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Screening for HIV Infection in Pregnant Women: A Systematic Review for the U.S. Preventive Services Task Force

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

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Structured Abstract

Background: A 2012 systematic review on human immunodeficiency virus (HIV) screening for the U.S. Preventive Services Task Force (USPSTF) found strong evidence that antiretroviral therapy (ART) greatly decreases the risk of mother-to-child HIV transmission but that use of ART may be associated with increased risk of preterm delivery. The USPSTF previously found HIV screening tests to be highly accurate.

Purpose: To systematically update the 2012 USPSTF review on HIV screening in pregnancy, focusing on research gaps identified in the prior review.

Data Sources: We searched the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and MEDLINE (2012 to June 2018), and manually reviewed reference lists.

Study Selection: We selected randomized controlled trials (RCTs) 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 ART during pregnancy.

Data Extraction: One investigator abstracted data and a second investigator checked data abstraction for accuracy. Two investigators independently assessed study quality using methods developed by the USPSTF.

Data Synthesis (Results): We identified no study on the benefits or harms of HIV screening versus no screening, or on the yield of repeat versus one-time screening or screening at different intervals. One new RCT and five new cohort studies were consistent with the 2012 USPSTF review in finding combination ART highly effective at reducing the risk of mother-to-child transmission of HIV infection, especially if started early in pregnancy (rate of mother-to-child transmission <1%). As in the prior USPSTF review, one new RCT and several observational studies found certain ART regimens associated with increased risk of preterm delivery without increased risk of low birth weight. One African RCT found prenatal tenofovir-based ART associated with very preterm delivery and early infant death versus zidovudine-based ART, but the trial had methodological limitations. Prenatal ART exposure to most currently recommended ART drugs was not associated with increased risk of overall birth defects, but limited evidence found certain ART agents and regimens associated with increased risk of congenital abnormalities, cardiac anomalies, and echocardiographic changes, with no association with adverse neurodevelopmental outcomes. Evidence on long-term maternal harms associated with short-term exposure to ART during pregnancy remains limited, with some evidence of short-term harms.

Limitations: Only English-language articles were included. Observational studies were included. Studies conducted in resource-poor settings were included, which might limit applicability to screening in the United States.

Conclusions: Combination ART is highly effective at reducing risk of mother-to-child HIV transmission. The USPSTF previously determined that avoidance of breastfeeding and Cesarean

delivery in women with HIV ribonucleic acid (RNA) levels >1000 copies/mL near the time of delivery is also effective at reducing mother-to-child transmission, and that prenatal screening is accurate at diagnosing HIV infection. Use of certain ART regimens during pregnancy is associated with increased risk of pre-term delivery and may be associated with other adverse pregnancy outcomes. Although more evidence is required to better understand short-and long-term maternal and infant harms, selection of ART regimens may help mitigate or reduce harms.

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Chapter 1. Introduction and Background

Purpose

Human immunodeficiency virus (HIV) infection is transmissible during pregnancy and the postpartum period. The purpose of this report is update a previous review[1,2] commissioned by the U.S. Preventive Services Task Force (USPSTF) on benefits and harms of prenatal screening for HIV infection. This report will be used to update the USPSTF's 2013 recommendation that clinicians screen all pregnant women for HIV, including those who present in labor who are untested and whose HIV status is unknown (**A Recommendation**),[3,4] a confirmation of the USPSTF's 2005 recommendation on prenatal HIV screening. The confirmation was based on confirmation of prior findings that antiretroviral therapy (ART) is acceptable to pregnant women and that early detection and treatment of HIV is associated with large reductions in the risk of mother-to-child transmission, as well as some evidence that newer antiretroviral regimens are more effective than older regimens for preventing perinatal transmission. Although the USPSTF found some evidence that perinatal ART is associated with increased risk for preterm delivery, there was no clear association with low birthweight, congenital abnormalities, or impaired infant neurodevelopment, and no data indicating serious maternal harms.[1,2]

Condition Background

Condition Definition

HIV is a ribonucleic acid (RNA) retrovirus that infects human immune cells, in particular CD4+ helper T lymphocyte (CD4) cells. Untreated, HIV infection results in progressive immunodeficiency and the acquired immune deficiency syndrome (AIDS).[5] AIDS is a life-threatening condition characterized by presence of HIV infection and severe immune dysfunction (CD4 count $\leq$200 cells/mm^3) or one or more AIDS-defining neoplastic conditions or opportunistic infections.[5] HIV-1 infection is the most common variant in the United States. HIV-2 infection is rare in the United States, less clinically severe, and endemic in parts of West Africa.[6]

In HIV-infected pregnant women, HIV can cross the placenta, is present in cervical secretions in blood, and is present in breast milk. Therefore, transmission of HIV infection from mother-to-child can occur during pregnancy, during labor and delivery, and in the postpartum period through breastfeeding.[7]

Prevalence and Burden of Disease/Illness

In 2016, women accounted for 19 percent of all new diagnoses of HIV infection among adults and adolescents in the United States.[8] Between 2005 and 2014, the number of new HIV diagnoses in women declined 40 percent.[9] About 232,692 U.S. women were living with HIV infection in 2016, with 7,529 new cases.[9] Approximately 359 diagnoses were in women 13 to 19 years of age.[10] An estimated 62 percent of infections were in black women, 18 percent in white women, and 16 percent in Hispanic/Latina women.[9] An estimated 11 percent of women with HIV infection are unaware of their status.[9]

Approximately 8,500 HIV-positive women give birth each year in the United States.[7] In 2005 to 2008, approximately 30 percent of HIV-infected women were unaware of their status

prior to pregnancy and approximately 4 percent were undiagnosed prior to the time of delivery.[11] Mother-to-child transmission accounts for approximately three-quarters of pediatric HIV infections in the United States and 90 percent of pediatric cases of AIDS.[7] Through 2013, there have been nearly 5,000 cumulative deaths of U.S. children below the age of 13 years with perinatally acquired HIV infection.[7] The number of cases of perinatal HIV infections in the United States peaked at about 1,650 in 1992, declining dramatically following the widespread adoption of routine prenatal screening, coupled with the use of effective therapies for preventing mother-to-child transmission. There were an estimated 215 to 370 cases of perinatal transmission in 2005[12] and 99 cases in 2016.[8] The Centers for Disease Control and Prevention (CDC) estimates that between 1994 and 2010, 21,956 cases of perinatally acquired HIV infections were prevented.[13,14] The overall annual rate of perinatally acquired HIV infection decreased from 6.0 per 100,000 live births in 2008 to 1.8 per 100,000 live births in 2013.[15] Rates of perinatally acquired HIV infection differ according to age group. In 2013, among blacks/African Americans, the rate was 11.3 per 100,000 live births (from 23.6 per 100,000 live births in 2008), compared with 1.8 among Hispanics/Latinos and 0.6 in white people.

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 remaining cases occurring during labor and delivery.[16] Most intrauterine transmission is thought to occur shortly before delivery.[17] HIV is present in and transmitted through breast milk[18] and breastfeeding is thought to be the only important mode for postpartum transmission to newborns and infants.[19,20] In resource-poor settings in which women breastfeed for prolonged periods, postpartum transmission accounts for about 44 percent of infant cases.[21] Antiretroviral treatment of the mother and infant does not completely eliminate breastfeeding transmission risk.[22] In the United States, HIV-infected women are advised against breastfeeding, given the risk of transmission and the availability of affordable and safe alternatives.[23]

Risk Factors

Most (87%) new HIV diagnoses in women (regardless of pregnancy status) are attributed to acquisition via heterosexual sex, followed by injection drug use (12%).[9] In HIV-infected pregnant women, about 50 percent were 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).[11] In about one-third of women, HIV exposure was unknown.

Well-established risk factors for perinatal transmission include higher viral load, immunologically or clinically advanced disease in the mother, prolonged rupture of membranes, maternal infection with other sexually transmitted infections, and labor and delivery procedures and events associated with an increased probability of bodily fluid contact between mother and infant (such as abruptio placentae, fetal scalp electrode use, episiotomy, and second degree or greater perineal laceration).[24]

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.[25,26]

Rationale for Screening/Screening Strategies

A major goal of prenatal screening for HIV is to reduce the risk of mother-to-child transmission through provision of subsequent interventions. Other important goals are to improve long-term clinical outcomes in HIV-infected women through initiation of ART and other interventions (e.g., prophylaxis for opportunistic infections in women with immunologically advanced disease), 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. The prior USPSTF review on prenatal HIV screening found that ART in combination with avoidance of breastfeeding and elective Cesarean section in women with viremia substantially reduces risk for mother-to-child transmission, from 9 to 22 percent with no ART to <1 to 2.4 percent with full-course combination ART.[3,4]

Interventions/Treatment

The current standard of care to prevent perinatal transmission of HIV infection in the United States is combination ART started at the time of diagnosis in all HIV-infected women (regardless of viral load or CD4 count), intravenous zidovudine and elective Cesarean section before labor or rupture of membranes in women with HIV RNA levels >1,000 copies/mL or unknown HIV RNA levels near the time of delivery, antiretroviral treatment of the infant in the postnatal period, and avoidance of breastfeeding.[23] The selection of antiretroviral drugs is based on evidence on 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, and may be informed by results of antiretroviral drug resistance testing. Because delayed treatment may reduce effectiveness of ART on risk of mother-to-child transmission, current guidelines recommend that clinicians consider initiating ART as soon as HIV is diagnosed during pregnancy, and not delay selection of the initial ART while awaiting results of drug resistance testing.[23] For women who present in labor with unknown HIV status, rapid testing with initiation of maternal (intravenous zidovudine during labor) and infant (combination ART) prophylaxis is recommended, with continuation of infant prophylaxis based on results of confirmatory testing. Consistent with management of nonpregnant people with HIV infection, guidelines now recommend that HIV-positive women diagnosed during pregnancy be offered long-term ART following delivery, regardless of CD4 count.[23,27]

HIV-positive women identified during pregnancy may also benefit from other interventions that would be considered in nonpregnant people with HIV infection, including long-term ART, prophylaxis for opportunistic infections, immunizations, and counseling to reduce high-risk behaviors for horizontal transmission; in addition, male sexual partners may benefit from pre-exposure prophylaxis (PrEP) with ART.[28]

Current Clinical Practice/Recommendations of Other Groups

The diagnostic accuracy of standard HIV testing is thought to be similar for pregnant and nonpregnant people.[29] A large, prospective cohort study of 5,744 pregnant women presenting in labor in six U.S. cities (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.[30] 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 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 tests prior to initiating interventions is recommended due to the possibility of false-positive tests,[30] 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.[23] 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, ~85 percent of HIV-infected women receive ART during pregnancy, with about 40 percent undergoing elective Cesarean section.[11] Over 95 percent of infants born to HIV-infected women receive ART during the postnatal period.

Many groups, including the American Congress of Obstetricians and Gynecologists (ACOG),[27] the American Academy of Pediatrics (AAP),[32,33] the American College of Physicians (ACP),[34] and the CDC,[31,35] recommend voluntary "opt out" testing for HIV in all pregnant women as part of routine prenatal care. The CDC[31,35] and ACOG[27] recommend repeat testing for women with risk factors and those in high incidence settings, and that clinicians consider repeat testing for all women with a negative test result early in pregnancy. The USPSTF recommends that women screened during a previous pregnancy be rescreened in subsequent pregnancies, but does not address repeat screening during the same pregnancy.[4] The American Academy of Family Physicians (AAFP) follows the 2013 USPSTF recommendation.[36]

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 the patient populations, interventions, and outcomes reviewed (**Figure 1**). Key Informants with expertise in HIV screening and HIV infection during pregnancy were surveyed for input, and the draft research plan was posted for public comment prior to finalization. The target population for HIV screening was pregnant women (including adolescents, defined as women 13 to <18 years of age) without signs or symptoms of HIV infection.

Key Questions

1. What are the benefits of screening for HIV infection in pregnant women on risk of mother-to-child transmission of HIV infection?
2. What is the yield (number of new diagnoses per number of tests performed) of repeat HIV screening at different intervals in pregnant women, and how does the yield of screening vary in different risk groups?
3. What are the harms of screening for HIV infection in pregnant women?
4. What is the effectiveness of currently recommended antiretroviral therapy regimens for reducing mother-to-child transmission of HIV infection?
5. What are the harms of currently recommended antiretroviral therapy regimens given during pregnancy to the mother and infant?

Search Strategies

We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews and Ovid MEDLINE (2012 through June 2018) for relevant studies and systematic reviews. Search strategies are available in **Appendix A1.** We also reviewed reference lists of relevant articles.

Study Selection

All titles and abstracts identified through searches were independently reviewed by two members of the research team for eligibility against predefined inclusion/exclusion criteria, as specified using the PICOTS (population, intervention, comparator, outcome, timing, study design/setting) framework (**Appendix A2**). Studies marked for possible inclusion by either reviewer underwent full-text review. All results were tracked using EndNote® reference management software (Thomson Reuters, New York, NY).

Each full-text article was independently reviewed by two trained members of the research team for inclusion or exclusion on the basis of the eligibility criteria. If the reviewers disagreed, conflicts were resolved by discussion and consensus or by consulting another member of the review team. Results of the full-text review were also tracked in the EndNote® database, including the reason for exclusion for full-text publications. The selection of literature is

summarized in the literature flow diagram (**Appendix A3**). **Appendix A4** lists excluded studies with reasons for exclusion.

Scope of Review

The prior USPSTF recommendation on prenatal HIV screening was an **A Recommendation**, based on convincing evidence that the benefits of prenatal screening substantially outweighs harms. This review focuses on key areas for which evidence was lacking in the prior USPSTF review, including direct evidence on benefits and harms (including false-positive results and anxiety) of screening and the yield of repeat screening during pregnancy. Given changes in ART regimens that are used in pregnant women, this review addresses evidence on effectiveness and harms of ART,[23] with a focus on regimens currently recommended by the U.S. Department of Health and Human Services Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. A list of currently recommended ART regimens in pregnant women is shown in **Appendix Table B1**. Most studies that reviewed various ART regimens evaluated outcomes associated with components of ART regimens, rather than entire regimens; we included studies that evaluated currently recommended regimens or ART agents that are part of currently recommended regimens. We excluded regimens and ART agents that are no longer recommended in current U.S. practice.

