Hispanic = 582 (32) Maternal viral load, n (%) copies/mL <400 = 362 (39) 401-5000 = 272 (29) 5000-50,000 = 235 (25) >50,000 = 67 (7) Unknown = 904	Children perinatally HIV exposed, uninfected enrolled in the clinical trial group between 1993-2006; had at least 1 neurodevelopmental functioning test by using the Bayley Scales of Infant Development (BSID)	Invalid BSID scores, missing ARV exposure information

Author, Year	Number screened/eligible/enrolled/withdrawals/% analyzed	Adjusted variables for statistical analysis
Aldrovandi, 2009[90]	213 uninfected infants born to HIV-infected women 411 healthy children born to HIV-uninfected women	For infant mDNA levels: mixed model analysis of variance controlled for: ARV exposure, maternal alcohol use, maternal cocaine/crack use, maternal hard drug use, maternal predelivery CD4 count, maternal predelivery plasma HIV RNA, maternal delivery CD4 count, maternal delivery CD4 %, maternal delivery HIV RNA level, infant birth weight, and infant age.
Alimenti, 2006[96]	64 children born to mothers in ART; 25 children unavailable or not eligible; 11 did not return phone calls; 8 declined participation; 3 language barrier; 3 excluded because of sibiling participation	Analysis of covariance used to allow for control of specific variables and on frequencies by using chi-square tests
Benhammou, 2008[103]	12,074 live born infants; 11,553 HIV uninfected; 9127 exposed to at least one NRTI during one or more of the pre-, peri-, or postpartum phases; 8853 children exposed to NRTIs in utero	Multivariate and univariate analyses performed.
Briand, 2009[73]	8192 mother-infant pairs 317 excluded due to illicit drug use 396 excluded due to twin pregnancies 439 HIV-infected neonates excluded	SGA studied using univariate and multivariate regression analysis; association with birthweight Z-scores used univariate and multivariate linear regression models fitted to obtain regression coefficients. Models adjusted for maternal geographic origin, maternal age, parity, and gestational age at booking. Birth weight Z-score adjusted for gestational age and sex lower than -2 SD. Similar analysis for head circumference and height.
Brogly, 2007[91]	1732 enrolled through August 2003; 1220 enrolled prior to 2 years of age and had completed 1 year of followup. 512 not included, enrolled earlier, followed longer before 3 years of age	Sex, race/ethnicity, year of birth, premature birth, neonatal ARV prophylaxis, peak maternal HIV RNA copy number during 3rd trimester or delivery, in utero psychoactive drug exposure
Bunders, 2005[100]	109 eligible; 93 with followup more than 2 years; 17 excluded	Multivariate model allowing for birthweight, gestational age