This update does not address diagnostic accuracy of screening, which the USPSTF previously found to be high.[38,39] 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[4,38,39] and part of standard U.S. practice. Effects of early initiation of long-term ART are addressed in a separate report on screening for HIV infection in nonpregnant adolescents and adults.[40]

The population of interest for prenatal screening is asymptomatic pregnant women not known to be HIV-positive. For Key Questions on benefits and harms of ART, the population was HIV-infected pregnant women. Patient subgroups included those defined by age and race/ethnicity. The screening intervention was standard or rapid HIV antibody testing with confirmatory testing. Outcomes were mother-to-child transmission, yield of screening (number of cases of HIV infection identified per number of tests performed), harms of screening (including labeling, anxiety, and other harms), and maternal and infant harms of treatment, including long-term harms following in utero exposure to ART. For Key Questions on screening, comparisons were screening versus no screening, one-time versus repeat screening, and repeat screening at different intervals. For Key Questions on benefits and harms of ART, we included studies that compared full course (initiated in first or early second trimester) combination ART versus no ART, abbreviated courses of ART, or one- or two-drug therapy. For all Key Questions, we included randomized controlled trials (RCTs), cohort studies, and case-control studies. We included studies conducted in primary care-applicable settings (e.g., prenatal, antenatal, and family planning clinics) and other health care settings in which screening is commonly performed (e.g., emergency room, urgent care, or labor and delivery). Although the target for treatment studies was those conducted in the United States and other high income/low HIV prevalence countries, we also included RCTs on effects of ART on mother-to-child transmission conducted in low- and middle-income settings. For harms associated with prenatal ART, we included RCTs and cohort studies from any setting but restricted cohort studies to those that adjusted for potential confounders.

Data Abstraction and Quality Rating

For studies meeting inclusion criteria, we abstracted data on characteristics of study populations, interventions, comparators, outcomes, study designs, settings, and methods. For each study, data abstraction was conducted by one investigator and reviewed for completeness and accuracy by another investigator.

Predefined criteria were used to assess the quality of individual controlled trials, systematic reviews, and observational studies developed by the USPSTF. Studies were rated as "good," "fair," or "poor" quality in accordance with USPSTF methods, based on the seriousness of the methodological shortcomings (**Appendix A5**).[37] For each study, quality assessment was independently performed by two team members. Any disagreements were resolved by consensus.

Data Synthesis

We did not attempt meta-analysis of studies on effectiveness of ART on mother-to-child transmission or on harms of ART due to differences across studies in ART regimens and comparisons evaluated, harms outcomes, geographic settings, and methodological factors (e.g., observational studies performed statistical adjustment on different variables). There were too few studies to consider meta-analysis for other Key Questions.

For all Key Questions, the overall quality of evidence was determined using the approach described in the USPSTF Procedure Manual.[37] Evidence was rated "good", "fair", or "poor", based on the number, quality and size of studies, consistency of results between studies, and directness of evidence, and is summarized in a table.[37]

External Review

The draft report was reviewed by content experts (**Appendix A6**), USPSTF members, AHRQ Project Officers, and collaborative partners, and will be posted for public comment; the report will be revised based on reviewer comments prior to finalization.

Chapter 3. Results

Key Question 1. What are the benefits of screening for HIV infection in pregnant women on risk of mother-to-child transmission of HIV infection?

As in the prior USPSTF review, no RCT or observational study compared clinical outcomes (including risk of perinatal transmission) between pregnant women screened and not screened for HIV infection. As previously noted by the USPSTF, the number of infants with perinatally acquired HIV transmission has markedly declined in the United States, likely due to a combination of screening during pregnancy and increased effectiveness and use of interventions to prevent transmission.

Key Question 2. What is the yield (number of new diagnoses per number of tests performed) of repeat HIV screening at different intervals in pregnant women, and how does the yield of screening vary in different risk groups?

Summary

No study compared the yield of one-time versus repeat screening or different frequencies of screening for HIV in pregnancy. Three studies conducted in the United States or the United Kingdom identified no cases of HIV infection among women who were rescreened for HIV during the third trimester of pregnancy, details regarding HIV risk status were not reported and not all women were rescreened.[41-43]

Evidence

As in the prior USPSTF review, we identified no RCT or observational study on the yield of repeat prenatal HIV screening compared with one-time screening, or that compared the yield of different strategies for repeat screening (e.g., risk-based repeat screening versus a routine repeat test). Three studies reported rescreening rates and positive screens in 3,473 pregnant women, but did not meet inclusion criteria because they did not compare different screening strategies.[41-43] One retrospective study of pregnant women (n=1,632) was conducted in Baltimore, Maryland, a state that mandates that pregnant women be screened for syphilis at presentation and again in the third trimester, providing an opportunity for HIV rescreening as well.[41] HIV rescreening was performed in 28 percent of women, with no cases of HIV infection identified. A second study of 2,392 women in the United Kingdom with an initial negative prenatal HIV screen found no cases of HIV infection in those retested during the third trimester.[42] The third study retested 75 women in ambulatory OB/GYN clinics in Philadelphia, Pennsylvania with a rapid HIV test in the third trimester and identified no new cases of HIV

infection.[43] In these studies, details were unavailable regarding risk of HIV acquisition (e.g., HIV risk category or prevalence of HIV risk behaviors), and not all women were rescreened.

Repeat screening and the optimal timing of repeat testing during pregnancy depends on the incidence of new HIV infections following an initial negative prenatal screen. One modeling study discussed in the 2005 USPSTF review 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.[44]

Key Question 3. What are the harms of screening for HIV infection in pregnant women?

As in the prior USPSTF review, no study compared psychological or other harms associated with screening for HIV in pregnant women or adverse clinical consequences of interventions given as a result of false-positive results.

Key Question 4. What is the effectiveness of currently recommended antiretroviral therapy regimens for reducing mother-to-child transmission of HIV infection?

Summary

The 2012 USPSTF review included eight cohort studies that found full-course (starting in first trimester or early in second trimester) combination ART associated with rates of mother-to-child transmission of <1 to 2.4 percent, compared with 9 to 22 percent with no ART. Consistent with the prior USPSTF review, five new European, North American, and Israeli cohort studies published since 2012 found perinatal full-course triple ART associated with a risk of mother-to-child transmission that ranged from <1 to 2.8 percent.[45-49] The prior USPSTF review included two African RCTs that found combination ART started at 26 to 28 weeks associated with mother-to-child transmission rates of 1 to 5 percent.[50,51] One new RCT conducted primarily in Africa found combination ART after 14 weeks associated with a lower rate of mother-to-child transmission than zidovudine monotherapy (0.5% vs. 1.8%).[52] Across studies, later initiation of ART during pregnancy or treatment with fewer than three antiretroviral medications was associated with increased risk of mother-to-child transmission.

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 in nonbreastfeeding women to 8 percent, compared with 25 percent with placebo.[53] The 2012 USPSTF review identified no completed trials on full-course combination ART during pregnancy in nonresource poor, nonbreastfeeding settings. It included eight United States or European cohort studies that found full-course combination ART associated with rates of

mother-to-child transmission that ranged from <1 to 2.4 percent, compared with 9 to 22 percent with no ART. The prior USPSTF review also included two RCTs of breastfeeding women in Africa that found triple ART 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 ART 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 generally higher transmission rates than with full-course, three-drug regimens. These RCTs are likely to be most applicable in the United States to HIV-infected women identified later in pregnancy, who cannot receive full-course regimens.

We identified no new RCTs on full-course combination ART during pregnancy in nonresource poor, nonbreastfeeding settings. Five fair-quality cohort studies conducted in high income settings and published since the prior USPSTF review evaluated the effectiveness of combination ART during pregnancy on risk of mother-to-child transmission[45-49] (**Table 1, Appendix Tables B2-B4**). Results were consistent with the findings from the prior review (**Table 1**). One large study (n=4,459) conducted an individual patient data meta-analysis of infants born between 1996 and 2010 in seven cohorts from six European countries who were at high risk of acquiring HIV infection (mother with viral load >50 copies/mL in the last 8 weeks of pregnancy or mother only received intrapartum ART or received no antenatal or intrapartum ART).[47] Over 25 percent of women did not receive ART during pregnancy. In women who received ART, the timing of initiation during pregnancy was not reported. Treatment with three or more antiretroviral drugs was associated with decreased risk of mother-to-child transmission compared to 0 drugs (2.8% versus 14.3%, adjusted odds ratio (OR) 0.36, 95% confidence interval [CI] 0.23 to 0.57). One or two antiretroviral drugs were also associated with decreased risk of mother-to-child transmission compared with no ART (adjusted OR 0.33, 95% CI 0.19 to 0.55 and OR 0.12, 95% CI 0.04 to 0.40, respectively).

The French Perinatal Cohort is an ongoing observational study involving 95 percent of all HIV-infected women in 90 perinatal centers throughout France.[45] Between 2000 and 2011, combination ART was initiated during pregnancy in 4583 women (8% in the first trimester, 32% in the second trimester, 12% in the third trimester, and 47% before conception). Most regimens were protease inhibitor (PI)-based triple therapy (82.5%). There were 50 cases of mother-to-child HIV transmission (1.2% of births). The rate of mother-to-child HIV transmission was highest in women who initiated ART during the third trimester and in whom viral loads nearest delivery were detectable (4.4%; 95% CI 2.1 to 7.9). There were no HIV transmissions among 2,651 women who started ART before pregnancy, continued ART throughout pregnancy, and had a viral load <50 copies/Ml at the time of delivery.

Two smaller cohort studies, one from Canada[46] and one from the United Kingdom and Ireland[48] reported rates of mother-to-child HIV transmission with combination ART of 1 percent and 0.5 percent, respectively. In the U.K./Ireland study, ritonavir-boosted lopinavir was associated with a higher transmission rate when ART was initiated during the third trimester (1.9%).[48] Some mother-infant pairs in this study may have been included in the individual patient data meta-analysis discussed above. An Israeli cohort study[49] found combination ART during pregnancy associated with decreased risk of vertical transmission (adjusted OR 0.4, 95% CI 0.1 to 0.8); transmission rates were 1.5 percent with vaginal delivery and 0.6 percent with caesarean section. Results were not stratified by timing of ART delivery.

One new, fair-quality RCT (PROMISE, n=3490) was conducted in India and Africa among HIV-infected women with CD4 counts at or above 350 cells/mm^1 who were at or beyond

14 weeks gestation[52] (**Table 2**). The rate of mother-to-child transmission at 1 week after birth was 1.8 percent with zidovudine alone, 0.5 percent with ART with zidovudine, lamivudine, and lopinavir-ritonavir, and 0.6 percent with ART with tenofovir, emtricitabine, and lopinavir/ritonavir (difference in rate for combined ART regimens vs. zidovudine alone -1.3%, 95% CI -2.1 to -0.4). The proportion of women who breastfed was 92 percent.

Key Question 5. What are the harms of currently recommended antiretroviral therapy regimens given during pregnancy to the mother and infant?

Summary

New evidence (2 trials[52,54] and 21 cohort studies in 30 publications)[45,55-83] on infant and maternal harms associated with perinatal exposure to ART was generally consistent with the evidence included in the 2012 USPSTF review. One fair-quality, RCT conducted in Africa and seven cohort studies published since the last review found antenatal ART associated with increased risk of preterm birth compared with no treatment or zidovudine monotherapy. The trial and 12 cohort studies found mixed results for the association between ART given during pregnancy and low birth weight, small for gestational age, and stillbirth. Five cohort studies, including the Antiretroviral Pregnancy Registry,[83] found that most antiretroviral drugs recommended in the United States as initial therapy for HIV in pregnancy were not associated with increased risk of birth defects. The trial reported increased risk of neonatal death with ART with tenofovir, emtricitabine, and lopinavir/ritonavir (4.4%) compared with ART with zidovudine, lamivudine, and lopinavir/ritonavir (0.6%) but there was no difference between the tenofovir combination ART regimen and zidovudine monotherapy in risk of early infant death (4.4% vs. 3.2%, p=0.43). In addition, the trial had some methodological limitations.

Evidence

Birth Outcomes: Preterm Delivery, Small for Gestational Age, Stillbirth, and Neonatal Death

The 2012 USPSTF review[1] included one RCT[84] and three prospective cohort studies[85-87] published after 2005 that found maternal exposure to combination ART with a protease inhibitor associated with increased risk of preterm delivery (<37 weeks) compared with nonnucleoside reverse transcriptase-based (NNRTI) ART (OR 2.0, 95% CI 1.3 to 3.3),[84] combination ART without a protease inhibitor (adjusted OR 1.8, 95 % CI 1.1 to 3.0),[85] dual therapy (adjusted OR 1.2, 95% CI 1.0 to 1.4),[86] or monotherapy (adjusted OR 3.4, 95% CI 1.1 to 10)[87] (**Table 3**). A fourth cohort study[88] found combination therapy associated with increased risk of preterm delivery (adjusted OR 1.4, 95% CI 1.1 to 1.8) compared with monotherapy or dual therapy, with no difference in risk according to whether the antiretroviral regimen included a protease inhibitor or not. There was no clear association between maternal exposure to ART and low birth weight or intrauterine growth restriction, based on seven cohort studies.

One open-label, Africa-based RCT[52] and 21 cohort studies in 30 publications)[45,55-83] published since the prior USPSTF review evaluated the association between maternal exposure to ART and risk of preterm delivery, low birth weight, and other birth outcomes (**Table 3;**

Appendix Tables B2-B4). Sample sizes ranged from 183 to 13,124 (total N=71,472). Eight studies were conducted in the United States, seven studies in Canada or Europe, and the remainder in Africa or Latin America. One cohort study, the Antiretroviral Pregnancy Registry[83] (n=22,360), is an international (69 countries), voluntary registry with 74 percent of data currently from the United States and its territories. ART regimens and comparisons varied across studies. Most cohort studies did not include a control group of women who did not receive ART; other methodological limitations were high attrition and unclear blinding of outcome assessors/data analysts.

The new, fair-quality RCT (PROMISE, n=3490) (see Key Question 4 for study details)[52] found ART with zidovudine, lamivudine, and lopinavir/ritonavir associated with increased risk of preterm delivery versus zidovudine monotherapy (20.5% vs. 13.1%, p<0.001). Zidovudine-containing combination therapy was also associated with increased risk of low birth weight (23% vs. 12%, p<0.001) and "any adverse birth outcome" (defined as low birth weight, preterm delivery, spontaneous abortion, stillbirth, or congenital anomaly; 40% vs. 27.5%, p<0.001). ART with tenofovir, emtricitabine, and lopinavir/ritonavir was associated with increased risk of low birth weight (16.9% vs. 8.9%, p=0.004) and any neonatal adverse event (34.7% vs. 27.2%, p=0.04) versus zidovudine monotherapy; effects on risk of preterm delivery were not statistically significant (18.5% vs. 13.5%, p=0.09). Tenofovir-containing ART was associated with increased risk of early infant death versus zidovudine-containing ART (4.4% vs. 0.6%, p<0.001) and increased risk of very preterm (prior to 34 weeks) delivery (6.0% vs. 2.6%, p=0.04), but there was no difference between tenofovir-containing ART versus zidovudine monotherapy in risk of early infant death (4.4% vs. 3.2%, p=0.43). There were also no differences in the rates of stillbirth between treatments. Methodological limitations of the trial included open-label design and changes in randomization from two ART groups (period 1) to three groups (period 2), resulting in a smaller sample for tenofovir-containing ART. Comparisons between zidovudine-containing ART and zidovudine monotherapy included outcomes from both period 1 and period 2 (N=3,084), whereas comparisons between tenofovir-containing ART (N=406) and zidovudine-containing ART (N=410) or zidovudine monotherapy (N=413) included only outcomes from period 2. In addition, there were unexplained differences in rates of events with zidovudine-containing ART between period 1 and period 2 for neonatal death (1.2% vs. 0.6%) and stillbirth (3.3% vs. 0.9%).

Consistent with the prior USPSTF review, one new RCT[52] and three new cohort studies[58,65,70,75] found ART containing a boosted PI associated with about a 30 percent increased risk of preterm birth versus treatment not containing a boosted PI (N=7,584). However, two new cohort studies (N=1,140) found treatment with a PI associated with a 50 percent decreased risk of preterm delivery[58] or no difference in risk[80] when compared with no ART.

The prior review found no clear evidence of an association between ART and increased risk of other adverse birth outcomes (e.g., low birth weight, small for gestational age, stillbirth). New evidence identified for this update also found mixed evidence on these birth outcomes. Four new cohort studies evaluated effects of ART on risk of low birth weight.[60,66,73,79] Two studies found combination ART associated with an approximate 80 percent decreased risk of low birth weight versus no ART (2 studies, N=3,192),[60,66] one study found no association between ART versus no ART and low birth weight (1 study, N=2,599),[79] and two studies found no difference between tenofovir-containing versus nontenofovir-containing ART in risk of low birth weight (two studies, N=3,650).[73,82]

Ten new cohort studies (in 11 publications) evaluated the association between ART and risk of being small for gestational age (SGA).[55,56,61,66,70,73,75,76,79-81] Four new cohort studies found about a 40 percent decreased risk of SGA with some regimens (3 studies, N=8,404),[55,75,76] and one study (N=1814) reported a decrease risk of SGA with the ART regimen tenofovir, emtricitabine, and efavirenz compared with no ART (adjusted OR 0.25, 95% CI 0.07 to 0.87).[66] Other studies found no effect between different ART regimens on risk of SGA,[55,70,73,80,81] or no effect of ART versus no ART on SGA.[79,80] One new cohort study (n=5,726) found treatment with the ART regimen zidovudine, lamivudine, and either nevirapine or ritonavir boosted lopinavir associated with increased risk for SGA versus zidovudine monotherapy (adjusted OR 1.5, 95% CI 1.2 to 1.9),[56] while two other studies reported no difference between ART and zidovudine monotherapy.[61,79]

Five studies evaluated the association between ART and risk of stillbirth.[60,66,75,76,78] One cohort study (N=5,726) found treatment with ART associated with increased risk of stillbirth versus zidovudine monotherapy (adjusted OR 2.5, 95% CI 1.6 to 3.9),[56] while two studies reported a significantly decreased risk of still birth compared with no ART.[60,66] Still birth was less likely with the regimen tenofovir, emtricitabine, and efavirenz compared with zidovudine, lamivudine, and nevirapine (N=3,837, aRR 0.43, 95% CI 0.31 to 0.61),[75] but the difference was not statistically significant when tenofovir, emtricitabine, and efavirenz was compared with other ART regimens grouped together (N=3,226, adjusted OR 0.6, 95% CI 0.3 to 1.3).[76] Two new cohort studies (N=4,381) reported no increase in risk of neonatal death with tenofovir-based ART[75,78] but one study (n=2,639) found increased risk of neonatal death with the ART regimen zidovudine, lamivudine, and ritonavir boosted lopinavir compared with tenofovir, emtricitabine, and efavirenz (aRR 4.01, 95% CI 1.78 to 9.11).[75] A combined analysis of two studies (N=1,621) found no difference in risk of fetal loss (undefined in this study but normally would include spontaneous abortion, fetal demise, and stillbirth) between initial therapy with tenofovir and emtricitabine combined with either ritonavir-boosted lopinavir or atazanavir versus zidovudine and lamivudine combined with ritonavir-boosted lopinavir.[82] This study also found no difference in risk of neonatal death within 14 days after birth between the three treatment regimens.

Overall Congenital Abnormalities

The 2012 USPSTF review found no association between perinatal exposure to ART and overall congenital abnormalities, based on three cohort studies.[89-91] Five new cohort studies (N=40,436),[57,59,64,71] including the Antiretroviral Pregnancy Registry,[83] evaluated the association between combination ART in HIV-infected pregnant women and risk of congenital anomalies (**Table 3**). All of the newer cohort studies included patients who received one or more of the preferred NRTIs for use in pregnancy (abacavir, lamivudine, tenofovir, or emtricitabine). Most antiretroviral agents and classes were not associated with an increased risk of congenital abnormalities, but findings were limited by small numbers of studies, imprecision in estimates, and multiple comparisons. One study found no antiretroviral agent associated with increased risk of birth defects.[57] One study found an association between atazanavir, ritonavir, or any protease inhibitor and increased risk of congenital abnormalities versus nonexposure,[71] one study found an association between lamivudine, first trimester abacavir, and first trimester exposure to zidovudine and risk of congenital abnormalities,[64] one study found an association between first trimester efavirenz and risk of congenital abnormalities,[59] and one study found emtricitabine associated with decreased risk of congenital anomalites.[64] The Antiretroviral Pregnancy Registry

found zidovudine associated with increased risk of overall birth defects, but ritonavir associated with decreased risk.[83]

One of the cohort studies (n=2,580) also reported specific categories of birth defects in children exposed in utero to ART.[71] Atazanavir was associated with increased risk for congenital musculoskeletal and skin anomalies (adjusted ORs 2.57, 95% CI 1.30 to 5.08; 6.01, 95% CI 1.43 to 25.3, respectively). Ritonavir as booster therapy was associated with musculoskeletal birth defects (adjusted OR 1.79, 95% CI 1.02 to 3.14) and zidovudine was associated with increased risk for male genital defects (primarily hypospadias and cryptorchidism, adjusted OR 3.18, 95% CI 1.10 to 9.22). An additional cohort study found exposure to ART during the first trimester associated with malformation of the small intestine (adjusted OR 10, 95% CI 2.85 to 37)[77] but there was no increase in risk of birth defects with prenatal ART exposure on the urogenital, musculoskeletal, nervous, and circulatory systems.

Cardiovascular Congenital Anomalies

The 2012 USPSTF review included one cohort study[92] that found no association between in utero exposure to zidovudine and acute or chronic abnormalities in left ventricular structure or function, though another study[93] found an association between in utero ART and echocardiographic findings with unknown clinical significance in children up to 2 years of age.

We identified one subsequent RCT and two cohort studies (in 3 publications) that also reported somewhat mixed results on the association between ART exposure and cardiac findings[63,68,71] (**Appendix B2**). A U.S. cohort study (the Surveillance Monitoring for ART Toxicities [SMARTT] study) of 2,580 HIV-uninfected children born between 1995 and 2008 with in utero ART exposure found no currently recommended ART drug associated with increased risk of cardiovascular defects, though there was a trend toward increased risk with ritonavir (adjusted OR 1.83, 95% CI 0.96 to 3.49).[71] A large French cohort study of 12,888 children born between 1994 and 2010 found first trimester exposure to zidovudine associated with congenital heart defects compared with no zidovudine exposure (1.5% vs. 0.77%; adjusted OR 2.2, 95% CI 1.5 to 3.2).[63,64] The most common condition was ventricular septal defect. A second analysis of 400 HIV-uninfected children exposed to ART in utero[68] found that at 2 to 7 years of age (median 4 years), exposure to some antiretroviral drugs, particularly during the first trimester, was associated with reduced stress velocity index, reduced left ventricular short-axis dimension, and increased left ventricular posterior wall thickness. None of the echocardiographic findings was associated with significant cardiovascular compromise.

Another study evaluated the association between in utero exposure to ART and echocardiographic measures. A nested RCT within a cohort (PRIMEVA ANRS 135) of combination ART (zidovudine, lamivudine, and ritonavir-boosted lopinavir) versus protease inhibitor monotherapy (ritonavir-boosted lopinavir alone) performed echocardiographic assessments at 1 month (n=53) and 1 year (n=42). There was no difference in echocardiographic parameters in boys, but in girls combination therapy was associated with higher left ventricular shortening fraction at 1 month (a measure of decreased left ventricular systolic function, p=0.02) and a trend toward increased posterior wall thickness at 1 year (p=0.07).[63]

A third study (n=367) found no effect of ART vs. no ART exposure during the first trimester on cardiovascular congenital anomalies (adjusted OR 0.75, 95% CI 0.31 to 1.85).[77]

Neurodevelopmental Outcomes in Children

The 2012 USPSTF review included three cohort studies that found no association between in utero exposure to ART and long-term adverse effects on child growth and development.[94-96] We identified two publications of a U.S. surveillance cohort (the SMARTT study) of HIV-exposed, uninfected infants and children (**Appendix B2**).[69,72] One study measured the Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI-III) at 5 years of age (n=369) and the Wechsler Abbreviated Scale of Intelligence (WASHI) and the Wechsler Individual Achievement Test (WIAT-II-A) at 7, 9, 11, and 13 years of age (n=451).[69] There was no association between in utero exposure to ART and lower scores on these tests, although test scores were lower overall than population norms. In younger children, in utero exposure to tenofovir was associated with higher performance intelligence quotient, based on the WPPSI-III than those not exposed to tenofovir ($p<0.05$). Another publication from the SMARTT study found in utero exposure to combination ART associated with less neurodevelopmental impairment than no in utero exposure to ART (adjusted RR 0.47, 95% CI 0.27 to 0.83) (**Appendix B2**).[72]

Maternal Harms

The 2012 USPSTF review included three studies that found receipt of ART during pregnancy associated with increased risk of gestational diabetes (adjusted OR 3.5, 95% CI 1.2 to 10) and anemia (adjusted OR 1.6, 95% CI 1.1 to 2.4) compared to no ART.[97-99] We identified no new studies on the association between use of ART during pregnancy versus no ART and risk of diabetes. One RCT conducted in three African countries (n=8848) of women with CD4 counts of 200 to 500 cells/mm^3 found no difference in risk of anemia between combination ART (zidovudine, lamivudine, and ritonavir-boosted lopinavir) beginning between 28 and 36 weeks gestation versus zidovudine monotherapy starting from 34 to 36 weeks gestation until onset of labor followed by zidovudine and a single dose of nevirapine at the onset of labor (**Appendix B2**).[54] Women were given iron and folic acid supplementation upon study enrollment.

In the previously discussed PROMISE trial (n=3,490, see Key Question 4 for study details), antenatal zidovudine-based combination ART was associated with a higher rate of maternal grade 2 or higher adverse events than zidovudine alone (21% vs. 17%, $p=0.008$, specific adverse events not reported) and increased risk of abnormalities in blood chemistries (5.8% vs. 1.3%, $p<0.001$), primarily elevation in alanine aminotransferase levels.[52] There was also an increased risk of abnormal blood chemistries (not specified) with tenofovir-based ART than with zidovudine monotherapy (2.9% vs. 0.8%, $p=0.03$). Few women left the study due to adverse events.

Chapter 4. Discussion

Summary of Review Findings

This report updates a 2012 USPSTF review on prenatal screening for HIV infection.[1,2] Evidence reviewed for this update is summarized in **Table 4**. As in the 2012 USPSTF review, we found no direct evidence on effects of prenatal screening versus no screening on risk of mother-to-child HIV transmission or maternal or infant clinical outcomes. We also identified no study on the yield of repeat prenatal screening versus one-time screening or different frequencies of screening for HIV in pregnancy. Although three studies conducted in the United States or the United Kingdom identified no cases of HIV infection among women who were rescreened for HIV during the third trimester of pregnancy,[41-43] results were difficult to interpret because the HIV risk of women who underwent rescreening was unclear, and not all women underwent rescreening. As discussed in the prior USPSTF report, the yield of repeat prenatal screening depends on HIV infection incidence during pregnancy. In addition, detecting HIV acquired during pregnancy may be important because some data suggest that acquisition of HIV during pregnancy is associated with markedly higher risk of mother-to-child transmission than HIV acquired prior to pregnancy.[100]

New evidence identified for this update[45-48] confirm findings from the 2012 USPSTF review that full-course combination ART is highly effective at reducing the risk of mother-to-child transmission, with some cohort studies reporting rates of mother-to-child transmission of less than 1 percent when started early in pregnancy.[45,48] Cohort studies and RCTs also found that combination therapy started in the second or third trimester are effective at reducing the risk of mother-to-child transmission. Shorter courses of ART were not as effective as full-course regimens, but also reduce risk of mother-to-child transmission compared with no ART, supporting benefits of screening and initiation of therapy later in pregnancy.[52,101-103]

New evidence on harms of ART was also largely consistent with the 2012 USPSTF review. Although some ART agents and regimens may be associated with increased risk of infant or maternal harms, such harms may be mitigated or reduced through appropriate selection of ART regimens. As in the prior USPSTF review, evidence from primarily observational studies found prenatal combination ART with a boosted protease inhibitor associated with increased risk of preterm delivery.[52,58,65,75] An African RCT found tenofovir-containing, lopinavir/ritonavir-based combination ART associated with increased risk of early infant death than zidovudine-containing, lopinavir/ritonavir-based combination ART.[52] However, there were methodological limitations with this trial, including two periods with different randomization protocols, and different rates of some adverse birth outcomes depending on period of randomization. The RCT found no difference in early infant death between tenofovir-based combination ART and treatment with zidovudine alone and no difference between treatments in risk of stillbirth. Tenofovir is a preferred backbone NRTI for use in pregnancy in most, but not all, guidelines due to its demonstrated efficacy, acceptable toxicity, ease of use, and no established teratogenicity; however, the use of lopinavir, rather than a preferred protease inhibitor, makes the ART combination evaluated in this trial an alternative regimen (lopinavir is associated with more nausea than preferred PIs).[83] The increased risk of early infant death in the trial could be related to a higher risk of very preterm delivery associated with this tenofovir-containing ART regimen, which is associated with increased risk of infant mortality in low-income settings. Other African

studies found no association between tenofovir-based ART and risk of stillbirth[66,75,76] or neonatal death.[75,78]