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Author, Year	Number screened/eligible/enrolled/withdrawals/% analyzed	Adjusted variables for statistical analysis
Carceller, 2009[74]	347 pregnant women with HIV screened 248 ART-exposed mother infant pairs eligible, 42 excluded due to insufficient data 206 ART-exposed mother-infant pairs included Control: 206 randomly selected infants of non-HIV-infected mothers % analyzed: A: 97%-99% B: 93%-97% C: 82%	Logistic regression analysis to examine effect of protease inhibitors on prematurity and SGA
Cote, 2008[92]	73 ART-exposed infants and 81 control infants born between July 2003 and June 2006 eligible. 87 controls initially, but 6 excluded due to febrile illness or abnormal lab values. For analysis of mtRNA level, 32 study and 62 control infants were ultimately analyzed for mtRNA content	Research site, length of in utero exposure to ART, maternal infection with HCV or HBV, birth weight, gestational age at delivery
Cotter, 2006[75]	999 women who received ART during pregnancy; 338 who did not receive therapy	History of preterm delivery; factors significant in univariate analysis, category of ART, race/ethnicity. Lowest CD4 count during pregnancy, CDC disease stage, illicit substance use, smoking, STD, time of initiation of prenatal care, ART duration, ART before pregnancy, year of delivery
El Beitune, 2005[76]	Treated cohort: 45 Untreated cohort: 12	None reported
Grosch-Woerner, 2008[77]	190 screened; 183 pairs included in analysis	AOR: race, maternal age, IDU during pregnancy, CD4 cell count at delivery, parity, and ART exposure
Lipschultz, 2011[99]	136 ART-exposed infants; 216 non-ART exposed infants	Interaction terms of ART exposures with sex, ethnicity, age that were significant at 0.05 were included in the final models
Marti, 2007[109]	179 pregnancies were recorded 12 pregnancies ended in spontaneous miscarriage or induced abortion With 3 sets of twins, there were 170 newborns	Multiple stepwise logistic regression analysis. For GDM: CD4 cell count, previous AIDS diagnosis, risk factors for HIV
Morris, 2005[78]	Records of 233 pregnancies were reviewed (11-91 per site). Outcomes for 3/231 (1.3%) lost to followup	Known risk factors for prematurity were tested using multiple logistic regression. A forward stepwise procedure was used with maximum likelihood estimation of the regression coefficients. The likelihood ratio criterion was used to determine significance of individual factors in the regression model.
Mussi-Pinhata, 2007[101]	803 women enrolled; 16 pregnancies excluded; 743 delivered 737 infants; 81 still on study; 21 lost to followup; 631 completed 6 month follow up after birth; 603 HIV uninfected (24 indeterminate, 8 infected) 603 infants; 541 gestational age >37 weeks, 539 discharged from hospital within 6 days of life; 533 infants mothers received one or more ARVs during pregnancy; 511 received ARVs for >28 days.	Adjusted for mother's country of residence, race/ethnicity, ARV regimen
Pacheco, 2006[102]	2171 enrolled;followup for 1-34 months; excluded not reported	Mulitvariate analysis adjusted for maternal antenatal use of hard drugs, maternal CD4 count at delivery, infant gestational age, infant birth weight, race/ethnicity, maternal CDC clinical classification, infant sex and age
Patel, 2005[93]	3740 mother-infant pairs enrolled; 1973 infants exposed to ART in utero, including 602 exposed to ART; 789/1973 (40%) women received ART in the first trimester and had initiated treatment before conception	Multiple variable logistic regression with all variables included; race, maternal age at delivery, CD4 count, gestational age
Paul, 2005[79]	1853 children enrolled in WITS as of October 1999. 1785 singletons, 1553 from 1st pregnancy. 1480 with known HIV status 1118 with complete HIV data 995 HIV-uninfected 163 HIV-infected	Cox proportional hazards modeling to assess effect of selected covariates on clinical events rate. For growth problems developed after 2 weeks of age: maternal education, maternal viral load at delivery, hard drug, alcohol and cigarette use during pregnancy; child's race,ethnicity and gender, number of caregiver changes

Appendix B6. Key Question 3c: Studies of Adverse Outcomes Associated With Antiretroviral Therapy

Author, Year	Number screened/eligible/enrolled/withdrawals/% analyzed	Adjusted variables for statistical analysis
Powis, 2011[72]	560 HIV infected pregnant women enrolled; 285 randomized to NRTI group, 27 randomized to PI group A: excluded: 1 LTFU prior to delivery, 5 stillborn birhts, 1 twin delivery, 1 preterm emergent cesarean B: excluded: 3 LTFU prior to delivery, 8 stillborn, 9 twin deliveries, 2 preterm emergent cesarean A: 263 mother infant pairs included B: 267 included	Self reported maternal income, maternal CD4 count at enrollment, HIV viral load
Rudin, 2011[80]	1241 in database; 762 pregnancies excluded in 695 women; adjusted analysis based on 365 pregnancies in 318 women	Maternal characteristics: lowest CD4 cell count during pregnancy, last HIV RNA load before delivery, age at conception, ethnicity, illicit drug use, smoking.
Schulte, 2007[81]	11,231 HIV exposed and HIV infected infants met inclusion criteria 8793 infants were born to HIV-infected mothers with prenatal care	Excluded preterm birth from multivariate assessment of low birth weight. Excluded low birth weight in asessment of preterm birth. All variables in univariate analyses were entered into logistic regression models. Risks significant at 0.10 level remained in the model using a stepwise method. Perinatal exposure to 2 ARV drugs was used as a referent group.
Tariq, 2011[59] See also Townsend, 2008[56]; European Collaborative Study, 2005[93]	7573 mother-child pairs analyzed (n=1263 from ECS, n=6310 from NSHPC)	AOR=OR adjusted for study, maternal age group
Townsend, 2007[82]	5009 reported pregnancies; 4939 included	OR = adjusted for repeat pregnancies AOR = OR adjusted for repeat pregnancies, injecting drug use as source of HIV infection, ethnic origin, maternal age, clinical status AOR2 = OR adjusted for repeat pregnancies, injecting drug use as source of HIV infection, ethnic origin, maternal age, clinical status, CD4 count (subset with count n = 3761)
Townsend, 2009[94]	8576 infants reported, including 92 stillbirths, 288 twins/triplets. Information available for 79% of inants, remainder reported only through the obstetric (10%) or pediatric (11%) scheme. Information on congenital abnormality available for 96.1% (8242/8576) infants. Timing of ART exposure data missing for 7.4% (609/8242) infants. Of these, most reports (88%, 538/609) were obtained from pediatric respondents.	Maternal CD4 count, iIntravenous drug use, age, ethnicity
Tuomala, 2005[108]	Maternal complications: 2543 women analyzed Obstetric outcomes: 2286 women analyzed	Major temporal changes in ART use; associations between variables and outcomes that had univariate probability values below 0.1 were included in a final logistic regression model; logistic regression using a stepwise elimination procedure with a logistic regression probablility value for entry and exit into the model set at 0.05 was performed to identify independent predictors of each specified outcome.
Watts, 2011[95]	1506 women enrolled in PACTG 316;1414 women with 1408 livebirths and 6 stillbirths analyzed for congenital defects by timing of ARV use	Only univariate analyses shown
Williams, 2010[97]	2342 uninfected, HIV exposed infants enrolled in PACTG; 2300 in recommended age range for testing; 1910 had at least one test reported; 1840 (96%) had both valid test results and known maternal ARV exposure.	Demographic factors (age at test, gender, race/ethnicity) and potential confounders: test version, primary language, primary caregiver, caregiver education, low birth weight, birth year; geographic location, urban/rural

3TC = lamivudine; AEs = adverse events; AIDS = acquired immunodeficiency syndrome; AOR = adjusted odds ratio; ART = antiretroviral; ARV = antiretroviral; cARV = combination antiretrovirals; BMI = body mass index; BSID = Bayley Scale of Infant Development; CDC = Centers for Disease Control and Prevention; CI = confidence interval; CHAART = cardiovascular status of HAART; ELISA = enzyme-linked immunosorbent assay; GDM = gestational diabetes mellitus; HAART = highly active antiretroviral therapy; HBV = hepatitis B virus; HCV = hepatitus C virus; Hgb = hemoglobin; IDU = injection drug user; IVDU = intravenous drug use; KAL-CBV = lopinavir/ritonavir/zidovudine/lamivudine; LBW = low birth weight; LTFU = loss to followup; LV = left ventricle; MD = mitochondrial dysfunction; MOCHIV = mothers of children with HIV; mtDNA = mitochondrial deoxyribonucleic acid; mtRNA =

mitochondrial ribonucleic acid; N/A = not applicable; NISDI = NICHD International Site Development Initiative; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NR = not reported; NSHPC = National Study of HIV in Pregnancy and Childhood; OR = odds ratio; PACTG = Pediatric AIDS Clinical Trials Group; PBMC = peripheral blood mononuclear cell; PI = protease inhibitor; RCT = randomized, controlled trial; RNA = ribonucleic acid; SD = standard deviation; SGA = small for gestational age; SHCS = Swiss HIV cohort study; SIDA = Swedish International Development Cooperation Agency; STD = sexually transmitted disease; WITS = Women and Infants Transmision Study; ZDV = zidovudine.