For other birth outcomes (low birth weight, small for gestational age, stillbirth, overall birth defects), results were mixed and depended on the specific antiretroviral drug or drug regimen given and timing of prenatal therapy. As in the prior USPSTF review, some evidence indicated that ART may be associated with cardiac findings such as ventricular septal defects[63,64] and echocardiographic changes,[63,68] though the clinical significance of findings is unclear. Evidence on congenital abnormalities was limited by small numbers of studies and imprecise estimates, though some studies found exposure to different drugs in the first trimester associated with increased risk of congenital abnormalities. Studies in older children exposed to ART in utero suggested no association with worse neurodevelopmental outcomes than unexposed children.[69,72]

Evidence on long-term maternal harms associated with short-term exposure to ART during pregnancy, or ART started during pregnancy and continued after pregnancy remains sparse, though one new study found evidence of increased short-term nonspecific adverse events.[52] Women found to be HIV-infected through prenatal screening would also benefit from standard HIV treatments following pregnancy, including long-term combination ART, prophylaxis from opportunistic infections, immunizations, and indicated screenings.[83,104]

Limitations

We excluded non-English-language articles, which could result in language bias, though we identified no non-English-language studies that would have met inclusion criteria. We did not attempt to pool studies because of differences in study designs, populations, study setting, antiretroviral regimens evaluated, and outcomes assessed. Because we could not pool, we also we could not formally assess for publication bias with graphical or statistical methods. We included observational studies, which are more susceptible to bias and confounding than well-conducted RCTs, though we restricted inclusion to observational studies that performed statistical adjustment for potential confounding. Another limitation is that RCTs of combination ART have only been conducted in Africa. The applicability of studies conducted in resource-poor and high-prevalence settings to U.S. practice is limited by differences in the antiretroviral drugs evaluated, evaluation of shorter regimens, inclusion of women who breastfeed, and other factors. Although we focused on new studies published since 2012, in most studies results were reported for individual ART agents and classes, rather than for currently recommended ART regimens, which could reduce applicability of findings to current U.S. practice. Restricting analyses to studies in which patients received treatment after 2006 (the earliest year a current preferred regimen was approved), or in whom results for currently recommended regimens could clearly be identified, did not appear to change conclusions, though formal stratified analyses were not possible.

Emerging Issues/Next Steps

ART regimens for use during pregnancy and indications for initiating long-term ART continue to evolve. Regularly updated guidelines on selection of ART in pregnant women are available.[83]

Relevance for Priority Populations, Particularly Racial/Ethnic Minorities

HIV disproportionately impacts women from ethnic and racial minorities, who often have less access to prenatal care, leading to reduced opportunities for early screening and initiation of ART during pregnancy. Identification of HIV infection during pregnancy provides an opportunity to link affected women to long-term care and treatment. Therefore, improving access to prenatal care is an important challenge for reducing the impact of HIV infection in these populations.

Future Research

Although there are no studies comparing the effects of screening for HIV in pregnancy versus no screening, such studies may no longer be indicated given epidemiological evidence showing marked decreases in the number of children with perinatally acquired HIV infection in the United States and strong evidence on the effectiveness of ART on preventing mother-to-child transmission. Studies comparing one-time screening versus repeat screening or that perform rescreening in well-defined cohorts of women would be helpful for understanding the yield of rescreening and for understanding when rescreening is indicated. Future research is needed to further clarify the effectiveness and harms of currently recommended antiretroviral regimens, understand effects of in utero exposure to ART on pregnancy outcomes, and long-term harms in exposed children, in order to optimize selection of ART regimens during pregnancy, and to understand the effects of screening and ART in pregnant adolescents.

Conclusions

Combination ART is highly effective at reducing risk of mother-to-child HIV transmission. The USPSTF previously determined that avoidance of breastfeeding and Cesarean delivery in women with HIV RNA levels >1000 copies/mL near the time of delivery is also effective at reducing mother-to-child transmission, and that prenatal screening is accurate at diagnosing HIV infection. Use of certain ART regimens during pregnancy is associated with increased risk of preterm delivery and other adverse pregnancy outcomes. Although more evidence is required to better understand short-and long-term maternal and infant harms, selection of ART regimens may help mitigate or reduce harms.

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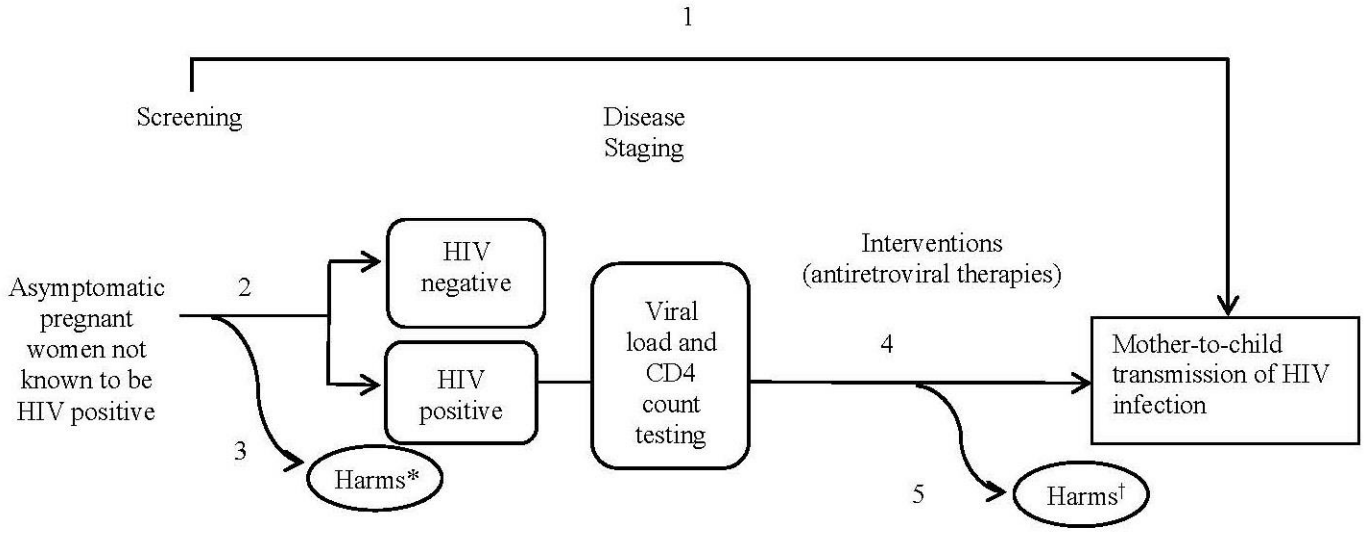
Figure 1. Analytic Framework



* Harms of screening include false-positive results, anxiety and effects of labeling, and partner discord, abuse, or violence.
† Harms of treatment include adverse maternal and infant outcomes associated with use of antiretroviral therapy.

Abbreviation: HIV=human immunodeficiency virus.

Table 1. U.S.-relevant 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[105] *Included in prior report*	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 Timing of infant HIV testing: NR	A: 18% (39/214) B: 8.6% (10/116) C: 0.6% (1/159) p<0.001	Fair
Harris et al, 2007[106] Enhanced Perinatal Surveil-lance project *Included in prior report*	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 Timing of infant HIV testing: Followup by health department every 6 months until HIV status determined; Analyses of data over 3 years	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[107] *Included in prior report*	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 Timing of infant HIV testing: Overall NR; some reported having results within 72 hours of birth	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[108] *Included in prior report*	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 Timing of infant HIV testing: NR	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

Author, Year	Setting	Intervention	Sample	Mother-to-child transmission rates by treatment group	Quality rating
Chiappini et al, 2013[47]	European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC); 7 cohorts from 6 countries; (Ukraine excluded due to heterogeneity)	A. 3 or more drugs B. 2 drugs C. 1 drug D. No therapy E. Unknown	4459 high risk mother-infant pairs due to: no therapy (28%), only intrapartum prophylaxis (17%), ART received but mothers viral load remained detectable (55%); % screen-detected HIV during pregnancy NR; 45% no antenatal or only intrapartum ART; None breastfed (Ukraine cohort not included in transmission analysis) Timing of infant HIV testing: NR	A. 2.8% (65/2355); AOR 0.36 (95% CI 0.23 to 0.57), p<0.001 B. 1.2% (3/255); AOR 0.12 (95% CI 0.04 to 0.40), p<0.001 C. 3.1% (21/681); AOR 0.33 (95% CI 0.19 to 0.55), p<0.005 D. 14.3% (158/1107); AOR 1 reference	Fair
Lu et al, 2014[46]	Canada, Canadian Perinatal HIV Surveillance Program (CPHSP)	ART A. Complete ART during pregnancy, ZDV during labor, infant received ZDV B. Incomplete ART C. No therapy	645 mother-child pairs analyzed Rate of Cesarean section 43% Breastfeeding rate NR Followup NR Proportion of mothers born in HIV-endemic country 65% Analysis of data over 12 year study period; % screen-detected HIV during pregnancy NR; 13% were considered late diagnoses (diagnosed at or after delivery) Timing of infant HIV testing: NR	A. 1% (3/251) B. 2% (8/336) C. 67% (39/58)	Fair
Mandelbrot et al, 2015[45]	France, national prospective multicenter French Perinatal Cohort (ANSR-EPF)	First ART A. Triple NRTI B. PI-based C. NNRTI-based D. Three classes E. Other	8075 mother-child pairs analyzed Rate of Cesarean section 57% Breastfeeding rate 0% Followup: Clinicians encouraged to followup from birth to 18-24 months Analysis of data over 11 year study period; % screen-detected HIV during pregnancy NR; 57% initiated ART during pregnancy; 72% of mothers born in Africa Timing of infant HIV testing: NR	Transmission rates did not differ based on choice of initial ART (PI- and NNRTI-based) Transmission based on timing of ART initiation Before conception 0.2%; AOR 1 (ref) 1st trimester 0.4%; AOR 2.9 (95% CI 0.6 to 17.7) 2nd trimester 0.9%; AOR 6.0 (95% CI 1.7 to 29.7) 3rd trimester 2.2% AOR 7.8 (95% CI 2.1 to 28.8)	Fair
Mor et al, 2017[49]	Israel, all HIV infected women who delivered in Israel (and were citizens) between 1988 and 2011	A. HAART (392) B. no HAART (404)	796 mother-infant pairs; 82% of mother born in Ethiopia; 8 infants were breastfed Timing of infant HIV testing: NR	HAART vs. no HAART during pregnancy: AOR 0.4, 95% CI 0.1 to 0.8 Overall transmission: 25/796 (3%) Transmission with HAART and vaginal delivery: 1.5% Transmission with HAART and C-section: 0.6%	Fair

Author, Year	Setting	Intervention	Sample	Mother-to-child transmission rates by treatment group	Quality rating
Tookey et al, 2016[48]	UK and Ireland, National Study of HIV in Pregnancy and Childhood (NSHPC)	A. LPV/r + ZDF + 3TC B. LPV/r + FTC + TDF C. LPV/r + ABC + 3TC D. LPV/r + other or missing NRTIs	4,864 enrolled; 2406 mother-infant pairs (2008-2012); 67% were given LPV/r + ZDF + 3TC; proportion of mothers born in Sub-Saharan Africa 77%; some mother-infant pairs at high risk for HIV transmission likely also counted in the Chiappini study Timing of infant HIV testing: NR	By timing of LPV/r initiation: Overall: 12/2406 (0.5%, 95% CI 0.2% to 0.8%) Before conception: 2/635 (0.3%, 95% CI 0.1% to 1.1%) First trimester: 0/77 (0%) Second trimester: 5/1397 (0.4%, 95% CI 0.2% to 0.8%) Third trimester: 5/264 (1.9%, 0.8% to 4.4%)	Fair

Abbreviations: 3TC=lamivudine; ABC=abacavir; AOR=adjusted odds ratio; ART=antiretroviral therapy; CI=confidence interval; FTC=emtricitabine; HAART=highly active antiretroviral therapy; HIV=human immunodeficiency virus; LPV/r=lopinavir/ritonavir; NR=not reported; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI=nucleoside/nucleotide reverse transcriptase inhibitors; PI=protease inhibitor; OR=odds ratio; UK=United Kingdom; ZDF=tenofovir disoproxil fumarate; ZDV=zidovudine.

Table 2. 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[101] Other publication: Chi, 2007[109] *Included in prior report*	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[51] Other publication: Kesho Bora Study Group, 2010[110] *Included in prior report*	Burkina Faso, Kenya, South Africa	From 28 weeks: A: ZDV + 3TC + LPV/r B: ZDV	A: ZDV, 3TC, LPV/r B: ZDV + sdNVP	A: Maternal ZDV, 3TC, LPV/r 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-trimoxazole 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 to13 RR reduction 0.43 p=0.03	Good
Gray et al, 2006[102] *Included in prior report*	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 regime 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

Author, year	Setting	Prenatal intervention	Peripartum intervention	Postpartum intervention	Sample	Mother-to-child transmission rates by treatment group	Quality rating
Shapiro et al, 2010[50] *Included in prior report*	Botswana	Randomization groups† From 26 weeks: A: ABC + ZDV + 3TC B: LPV/r + ZDV + 3TC Observational group‡ From 18 weeks: C: NVP + ZDV + 3TC	A: ABC + ZDV + 3TC B: LPV/r + 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[103] *Included in prior report*	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[111] *Included in prior report*	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
Fowler et al, 2016[50]	India, Malawi, South Africa, Tanzania, Uganda, Zambia, Zimbabwe	Randomized From 14 weeks: A. ZDV B. ZDV + 3TC + LPVr C. TDF + FTC + LPVr	A. sdNVP (ZDV only group)	A. TDF + FTC (6-14 days; ZVD only group) B.ZDV + 3TC + LPV/r C. TDF + FTC + LPV/r	3202 live born infants; mothers primarily black African; 92% breastfed; % screen-detected HIV during pregnancy NR	A. 1.8% (25/1386) B. 0.5% (7/1385) C. 0.6% (2/325) B + C vs. A difference in percentage points -1.3, 95% CI -2.1 to -0.4	Fair

*Began after protocol change in December 2006 (enrollment commenced June 2005).
†Women with CD4 count >200 cells/mm^3.