Appendix B7. Key Question 3c: Quality Rating of a Randomized, Controlled Trial of Adverse Outcomes Associated With Antiretroviral Therapy

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup differential/ high?	Intention -to-treat analysis	Quality rating	Funding
Powis, 2011[72]	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Unclear	Fair	Harvard University Center for AIDS Research, Global Infectious Disease Program, Global Health Scholars Program; National Institute of Allergy and Infectious Diseases

Appendix B8. Key Question 3c: Quality Ratings of Cohort Studies of Adverse Outcomes Associated With Antiretroviral Therapy

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (by restriction or matching)?	Did the study maintain comparable groups through the study period?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?
Aldrovandi, 2009[90]	No	No	Unclear	Unclear	Yes	No	Yes
Alimenti, 2006[96]	Yes	Yes	Yes	Yes	No	No	Yes
Benhammou, 2008[103]	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes
Briand, 2009[73]	Yes	Unclear	Unclear	Yes	Unclear	No	Yes
Brogly, 2007[91]	Yes	Yes	Yes	Yes	Yes	No	Yes
Bunders, 2005[100]	Yes	Yes	Yes	Yes	No	No	Yes
Carceller, 2009[74]	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Cote, 2008[92]	Yes	No	Yes	Yes	Unclear	No	Yes
Cotter, 2006[75]	Yes	No	Unclear	Yes	Unclear	N/A	Yes
El Beitune, 2005[76]	Unclear	Yes	Yes	Unclear	Unclear	No	No
Grosch-Woerner, 2008[77]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Lipschultz, 2011[99]	Yes	Yes	Yes	Yes	No	No	Yes
Marti, 2007[109]	Yes	Unclear	Unclear	Yes	Unclear	No	Yes
Morris, 2005[78]	Yes	NA	NA	Yes	Unclear	Yes	Yes
Mussi-Pinhata, 2007[101]	Yes	Unclear; groups not separated by HAART regimen	Unclear	Yes	No	Yes	Yes
Pacheco, 2006[102]	Yes	No; groups differ on multiple variables	Unclear	Yes	No	Unclear	Yes
Patel, 2005[93]	Yes	Yes	Yes	Yes	No	No	Yes
Paul, 2005[79]	Yes	Unclear	Unclear	Unclear	Unclear	No	Yes
Rudin, 2011[80]	Yes	Unclear	Unclear	Yes	No	Yes	Yes
Schulte, 2007[81]	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes
Tariq, 2011[59]	Yes	No; differences on several variables	Unclear	Yes	Unclear	Yes	Yes
Townsend, 2007[82]	Yes	Yes	Yes	Yes	No	No	Yes
Townsend, 2009[94]	Yes	Unclear; baseline characteristics are not divided by ART groups	Yes	Yes	Unclear	Yes	Yes
Tuomala, 2005[108]	Yes	No; between groups on multiple variables	Unclear	Yes	Yes	No	Yes
Watts, 2011[95]	Yes	Unclear; baseline characteristics not divided by ART group	Unclear	Unclear	Yes	Yes	Yes
Williams, 2010[97]	Yes	No; differ by birth year, test used to assess neurodevelopment	Unclear	Yes	Unclear	No	Yes

Appendix B8. Key Question 3c: Quality Ratings of Cohort Studies of Adverse Outcomes Associated With Antiretroviral Therapy