‡Women with CD4 count <200 cells/mm^3 or with AIDS defining illness.
§Study not powered for between group comparisons of transmission rates
‖ART was offered to women with CD4 counts <200 cells/mm^3 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.
** 369/2156 women randomized as part of a placebo controlled toxicity study in Uganda to NVP- or ABC-containing first-line ART.
Abbreviations: 3TC=lamivudine; ABC=abacavir; ABT-378=lopinavir; ART=anti-retroviral therapy; CI=confidence interval; d4T=stavudine; ddI=didanosine; FTC=emtricitabine; HIV=human immunodeficiency virus; LPV/r=lopinavir+ritonavir; NVP=nevirapine; RR=relative risk; RTV=ritonavir; sdNVP=single dose nevirapine; SD=standard deviation; TDF=tenofovir; ZDV=zidovudine.

Table 3. Studies Examining the Association between Birth Outcomes and HIV Antiretroviral Therapy

Harm category	Study, year Country Study Name	ART regimen (n;%)	Birth Outcome Definition	Birth Outcome Distribution	Magnitude of Risk: Adjusted OR (95% CI), p-value
Preterm Delivery	Cotter et al, 2006[85] USA University of Miami study *Included in prior report*	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	Preterm delivery <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)
Preterm Delivery	Grosch-Warner et al, 2008[87] Germany, Austria *Included in prior report*	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	Preterm delivery <36 weeks	<36 weeks 34%* (crude rate)	A. 1 reference C. ART (-) PI: 0.89 (0.38 to 2.12), p=0.8 D. ART (+) PI: 3.40 (1.13 to 10.2), p=0.03
Preterm Delivery	Powis et al, 2011[84] Botswana *Included in prior report*	A: PI group (lopinavir/ritonavir/ zidovudine/lamivudine) (n=275; 49%) B: NRTI group, TZV (abacavir/zidovudine/lamivudine) (n=285; 51%) Total N=560	Preterm delivery <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	A. ART (+) PI: 2.03 (1.26 to 3.27), p=0.004 B. ART (-) PI (NRTI-based): 1.0
Preterm Delivery	Schulte et al, 2007[86] USA Pediatric Spectrum of HIV Disease cohort *Included in prior report*	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	Preterm delivery <37 weeks	Mean 37 weeks (range 26-42)	C. 1 reference E. 1.21 (1.04 to1.48), p-value NR
Preterm Delivery	Townsend et al, 2007[88] UK, Ireland *Included in prior report*	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	Preterm delivery <37 weeks	<37 weeks 14.1%* <35 weeks 7.8% <32 weeks 1.4%	A. <37 weeks: 1.39 (1.05 to1.83) p=0.02 A. <35 weeks: 2.02 (1.35 to 3.04), p=0.001 A. <32 weeks: 2.63 (1.3 to 5.33), p=0.007 B. 1 reference all comparisons

Harm category	Study, year Country Study Name	ART regimen (n;%)	Birth Outcome Definition	Birth Outcome Distribution	Magnitude of Risk: Adjusted OR (95% CI), p-value
Preterm Delivery	Chagomerana et al, 2017[74] Malawi	Started ART before 27 weeks or not at all A. ART (2,909; 95%) B. no ART (165; 5%) Total N=3,074	Preterm delivery 27 weeks to 37 weeks	24%	Deliveries after 27 weeks: A. 1 reference B. aRR 1.14 (0.84 to 1.55)
Preterm Delivery	Chen et al, 2012 [56] Botswana Approx. 87% received ZDV/3TC/NVP	A. Initiated HAART during pregnancy (ZVD/3TC/NVP or ZVD/3TC/LVPr (1101; 12%) B. Initiated ZVD only during pregnancy (4625; 51%) C. No ART (1234; 13%) D. HAART continued from before pregnancy (2189; 24%) Total N=9,149	Preterm delivery <37 weeks	24%*	Initiated HAART vs. initiated ZDV: 1.4 (1.2 to 1.8) Continued HAART vs. all others: 1.2 (1.1 to 1.4)
Preterm Delivery	Duryea, 2015[80] USA University of Texas study	A. ART with PI (597; 59%) B. ART without PI (230; 23%) C. No ART (177; 18%) Total N=1,004	Preterm delivery < 37 weeks	13% to 21% depending on ART regimen	A. 1 reference B. 0.9 (0.5 to 1.5) C. 1.0 (0.5 to 2.0)
Preterm Delivery	Kakkar et al, 2015[58] Canada	A. NRTI/NNRTI (159; 30%) B. Boosted PI (119; 23%) C. Unboosted PI (195; 37%) D. No treatment (52; 10%) Total N=525	Preterm delivery <37 weeks	14%*	A. 0.67 (0.27 to 1.63), p=0.37 B. 2.17 (1.05 to 4.51), p=0.038 C. 1 reference D. 1.50 (0.33 to 6.78), p=0.60
Preterm Delivery	Kreitchmann et al, 2014[60] Latin America Caribbean	At least 28 days 3rd trimester: A. HAART + PI (888; 59%) B. HAART no PI (410; 27%) C. Non-HAART (134; 9%) D. No ARV (80; 5%) Total N=1,512	Preterm delivery <37 weeks	<37weeks 21%*	Receiving ART at conception vs. no ART at conception: 1.53 (1.11 to 2.09)
Preterm Delivery	Li et al, 2016[61] Tanzania	A. Initiated ZDV during pregnancy (1768; 53%) B. Initiated HAART during pregnancy (512; 15%) C. Continued HAART from before pregnancy (582; 18%) D. No ART (452; 14%) Total N=3,314	Preterm delivery <37 weeks Very preterm <34 weeks	No infants had HIV <37 weeks 29%* <34 weeks 10%*	HAART vs. ZDV started during pregnancy: <37 weeks: 0.85 (0.70 to 1.02), p=0.14 <34 weeks: 0.87 (0.60 to 1.25), p=0.45

Harm category	Study, year Country Study Name	ART regimen (n;%)	Birth Outcome Definition	Birth Outcome Distribution	Magnitude of Risk: Adjusted OR (95% CI), p-value
Preterm Delivery	Lopez et al, 2012[62] Spain	A. HAART entire pregnancy (226; 44%) B. HAART 2nd half of pregnancy only (72; 14%) C. PI during pregnancy (178; 34%) D. No HAART (221; 43%) Total N=697	Preterm delivery <37 weeks	20%*	Spontaneous preterm birth: A. 0.55 (0.20 to 1.51) B. 0.55 (0.18 to 1.68) C. 1.95 (0.87 to 4.38) D. HIV uninfected women Iatrogenic preterm birth: A. 3.42 (0.80 to 14.63) B. 6.16 (1.42 to 26.8) C. 0.44 (0.18 to 1.10) D. HIV uninfected women
Preterm Delivery	Moodley et al, 2016[66] South Africa	A. No ART (148; 4%) B. AZT + NVP (974; 26%) C. D4T + 3TC + NVP (907; 25%) D. EFV + TDF + FTC (1666; 45%) Total N=3,695	Preterm delivery <37 weeks	22.3%	A. 1 reference B. 0.20 (0.08 to 0.51), p=0.001 C. 0.21 (0.08 to 0.55), p=0.001 D. 0.31 (0.11 to 0.90), p=0.03
Preterm Delivery	Pintye et al, 2017[78] Kenya and Uganda	A. TDF-containing ART (208; 49%) B. NonTDF-containing ART (214; 51%) Total N=422	Preterm delivery <37 weeks	8%	A vs. B: adjusted prevalence rate ratio 0.37 (0.15 to 0.89), p=0.03
Preterm Delivery	Ramokolo et al, 2017[79] South Africa	A. Postconception ART (780; 30%) B. ZDV (873; 34%) C. No ART (330; 13%) D. Preconception ART (616; 24%) Total =2,599	Preterm delivery <37 weeks	12.5%	A. 1 reference B. 1.4 (0.9 to 2.0), p=0.11 C. 1.9 (1.1 to 3.1), p=0.01 D. 1.7 (1.1 to 2.5), p=0.02
Preterm Delivery	Rough et al, 2018[82] USA PHACS and IMPAACT	A. TDF + FTC + LPV/r (128; 8%) B. ZDV + 3TC + LPV/r (954; 59%) C. TDF + FTC + ATV/r (539; 33%) Total=1,621	Preterm delivery <37 weeks Very preterm delivery <34 weeks	18% preterm delivery 5% very preterm delivery	Preterm delivery, adjusted OR: A vs. B: 0.90 (0.60 to 1.33) C vs. B: 0.69 (0.51 to 0.94) A vs. C: 1.14 (0.75 to 1.72) Very preterm delivery, unadjusted OR: A vs. B: 0.85 (0.34 to 2.13) C vs. B: 1.04 (0.60 to 1.83) A vs. C: 0.82 (0.31 to 2.17)

Harm category	Study, year Country Study Name	ART regimen (n;%)	Birth Outcome Definition	Birth Outcome Distribution	Magnitude of Risk: Adjusted OR (95% CI), p-value
Preterm Delivery	Short et al, 2013[67] UK	A. ZDV (65; 20%) B. Dual NRTI (7; 2%) C. Triple NRTI (5; 2%) D. Short-term combination ART (59; 18%) E. Preconception combination ART (131; 40%) F. New continuous combination ART (56; 17%) G. No therapy (8; 2%) Total N=331	Preterm delivery <37 weeks	13%*	Short-term combination ART vs. ZVD: 5.00 (1.49 to 16.79)
Preterm Delivery	Sibiude et all, 2012[65] France	A. HAART (6738; 59%) a. HAART w/boosted PI (1066; 9%) b. HAART nonboosted PI (187; 2%) B. Dual therapy (1664; 15%) C. Monotherapy (2975; 26%) Total N=11,377	Preterm delivery <37 weeks	14%*	A. 1.69 (1.38 to 2.07) a. boosted PI 2.03 (1.06 to 3.89), p=0.03 vs. nonboosted PI B. 1.24 (0.96 to 1.60) C. 1 reference
Preterm Delivery	Snijdewind et al, 2018 [81] The Netherlands	A. PI-based (928; 67%) B. NNRTI-based (438; 31%) C. Both or NRTI (12; 1%) Total=1,378	Preterm delivery <37 weeks	15%	Unadjusted OR: A. 1 (reference) B. 1.30 (0.95 to 1.77), p=0.11 C. 1.15 (0.41 to 3.19), p=0.78
Preterm Delivery	Watts et al, 2013[70] USA PHACS/SMARTT	A. Combination, with PI (1319; 74%) B. Combination, with NNRTI, no PI (160; 9%) C. Combination, with ≥3 NRTIs (193; 10%) Total N=1,672	Preterm delivery <37 weeks	Any preterm birth: <37 weeks 19%* Spontaneous preterm birth: <37 weeks 10%*	Any preterm birth: A. 1.49 (0.83 to 2.67), p=0.18 B. 1.28 (0.62 to 2.66), p=0.50 C. 1.04 (0.50 to 2.14), p=0.93) Spontaneous preterm birth: A. 1.41 (0.66 to 2.99), p=0.38 B. 1.53 (0.62 to 3.81), p=0.36 C. 0.88 (0.34 to 2.29), p=0.80) (all vs. mono or dual therapy)
Preterm Delivery	Zash et al, 2016[76] Botswana	All CD4 counts: A. TDF/FTC/EFV (1054; 33%) B. other ART (2172; 64%) Total N=3226 CD4 counts >350 A. TDF/FTC/EFV (335; 31%) B. ZDF (752; 69%) Total N=1,087	Preterm delivery <37 weeks	27%	A vs. B (all CD4 counts): 0.7 (0.5 to 1.1) A vs. B (CD4 >350): 1.1 (0.6 to 2.1)

Harm category	Study, year Country Study Name	ART regimen (n;%)	Birth Outcome Definition	Birth Outcome Distribution	Magnitude of Risk: Adjusted OR (95% CI), p-value
Preterm Delivery	Zash et al, 2017[75] Botswana	A. TDF/FTC/EFV (2472; 49%) B. TDF/FTC/NVP (760; 15%) C. TDF/FTC/LPV/r (231; 5%) D. ZDV/3TC/NVP (1365; 27%) E. ZDV/3TC/LPV/r (167; 3%) Total N=4,995	Preterm delivery <37 weeks Very preterm delivery <32 weeks	22% 5%	Adjusted Relative Risks: A. 1 reference B. 0.88 (0.75 to 1.05) preterm delivery B. 1.23 (0.84 to 1.80) very preterm delivery C. 1.12 (0.88 to 1.43) preterm delivery C. 1.36 (0.76 to 2.45) very preterm delivery D. 1.14 (1.01 to 1.29) preterm delivery D. 1.44 (1.07 to 1.95) very preterm delivery E. 1.36 (1.06 to 1.75) preterm delivery E. 2.21 (1.29 to 3.79) very preterm delivery
Low Birthweight	Kreitchmann et al, 2014[60] Latin America Caribbean	At least 28 days 3rd trimester: A. HAART + PI (888; 59%) B. HAART no PI (410; 27%) C. Non-HAART (134; 9%) D. No ARV (80; 5%) Total N=1,512	Low birthweight <2500 g	16%*	HAART w/PI vs. no ART: 0.59 (0.28 to 1.26) HAART no PI vs. no ART: 0.33 (0.14 to 0.74) Non-HAART 0.40 (0.15 to 1.05) vs. no ART
Low Birthweight	Moodley et al, 2016[66] South Africa	A. No ART (148; 4%) B. AZT + NVP (974; 26%) C. D4T +3TC + NVP (907; 25%) D. EFV + TDF + FTC (1666; 45%) Total N=3,695	Low birthweight <2500 g	13.5%	A. 1 reference B. 0.06 (0.02 to 0.18), p<0.001 C. 0.09 (0.03 to 0.24), p<0.001 D. 0.12 (0.04 to 0.37), p<0.001
Low Birthweight	Ramokolo et al, 2017[79] South Africa	A. Postconception ART (780; 30%) B. ZDV (873; 34%) C. No ART (330; 13%) D. Preconception ART (616; 24%) Total =2,599	Low birthweight <2500 g	10.7%	A. 1 reference B. 0.8 (0.6 to 1.1), p=0.14 C. 1.1 (0.8 to 1.6), p=0.47 D. 0.9 (0.6 to 1.3), p=0.54
Low Birthweight	Rough et al, 2018[82] USA PHACS and IMPAACT	A. TDF + FTC + LPV/r (128; 8%) B. ZDV + 3TC + LPV/r (954; 59%) C. TDF + FTC + ATV/r (539; 33%) Total=1,621	Low birthweight <2500 g Very Low birthweight <1500 g	18% Low birth weight 2% Very low birth weight	Low birth weight, adjusted OR: A vs. B: 1.13 (0.78 to 1.64) C vs. B: 0.80 (0.60 to 1.09) A vs. C: 1.45 (0.96 to 2.17) Very low birth weight, unadjusted OR: A vs. B: 0.41 (0.06 to 3.06) C vs. B: 0.89 (0.40 to 2.00) A vs. C: 0.49 (0.07 to 3.57)
Low Birthweight	Siberry et al, 2012[73] USA PHACS/SMARTT	A. TDF-containing ART (449; B. nonTDF-containing ART (1580; Total=2,029	Low birthweight <2500 g	19%	A vs B: 0.73 (0.48 to 1.11), p=0.14
Low Birthweight	Snijdewind et al, 2018 [81] The Netherlands	A. PI-based (928; 67%) B. NNRTI-based (438; 31%) C. Both or NRTI (12; 1%) Total=1,378	Low birthweight <2500 g	16%	Unadjusted OR: A. 1 (reference) B. 1.19 (0.88 to 3.97), p=0.26 C. 1.47 (0.54 to 3.97), p=0.45

Harm category	Study, year Country Study Name	ART regimen (n;%)	Birth Outcome Definition	Birth Outcome Distribution	Magnitude of Risk: Adjusted OR (95% CI), p-value
Small for Gestational Age	Aaron et al, 2012 [55] USA Drexel University study	A. NRTIs + NNRTI (39; 21%) B. NRTI + PI (117; 64%) C. NRTIs alone (27; 15%) Total N=183	SGA <10th percentile of birth weight by gestational age (based on infant gender and mother's parity)	<10th percentile 31%* <3rd percentile 13%*	<10th percentile: A. 0.28 (0.10 to 0.75), p<0.05 vs. others B. 1.68 (0.79 to 3.55), p>0.05 vs. others <3rd percentile: A. 0.16 (0.03 to 0.91), p<0.05 vs. others B. 2.73 (0.83 to 9.00), p>0.05 vs. others
Small for Gestational Age	Chen et al, 2012 [56] Botswana	A. Initiated HAART during pregnancy (ZVD/3TC/NVP or ZVD/3TC/LVP/r (1101; 12%) B. Initiated ZVD only during pregnancy (4625; 51%) C. No ART (1234; 13%) D. HAART continued from before pregnancy (2189; 24%) Total N=9,149	SGA<10th percentile	13.5%*	Initiated HAART vs. initiated ZDV: 1.5 (1.2 to 1.9) Continued HAART vs. initiated HAART: 1.3 (1.0 to 1.5) Continued HAART vs. all others: 1.8 (1.6 to 2.1)
Small for Gestational Age	Duryea, 2015[80] USA University of Texas study	A. ART with PI (597; 59%) B. ART without PI (230; 23%) C. No ART (177; 18%) Total N=1,004	SGA <10th percentile of birth weight by gestational age	4% to 10% depending on ART regimen	A. 1 reference B. 1.3 (0.8 to 1.9) C. 1.1 (0.6 to 2.0)
Small for Gestational Age	Li et al, 2016 [61] Tanzania	A. Initiated ZDV during pregnancy (1768; 53%) B. Initiated HAART during pregnancy (512; 15%) C. Continued HAART from before pregnancy (582; 18%) D. No ART (452; 14%) Total N=3,314	SGA <10th percentile of birth weight by gestational age; <3rd percentile for severe SGA	3-10th percentile 9%* <3rd percentile 11%*	HAART vs. ZDV started during pregnancy: 3-10th %: 1.09 (0.88 to 1.35), p=0.41 <3rd %: 1.47 (1.09 to 1.98), p=0.01
Small for Gestational Age	Moodley et al, 2016[66] South Africa	A. No ART (148; 4%) B. AZT + NVP (974; 26%) C. D4T +3TC + NVP (907; 25%) D. EFV + TDF + FTC (1666; 45%) Total N=3,695	SGA	8.2%	A. 1 reference B. 0.37 (0.10 to 1.45), p=0.15 C. 0.29 (0.08 to 1.07), p=0.06 D. 0.25 (0.07 to 0.87), p=0.03
Small for Gestational Age	Ramokolo et al, 2017[79] South Africa	A. Postconception ART (780; 30%) B. ZDV (873; 34%) C. No ART (330; 13%) D. Preconception ART (616; 24%) Total =2,599	SGA <10th percentile of birth weight by gestational age	14.9%	A. 1 reference B. 0.7 (0.5 to 1.0), p=0.05 C. 0.7 (0.4 to 1.1), p=0.08 D. 0.9 (0.6 to 1.3), p=0.52
Small for Gestational Age	Siberry et al, 2012[73] USA PHACS/SMARTT	A. TDF-containing ART (449; B. nonTDF-containing ART (1580; Total=2,029	SGA	8.6%	A vs B: 0.96 (0.60 to 1.52), p=0.85

Harm category	Study, year Country Study Name	ART regimen (n;%)	Birth Outcome Definition	Birth Outcome Distribution	Magnitude of Risk: Adjusted OR (95% CI), p-value
Small for Gestational Age	Snijdewind et al, 2018[81] The Netherlands	A. PI-based (928; 67%) B. NNRTI-based (438; 31%) C. Both or NRTI (12; 1%) Total=1,378	SGA <10th percentile of birth weight by gestational age	24%	Unadjusted OR: A. 1 (reference) B. 1.04 (0.80 to 1.16), p=0.76 C. 2.51 (1.16 to 5.53), p=0.02 Adjusted OR: A. 1 (reference) B. 0.95 (0.71 to 1.27), p=0.73 C. 2.11 (0.98 to 4.57), p=0.06
Small for Gestational Age	Watts et al, 2013[70] USA PHACS/SMARTT	A. Combination, with PI (1319; 74%) B. Combination, with NNRTI, no PI (160; 9%) C. Combination, with ≥3 NRTIs (193; 10%) Total N=1,672	SGA <10th percentile of birth weight by gestational age	7%*	All vs. no ARV 1st trimester: A. 0.79 (0.49 to 1.26), p=0.32 B. 1.17 (0.54 to 2.54), p=0.70 C. 0.99 (0.34 to 2.86), p=0.99 All vs. mono or dual therapy: A. 1.79 (0.64 to 5.04), p=0.27 B. 1.77 (0.53 to 5.99), p=0.36 C. 1.45 (0.43 to 4.89), p=0.55
Small for Gestational Age	Zash et al, 2016[76] Botswana	All CD4 counts: A. TDF/FTC/EFV (1054; 33%) B. other ART (2172; 64%) Total N=3226 CD4 counts >350 A. TDF/FTC/EFV (335; 31%) B. ZDF (752; 69%) Total N=1,087	SGA <10th percentile of birth weight by gestational age (Botswana norms)	19%	A vs. B (all CD4 counts): 0.4 (0.3 to 0.6) A vs. B (CD4 >350): 0.6 (0.4 to 1.0)
Small for Gestational Age	Zash et al, 2017[75] Botswana	A. TDF/FTC/EFV (2472; 49%) B. TDF/FTC/NVP (760; 15%) C. TDF/FTC/LPV/r (231; 5%) D. ZDV/3TC/NVP (1365; 27%) E. ZDV/3TC/LPV/r (167; 3%) Total N=4,995	SGA <10th percentile of birth weight by gestational age Very SGA <3rd percentile	22% 10%	Adjusted Relative Risks: A. 1 reference B. 1.44 (1.24 to 1.68) SGA B. 1.52 (1.18 to 1.94) VSGA C. 1.56 (1.25 to 1.97) SGA C. 1.81 (1.26 to 2.59) VSGA D. 1.66 (1.46 to 1.87) SGA D. 1.76 (1.44 to 2.16) VSGA E. 1.13 (0.82 to 1.56) SGA E. 1.70 (1.10 to 2.62) VSGA

Harm category	Study, year Country Study Name	ART regimen (n;%)	Birth Outcome Definition	Birth Outcome Distribution	Magnitude of Risk: Adjusted OR (95% CI), p-value
Stillbirth	Chen et al, 2012[56] Botswana	A. Initiated HAART during pregnancy (ZVD/3TC/NVP or ZVD/3TC/LVPr (1101; 12%) B. Initiated ZVD only during pregnancy (4625; 51%) C. No ART (1234; 13%) D. HAART continued from before pregnancy (2189; 24%) Total N=9,149	Stillbirth (Fetal death with APGAR of 0)	3.3%*	HAART initiation vs. ZDV initiation: 2.5 (1.6 to 3.9) Continued HAART vs. all others: 1.5 (1.2 to 1.8)
Stillbirth	Kreitchmann et al, 2014[60] Latin America Caribbean	At least 28 days 3rd trimester: A. HAART + PI (888; 59%) B. HAART no PI (410; 27%) C. Non-HAART (134; 9%) D. No ARV (80; 5%) Total N=1,512	Stillbirth Birth at 20 weeks gestation or later with no signs of life	2%*	HAART w/PI vs. no ART: 0.14 (0.05 to 0.34) HAART no PI vs. no ART: 0.11 (0.04 to 0.34)
Stillbirth	Moodley et al, 2016[66] South Africa	A. No ART (148; 4%) B. AZT + NVP (974; 26%) C. D4T +3TC + NVP (907; 25%) D. EFV + TDF + FTC (1666; 45%) Total N=3,695	Stillbirth	3.1%	A. 1 reference B. 0.08 (0.04 to 0.16), p<0.001 C. 0.20 (0.11 to 0.38), p<0.001 D. 0.18 (0.10 to 0.34), p<0.001
Stillbirth	Rough et al, 2018[82] USA PHACS and IMPAACT	A. TDF + FTC + LPV/r (128; 8%) B. ZDV + 3TC + LPV/r (954; 59%) C. TDF + FTC + ATV/r (539; 33%) Total=1,621	Fetal loss was undefined, included stillbirth (likely also included spontaneous abortion and fetal demise)	0.6%	Unadjusted odds ratio (our analysis) for initial drug regimen: A vs. B: 2.51 (0.50 to 13) A vs. C: 4.26 (0.60 to 31) B vs. C: 1.70 (0.34 to 8.45)
Stillbirth	Zash et al, 2016[76] Botswana	All CD4 counts: A. TDF/FTC/EFV (1054; 33%) B. other ART (2172; 64%) Total N=3226 CD4 counts >350 A. TDF/FTC/EFV (335; 31%) B. ZDF (752; 69%) Total N=1,087	Stillbirth	3%	A vs. B (all CD4 counts): 0.6 (0.3 to 1.3) A vs. B (CD4 >350): 0.9 (0.4 to 2.1)
Stillbirth	Zash et al, 2017[75] Botswana	A. TDF/FTC/EFV (2472; 49%) B. TDF/FTC/NVP (760; 15%) C. TDF/FTC/LPV/r (231; 5%) D. ZDV/3TC/NVP (1365; 27%) E. ZDV/3TC/LPV/r (167; 3%) Total N=4,995	Stillbirth	3.6%	Adjusted Relative Risks: A. 1 reference B. 1.15 (0.70 to 1.89) C. 1.81 (0.94 to 3.50) D. 2.31 (1.64 to 3.26) E. 1.53 (0.67 to 3.49)

Harm category	Study, year Country Study Name	ART regimen (n;%)	Birth Outcome Definition	Birth Outcome Distribution	Magnitude of Risk: Adjusted OR (95% CI), p-value
Neonatal Death	Pintye et al, 2017[78] Kenya and Uganda	A. TDF-containing ART (208; 49%) B. NonTDF-containing ART (214; 51%) Total N=422	Neonatal death within 3 days of live birth	2%	A vs. B: adjusted prevalence rate ratio 0.55 (0.17 to 1.77), p=0.30
Neonatal Death	Rough et al, 2018[82] USA PHACS and IMPAACT	A. TDF + FTC + LPV/r (128; 8%) B. ZDV + 3TC + LPV/r (954; 59%) C. TDF + FTC + ATV/r (539; 33%) Total=1,621	Neonatal death within 14 days of live birth	0.1% (2 events)	Unadjusted odds ratio (our analysis) for initial drug regimen: A vs. B. 2.47 (0.10 to 61) A vs. C: 1.40 (0.06 to 34) B vs. C: 0.56 (0.04 to 9.04)
Neonatal Death	Zash et al, 2017[75] Botswana	A. TDF/FTC/EFV (2472; 49%) B. TDF/FTC/NVP (760; 15%) C. TDF/FTC/LPV/r (231; 5%) D. ZDV/3TC/NVP (1365; 27%) E. ZDV/3TC/LPV/r (167; 3%) Total N=4,995	Neonatal death at less than 28 days	1.6%	Adjusted Relative Risks: A. 1 reference B. 1.57 (0.81 to 3.06) C. 1.60 (0.56 to 4.56) D. 1.94 (1.13 to 3.33) E. 4.01 (1.78 to 9.11)
Congenital Abnormalities	Antiretroviral Pregnancy Registry Interim Report (1989 through 2018[83] Multinational (69 countries), 75% USA and its territories	Preferred initial treatment drugs in US: A. ABC (1131; 12%) B. 3TC (5008; 54%) C. TDF (3535; 38%) D. FTC (2785; 30%) E. ATV (1279; 14%) F. Ritonavir (3155; 34%) G. Darunavir (456; 5%) H. Raltegravir (291; 3%) Alternative initial treatment drugs in US: I. ZDV (4178; 45%) J. LPV (1418; 15%) K. EFV (1023; 11%) L. RPV (297; 3%) Total N=9,336	Follows Centers for Disease Control and Prevention guidelines	2.73% First trimester exposure 2.77% Any trimester exposure	First-trimester exposed vs. unexposed, unadjusted OR (our analysis): A. 1.04 (0.72 to 1.52) B. 1.26 (0.98 to 1.63) C. 0.77 (0.59 to 1.01) D. 0.85 (0.64 to 1.13) E. 0.77 (0.52 to 1.15) **F. 0.74 (0.56 to 0.97)** G. 0.88 (0.48 to 1.61) H. 1.14 (0.58 to 2.24) **I. 1.38 (1.08 to 1.77)** J. 0.74 (0.50 to 1.09) K. 0.84 (0.55 to 1.29) L. 0.36 (0.11 to 1.12)