Author, Year	Is there important differential loss to followup or overall high loss to followup?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Quality rating	Funding source
Aldrovandi, 2009[90]	Unclear	Unclear	Poor	Not reported
Alimenti, 2006[96]	No	Yes	Good	British Columbia Medical Services Foundation; Health Canada Hepatitis C Vertical Transmission Study
Benhammou, 2008[103]	No	Yes	Fair	Agence Nationale de Recherche sur le SIDA, Agence Francaise de Securite Sanitaire des Produits de Sante
Briand, 2009[73]	Unclear	Yes	Fair	Agence Nationale de Recherches sur le SIDA et les Hepatites Virales
Brogly, 2007[91]	No	Yes	Good	National Institute of Allergy and Infectious Disease; National Institute of Child Health and Human Development; Statistical and Data Analysis Center of Pediatric AIDS Clinical Trials Group,Harvard School of Public Health
Bunders, 2005[100]	No	Yes	Fair	Academic Medical Center, Amsterdam; International AIDS Therapy Evaluation Center
Carceller, 2009[74]	Unclear	Yes	Poor	Not reported
Cote, 2008[92]	No	Yes	Good	Hospital for Sick Children, Toronto
Cotter, 2006[75]	No; all data reviewed for all births in time period of interest as per study	Yes	Fair	Not reported
El Beitune, 2005[76]	Unclear	Yes	Poor	FAPESP
Grosch-Woerner, 2008[77]	No	Yes	Fair	Ministry of Health of Germany; World Childhood Foundation
Lipschultz, 2011[99]	Unclear	Yes	Fair	National Heart, Lung, and Blood Institute
Marti, 2007[109]	No	Yes	Fair	Not reported
Morris, 2005[78]	No	Yes	Fair	Agouron Pharmaceuticals
Mussi-Pinhata, 2007[101]	No	Yes	Fair	National Institute of Child Health and Human Development International Site Development Initiative (NISDI) Perinatal Study Group
Pacheco, 2006[102]	Unclear	Yes	Fair	National Institute of Allergy and Infectious Diseases; National Institute on Drug Abuse; National Institute of Child Health and Human Development
Patel, 2005[93]	No	Yes	Fair	European Comission; Medical Research Council
Paul, 2005[79]	Unclear	Yes	Poor	National Institute of Allergy and Infectious Diseases, National Institute of Child Health and Human Development; National Institute on Drug Abuse; General Clinical Research Centers
Rudin, 2011[80]	No	Yes	Fair	Swiss HIV Cohort Study, Swiss National Science Foundation
Schulte, 2007[81]	Unclear	Yes	Fair	Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention
Tariq, 2011[59]	No Yes	Yes	Fair	UK Medical Research Council; Wellcome Trust Research Career Development Fellowship, Health Protection Agency, Department of Health's National Institute for Health Research Biomedical Research Centers
Townsend, 2007[82]	No	Yes	Fair	Ministry of Health and Child Welfare, Zimbabwe; Canadian International Development Agency
Townsend, 2009[94]	No	Yes	Fair	National Study of HIV in Pregnancy and Childhood, Institute of Child Health, Health Protection Agency Center for Infections and Health Protection, Scotland
Tuomala, 2005[108]	Unclear	Yes	Fair	National Institute of Allergy and Infectious Diseases, National Institiute of Child Health and Human Development, National Institute on Drug Abuse, General Clinical Research Centers

Appendix B8. Key Question 3c: Quality Ratings of Cohort Studies of Adverse Outcomes Associated With Antiretroviral Therapy

Author, Year	Is there important differential loss to followup or overall high loss to followup?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Quality rating	Funding source
Watts, 2011[95]	No	Yes	Fair	National Institute of Allergy and Infectious Diseases, National Institiute of Child Health and Human Development, National Institute on Drug Abuse, and General Clinical Research Centers
Williams, 2010[97]	Unclear	Yes	Fair	National Institute of Allergy and Infectious Diseases and the National Institutes of Child Health and Human Development International and Domestic Pediatric and Maternal HIV Clincial Trials Network