Harm category	Study, year Country Study Name	ART regimen (n;%)	Birth Outcome Definition	Birth Outcome Distribution	Magnitude of Risk: Adjusted OR (95% CI), p-value
Congenital Abnormalities	Floridia et al, 2013[57] Italy	Preferred initial treatment drugs in US: A. ABC (88; 7%) B. 3TC (544; 43%) C. TDF (173; 14%) D. FTC (87; 7%) E. ATV (63; 5%) F. Ritonavir (231; 18%) Alternative initial treatment drugs in US: G. ZDV (358; 28%) H. LPV (140; 11%) I. EFV (80; 6%) J. Any NRTI (716; 56%) K. Any PI (353; 28%) L. Any NNRTI (273; 21%) Total N=1,257	Birth Defects Not defined	3.4%*	Not clear if ORs are adjusted; 1st Trimester exposure vs. unexposed: ABC 1.01 (0.29 to 3.47), p=0.99 3TC 1.14 (0.61 to 2.15), p=0.67 TDF 0.85 (0.31 to 2.31), p=0.75 FTC 0.67 (0.15 to 2.93), p=0.60 ATV 0.93 (0.21 to 4.11), p=0.93 Ritonavir 1.02 (0.44 to 2.37), p=0.96 ZDV 0.65 (0.28 to 1.51), p=0.32 LPV 1.28 (0.50 to 3.26), p=0.61 EFV 0.73 (0.17 to 3.20), p=0.68 Any NRTI 0.95 (0.51 to 1.76), p=0.86 Any PI 0.92 (0.43 to 1.95), p=0.82 Any NNRTI 1.20 (0.56 to 2.55), p=0.64
Congenital Abnormalities	Knapp et al, 2012 [59] USA (IMPAACT) These patients may also be represented in the Antiretroviral Pregnancy Registry	Preferred initial treatment drugs in US: A. ABC (312; 28%) B. 3TC (979; 88%) C. TDF (235; 21%) D. FTC (121; 11%) E. ATV (104; 9%) F. Ritonavir (131; 12%) Alternative initial treatment drugs in US: G. ZDV (924; 83%) H. LPVr (306; 28%) I. EFV (56; 5%) J. Any NRTI (1097; 99%) K. Any PI (804; 72%) L. Any NNRTI (205; 18%) Total N=1,112	Birth Defects Metropolitan Atlanta Congenital Defects Program (MACDP)	5%*	All vs. unexposed: ABC 1st T 1.45 (0.68 to 3.10) ABC 2-3 T 1.25 (0.62 to 2.51) 3TC 1st T 1.68 (0.61 to 4.58) 3TC 2-3 T 1.52 (0.56 to 4.08) TDF 1st T 1.69 (0.83 to 3.44) TDF 2-3 T 1.01 (0.38 to 2.65) FTC 1st T 1.33 (0.49 to 3.60) FTC 2-3 T 0.56 (0.06 to 2.31) ATV 1st T 1.83 (0.73 to 4.58) ATV 2-3 T 0.87 (0.10 to 3.65) Ritonavir 1st T 1.60 (0.64 to 3.99) Ritonavir 2-3 T 1.18 (0.29 to 3.54) ZDV 1st T 1.02 (0.45 to 2.28) ZDV 2-3 T 1.02 (0.48 to 2.17) LPVr 1st T 1.66 (0.81 to 3.38) LPVr 2-3 T 0.80 (0.35 to 1.82) **EFV 1st T 2.84 (1.13 to 7.16)** EFV 2-3 T NA (0 to 9.05) Any NRTI 1st T 0.84 (0.11 to 39.45) Any NRTI 2-3 T 0.62 (0.08 to 29.05) Any PI 1st T 1.32 (0.64 to 2.71) Any PI 2-3 T 1.15 (0.58 to 2.29) Any NNRTI 1st T 1.53 (0.72 to 3.25) Any NNRTI 2-3 T 0.77 (0.14 to 2.69)

Harm category	Study, year Country Study Name	ART regimen (n;%)	Birth Outcome Definition	Birth Outcome Distribution	Magnitude of Risk: Adjusted OR (95% CI), p-value
Congenital Abnormalities	Sibiude et al, 2014 [64] France	Preferred initial treatment drugs in US: A. ABC (1104; 8%) B. 3TC (9170; 70%) C. TDF (1031; 8%) D. FTC (670; 5%) E. ATV (513; 4%) F. Ritonavir (5087; 39%) Alternative initial treatment drugs in US: G. ZDV (10760; 82%) H. LPV (3704; 28%) I. EFV (389; 3%) J. Any NRTI (12663; 96%) K. Any PI (7235; 55%) L. Any NNRTI (1504; 11%) Total N=13,124	Birth Defects European Surveillance of Congenital Anomalies (EUROCAT) and Metropolitan Atlanta Congenital Defects Program (MACDP) classifications	EUROCAT 4.4%* MACDP 7.0%*	All vs. unexposed (EUROCAT): **ABC 1st T 1.39 (1.06 to 1.83)** ABC 2-3 T 1.16 (0.90 to 1.51) **3TC 1st T 1.37 (1.06 to 1.73)** **3TC 2-3 T 1.26 (1.01 to 1.57)** TDF 1st T 0.75 (0.51 to 1.10) TDF 2-3 T 0.82 (0.40 to 1.69) **FTC 1st T 0.52 (0.30 to 0.90)** FTC 2-3 T 1.38 (0.63 to 3.02) ATV 1st T 0.58 (0.32 to 1.05) ATV 2-3 T 1.23 (0.38 to 4.01) Ritonavir 1st T 0.86 (0.67 to 1.10) Ritonavir 2-3 T 0.92 (0.74 to 1.15) **ZDV 1st T 1.39 (1.06 to 1.83)** ZDV 2-3 T 1.16 (0.90 to 1.51) LPV 1st T 0.92 (0.68 to 1.23) LPV 2-3 T 1.13 (0.90 to 1.41) EFV 1st T 1.16 (0.73 to 1.85) EFV 2-3 T 1.83 (0.23 to 14.5) Any NRTI 1st T 2.36 (0.86 to 6.47) Any NRTI 2-3 T 2.04 (0.75 to 5.59) Any PI 1st T 0.91 (0.73 to 1.13) Any PI 2-3 T0.94 (0.77 to 1.16) Any NNRTI 1st T 1.02 (0.76 to 1.37) Any NNRTI 2-3 T 1.21 (0.72 to 2.03)

Harm category	Study, year Country Study Name	ART regimen (n;%)	Birth Outcome Definition	Birth Outcome Distribution	Magnitude of Risk: Adjusted OR (95% CI), p-value
Congenital Abnormalities	Williams, 2015[71] USA PHACS/SMARTT	Preferred initial treatment drugs in US: A. ABC (222; 9%) B. 3TC (797; 32%) C. TDF (431; 17%) D. FTC (374; 15%) E. ATV (222; 9%) F. Ritonavir (635; 25%) G. Darunavir (54; 2%) Alternative initial treatment drugs in US: H. ZDV (726; 29%) I. LPV (341; 9%) J. EFV (94; 4%) K. Any NRTI (1211; 48%) L. Any PI (887; 35%) M. Any NNRTI (214; 9%) Total N=2,580	Antiretroviral Pregnancy Registry modification to MACDP	6.8%	All vs. unexposed: A. 0.94 (0.53 to 1.65) B. 1.14 (0.81 to 1.60) C. 1.14 (0.76 to 1.71) D. 1.14 (0.74 to 1.74) E. **1.95 (1.24 to 3.05)** F. **1.56 (1.11 to 2.20)** G. 0.30 (0.04 to 2.21) H. 1.10 (0.78 to 1.56) I. 1.37 (0.90 to 2.09) J. 1.13 (0.51 to 2.50) K. 1.19 (0.86 to 1.65) L. **1.39 (1.00 to 1.92)** M. 0.97 (0.54 to 1.74)

Note: Studies that adjusted for confounders.

*Percent of study population.

Abbreviations: 3TC=lamivudine; ABC=abacavir; APGAR=appearance, pulse, grimace, activity, respiration; aRR=adjusted relative risk; ART=antiretroviral therapy; ARV=antiretroviral; ATV=atazanavir; AZT=zidovudine; CI=confidence interval; D4T=stavudine; EFV=efavirenz; FTC=emtricitabine; HAART=highly active antiretroviral therapy; LPV=lopinavir; LPVr=lopinavir/ritonavir; NR=not reported; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI=nucleoside/nucleotide reverse transcriptase inhibitors; NS=not significant; NVP=nevirapine; OR=odds ratio; PI=protease inhibitor; SGA=small for gestational age; 1st T=first trimester; 2-3 T=second and third trimester; TDF=tenofovir; ZDV=zidovudine.

Table 4. Summary of Evidence

Key Question	No. of Studies (k) No. of Participants (n) Study Design	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Risk for Bias/ Quality	Body of Evidence Limitations	EPC Assessment of SOE for Key Question	Applicability
KQ 1. Benefits of screening	No studies	No studies	No studies	No studies	No studies	No studies	No studies	No studies
KQ 2. Yield of repeat HIV screening at different intervals	No studies	No studies	No studies	No studies	No studies	No studies	No studies	No studies
KQ 3. Harms of screening	No studies	No studies	No studies	No studies	No studies	No studies	No studies	No studies
KQ 4. Effectiveness of currently recommended antiretroviral therapy regimens	2012 USPSTF review: 3 RCTs (N=1,878) and 8 cohort studies (N=27,776) New: 1 RCT (n=3,490), 4 cohort studies (N=14,344), and 1 individual patient data analysis of 7 cohorts (n=4,459)	The prior USPSTF review included 8 cohort studies that found full-course combination ART associated with rates of mother-to-child transmission of <1% to 2.4%, compared to 9% to 22% with no antiretroviral therapy Five new cohort studies found full-course combination ART associated with a risk of mother-to-child transmission of <1% to 2.8%. One African RCT reported a rate of mother-to-child transmission of 0.5%.	Consistent No imprecision	No reporting bias detected	Moderate	Most evidence observational, with no RCT conducted in the U.S. or other high-income setting	High	Cohort studies conducted in high-income settings but RCT was conducted in Africa. Exact ART regimen not specified in most studies. Variability in timing of ART initiation.

Key Question	No. of Studies (k) No. of Participants (n) Study Design	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Risk for Bias/ Quality	Body of Evidence Limitations	EPC Assessment of SOE for Key Question	Applicability
KQ 5. Harms of currently recommended antiretroviral therapy regimens	**Preterm Birth** 2012 USPSTF review: 1 RCT (n=560), 5 cohort studies (15,812) New: 1 RCT (3,490) and 17 cohort studies (48,452)	**Preterm Birth** The prior USPSTF review included 1 RCT and 4 cohort studies that found increased PTD associated with ART, 1 RCT and 3 cohort studies that found increased risk of preterm birth associated with ART that included a PI 1 new RCT and 4 new cohort studies found increased risk of preterm birth with ART; 3 new cohort studies (all from Africa) found decreased risk of PTD with ART 1 RCT and 3 cohort studies found ART that included a boosted PI associated with increased risk of PTD	Inconsistent No imprecision	No reporting bias detected	Moderate	No US RCTs or trials from non-resource-poor countries	Low	Cohort studies conducted in all settings; RCTs was conducted primarily in Africa. Exact ART regimen not specified in most studies. Variability in timing of ART initiation.
KQ 5 cont.	**Overall Birth Defects** 2012 USPSTF review: 3 cohort studies (13,730) New: 5 cohort studies (27,409)	**Overall Birth Defects** The prior USPSTF review found no association between ART and birth defects 5 new cohort studies found most currently recommended ART drugs not associated with increased risk of birth defects	Consistent Precise	No reporting bias detected	Moderate	No RCTs	Moderate	Cohort studies conducted in high-resource settings. Individual ART drugs specified.

Key Question	No. of Studies (k) No. of Participants (n) Study Design	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Risk for Bias/ Quality	Body of Evidence Limitations	EPC Assessment of SOE for Key Question	Applicability
KQ 5 cont.	**Low Birth Weight** 2012 USPSTF review: 7 cohort studies (n=352 to 8,192) New: 1 RCT (n=3,490) and 5 cohort studies (n=11,213) **SGA** 2012 USPSTF review: none New: 10 cohort studies (n=37,670) **Stillbirth** 2012 USPSTF review: none New: 6 cohort studies (n=30,417) **Neonatal Death** 2012 USPSTF review: none New: 1 RCT (n=3,490) and 3 cohort studies (7,038)	**Low Birth Weight** Prior evidence: No clear association between prenatal ART and LBW or IGR 1 new RCT and 4 cohort studies found no clear association between ART and LBW **SGA** 9 new cohort studies found no clear association between ART and SGA **Stillbirth** 3 new cohort studies found no clear association between ART and stillbirth; 3 new cohort studies found mixed results for treatment with TDF/FTC vs. ZSV/3TC **Neonatal Death** 1 new RCT and 3 cohort studies found mixed results for neonatal death	Consistent Imprecise	No reporting bias detected	Moderate	No US RCTs or trials from non-resource-poor countries;	Low	Cohort studies conducted in all settings; RCT was conducted in Africa. Exact ART regimen not specified in most studies. Variability in timing of ART initiation.

Key Question	No. of Studies (k) No. of Participants (n) Study Design	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Risk for Bias/ Quality	Body of Evidence Limitations	EPC Assessment of SOE for Key Question	Applicability
KQ 5 cont.	**Infant Cardiac Harms** 2012 USPSTF review: 1 cohort study (n=352) New: 3 cohort studies (n=15,888)	**Infant Cardiac Harms** The prior USPSTF review included 1 cohort study that reported reduced LV mass, increased LV contractility at age 2 with in utero ART exposure; no echocardiographic differences in children 2-5 years 3 new cohort studies found mixed evidence for zidovudine in first trimester for increased congenital heart defects; mixed evidence for several ART drugs and echocardiographic changes but not clinical changes	Consistent Imprecise	No reporting bias detected	Moderate	No RCTs; no studies of in utero exposed, HIV-uninfected children beyond age 7	Low	Cohort studies conducted in high-resource settings. Variability in timing of ART initiation.
KQ 5 cont.	**Infant Neuro-developmental Harms** 2012 USPSTF review: 3 cohort studies (n=2,590) New: SMARTT cohort (n=3,542)	**Infant Neuro-developmental Harms** The prior USPSTF review found no association between in utero ART exposure and worse neurodevelopmental outcomes New evidence from the SMARTT cohort found no association to positive association between ART and neurological development	Consistent Precise	No reporting bias detected	Moderate	No RCT; drug regimens often not provided	Low	Cohort studies conducted in high-income settings. Variability in timing of ART initiation.

Key Question	No. of Studies (k) No. of Participants (n) Study Design	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Risk for Bias/ Quality	Body of Evidence Limitations	EPC Assessment of SOE for Key Question	Applicability
KQ 5 cont.	**Maternal Harms** 2012 USPSTF review: 1 meta-analysis of 4 observational studies (n=1,391) and 3 cohort studies (n=4,117) New: 2 RCTs (n=12,338)	**Maternal Harms** No association between zidovudine monotherapy and maternal death or long-term harms; possible association between increased risk for gestational diabetes; increased risk of anemia Anemia in HIV-infected pregnant women improved with ART, iron, and folic acid; treatment with zidovudine-based ART or tenofovir-based ART resulted in increased risk for any grade 2 or higher maternal adverse event vs. zidovudine monotherapy but few women left the study due to adverse events	Inconsistent Precise	No reporting bias detected	Moderate	No US RCTs or trials from non-resource-poor countries	Low	Cohort studies conducted in all settings; RCTs conducted in Africa. Exact ART regimen not specified in most studies. Variability in timing of ART initiation.

Abbreviations: ART=antiretroviral therapy; HIV=human immunodeficiency virus; IGR=intrauterine growth restriction; LBW=low birth weight; LV=left ventricular; PI=protease inhibitor; RCT=randomized controlled trial; SGA=small for gestational age; SMARTT=Surveillance Monitoring for ART Toxicities Study; US=United States; USPSTF=United States Preventive Services Task Force.

Appendix A1. Search Strategies

Screening

Database: Ovid MEDLINE(R) without Revisions

1 exp HIV/
2 HIV Antibodies/
3 HIV Antigens/
4 HIV Seroprevalence/
5 HIV Seropositivity/
6 HIV Seronegativity/
7 AIDS Serodiagnosis/
8 human immunodeficiency virus.ti,ab
9 hiv.ti,ab.
10 Mass Screening/
11 screen$.ti.
12 or/1-9
13 10 or 11
14 12 and 13
15 limit 14 to (english language and humans)
16 limit 15 to yr="2012 - 2018"
17 16 and pregnan*.ti,ab.
18 16 and mother*.ti,ab.
19 17 or 18

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

1 exp HIV/
2 HIV Antibodies/
3 HIV Antigens/
4 HIV Seroprevalence/
5 HIV Seropositivity/
6 HIV Seronegativity/
7 AIDS Serodiagnosis/
8 human immunodeficiency virus.ti.
9 hiv.ti,ab.
10 Mass Screening/
11 screen$.ti.
12 or/1-9
13 10 or 11
14 12 and 13
15 limit 14 to yr="2012 - 2018"
16 limit 15 to english language
17 16 and (pregnan* or mother*).ti,ab.

Treatment

Database: Ovid MEDLINE(R) without Revisions and EBM Reviews - Cochrane Central Register of Controlled Trials

1 exp HIV Infections/dt, pc, th
2 exp Anti-Retroviral Agents/ad, tu
3 Antiretroviral Therapy, Highly Active/
4 or/1-3
5 Infectious Disease Transmission, Vertical/
6 ((mother* or child*) and transmission).mp.
7 5 or 6

8 4 and 7
9 limit 8 to yr="2012 - 2018"
10 limit 9 to (clinical trial, all or comparative study or meta analysis or randomized controlled trial or systematic reviews)
11 9 and (random* or control* or cohort).ti,ab.
12 10 or 11 (630)
13 12 and pregnan*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (450)

Treatment harms

Database: Ovid MEDLINE(R) without Revisions and EBM Reviews - Cochrane Central Register of Controlled Trials

1 exp HIV Infections/dt, pc, th [
2 exp Anti-Retroviral Agents/ad, tu
3 Antiretroviral Therapy, Highly Active/
4 or/1-3
5 4 and (harm* or safety or adverse).ti,ab.
6 limit 5 to yr="2012 - 2018"
7 6 and (pregnan* or mother*).mp.

Screening and treatment

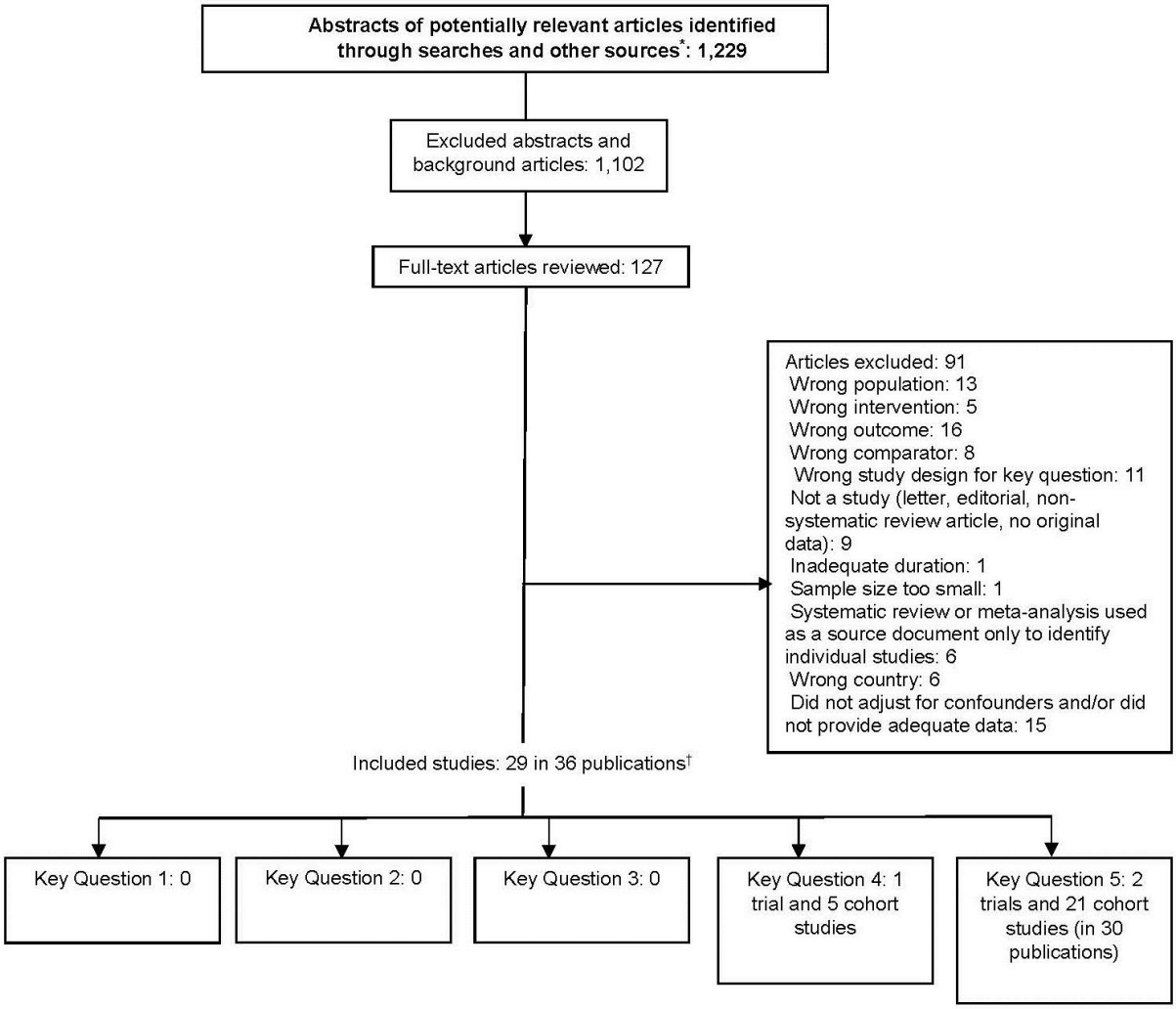
Database: EBM Reviews - Cochrane Database of Systematic Reviews
1 (hiv or "human immunodeficiency virus").ti.
2 1 and screen*.ti.
3 1 and (treatment or antiretroviral or therapy).ti.
4 2 or 3
5 4 and pregnan*.mp.

Appendix A2. Inclusion and Exclusion Criteria

Category	Include	Exclude
Settings	**KQs 1-3:** Primary care or other settings generalizable to primary care (e.g., prenatal, antenatal, and family planning clinics) and other health care settings in which screening is commonly performed (e.g., emergency room or urgent care) **KQs 4-5:** Focus on studies conducted in the U.S. and other high-income countries with low prevalence of HIV infection and in which management of HIV infection is similar to that in the U.S., except for RCTs of ART and harms of treatment if currently recommended regimens or drugs are used	Studies of screening conducted in low and middle-income countries, unless fair- or good-quality studies in the U.S. are not available
Populations	**KQs 1–3:** Asymptomatic pregnant women not known to be HIV-positive, including adolescents (13 to 18 years of age) **KQ 4:** Pregnant women living with HIV and their infants **KQ 5:** Women who received ART regimens while pregnant; neonates, infants, and children who were exposed to ART in utero	**KQs 1–3:** Women who have known HIV infection, are on dialysis, are posttransplant, or have occupational exposure (due to risk of needle stick or other parenteral exposure); women with known infection with hepatitis C virus, hepatitis B virus, or tuberculosis **KQs 4, 5:** Women who are already or were previously taking ART prior to pregnancy; women with acute HIV infection; studies limiting enrollment to people with hepatitis C virus, hepatitis B virus, or tuberculosis coinfection
Interventions	**KQs 1–3:** Rapid or standard HIV antibody testing with confirmatory testing **KQs 4, 5:** Currently recommended ART regimens or drugs, or studies published since 2012 that reported outcomes for combination antiretroviral regimens and reported the categorizations for ART regimens used in the study	**KQs 4, 5:** Regimens that are clearly outside of current U.S. practice Discontinued ART during pregnancy; Treatment interruption
Comparisons	**KQs 1, 3:** HIV screening vs. no screening **KQ 2:** Repeat HIV screening during pregnancy vs. one-time screening; screening at one interval vs. another **KQs 4, 5:** Currently recommended ART regimens; full course combination ART versus no ART, abbreviated courses of ART, or one- or two drug therapy	
Outcomes	**KQ 1:** Mother-to-child HIV transmission rates **KQ 2:** Yield of screening (number of cases of HIV infection identified per number of tests performed) **KQ 3:** Harms of screening, including false-positive results, anxiety and effects of labeling, and partner discord, abuse, or violence **KQ 4:** Mother-to-child HIV transmission rates **KQ 5:** Maternal and infant harms of treatment, including long-term harms following in utero exposure to ART	**KQs 1, 5:** Pharmacokinetic outcomes
Study designs/ countries	**KQs 1–3:** RCTs and controlled observational studies **KQ 4:** RCTs in any country as long as recommended ART regimens were evaluated, and observational studies in countries similar to the U.S. **KQ 5:** RCTs and observational studies that controlled for potential confounders; any countries as long as recommended ART regimens were evaluated	**KQs 1–4:** Modeling studies
Timing	**KQ 5:** Any timing	

Abbreviation: ART=antiretroviral therapy; HIV=human immunodeficiency syndrome; KQ=key question; RCT=randomized controlled trial; U.S.=United States.

Appendix A3. Literature Flow Diagram



* Other sources include prior reports, reference lists of relevant articles, systematic reviews, etc.
†Some papers are included in multiple Key Questions.

Appendix A4. Excluded Studies List

1. Abimpaye M, Kirk CM, Iyer HS, et al. The impact of "Option B" on HIV transmission from mother to child in Rwanda: An interrupted time series analysis. PLoS ONE. 2018;13(2):e0192910. doi: 10.1371/journal.pone.0192910. PMID: 29451925. Excluded: wrong population.

2. Ajibola G, Zash R, Shapiro RL, et al. Detecting congenital malformations - Lessons learned from the Mpepu study, Botswana. PLoS One. 2017;12(3):e0173800. doi: 10.1371/journal.pone.0173800. PMID: 28339500. Excluded: did not adjust for confounders and/or did not provide adequate data.

3. Ambia J, Mandala J. A systematic review of interventions to improve prevention of mother-to-child HIV transmission service delivery and promote retention. J Int AIDS Soc. 2016;19(1):20309. doi: 10.7448/IAS.19.1.20309. PMID: 27056361. Excluded: wrong outcome.

4. Association of Women's Health Obstetric Neonatal Nursing. HIV screening for pregnant women and infants. Nurs Womens Health. 2012 Feb-Mar;16(1):88-9. doi: 10.1111/j.1751-486X.2012.01711.x. PMID: 22900734. Excluded: wrong study design for Key Question.

5. Awodele O, Popoola D, Odunsi P, et al. Assessing the risk of birth defects associated with exposure to highly active anti-retroviral therapy during organogenesis in rats. Tokai J Exp Clin Med. 2013 Jul;38(2):82-92. PMID: 23868740. Excluded: wrong population.

6. Bera E, Mia R. Safety of nevirapine in HIV-infected pregnant women initiating antiretroviral therapy at higher CD4 counts: a systematic review and meta-analysis. S Afr Med J. 2012 Nov;102(11 Pt 1):855-9. doi: 10.7196/samj.5700. PMID: 23116743. Excluded: systematic review or meta-analysis used as a source document only to identify individual studies.

7. Bisio F, Nicco E, Calzi A, et al. Pregnancy outcomes following exposure to efavirenz-based antiretroviral therapy in the Republic of Congo. New Microbiol. 2015 Apr;38(2):185-92. PMID: 25938743. Excluded: did not adjust for confounders and/or did not provide adequate data.

8. Bispo S, Chikhungu L, Rollins N, et al. Postnatal HIV transmission in breastfed infants of HIV-infected women on ART: a systematic review and meta-analysis. J Int AIDS Soc. 2017 02 22;20(1):21251. doi: 10.7448/IAS.20.1.21251. PMID: 28362072. Excluded: wrong population.

9. Bokharaei-Salim F, Kalantari S, Gholamypour Z, et al. Investigation of the effects of a prevention of mother-to-child HIV transmission program among Iranian neonates. Arch Virol. 2018 May;163(5):1179-85. doi: 10.1007/s00705-017-3661-1. PMID: 29383588. Excluded: did not adjust for confounders and/or did not provide adequate data.

10. Bolduc P, Roder N, Colgate E, et al. Care of patients with HIV infection: diagnosis and monitoring. Fp Essent. 2016 Apr;443:11-5. PMID: 27092562. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

11. Browne JL, Schrier VJ, Grobbee DE, et al. HIV, antiretroviral therapy, and hypertensive disorders in pregnancy: a systematic review and meta-analysis. J Acquir Immune Defic Syndr. 2015 Sep 1;70(1):91-8. doi: 10.1097/QAI.0000000000000686. PMID: 26322669. Excluded: systematic review or meta-analysis used as a source document only to identify individual studies.

12. Bunupuradah T, Phupitakphol T, Sophonphan J, et al. Prevalence of persistent renal dysfunction in perinatally HIV-infected Thai adolescents. Pediatr Infect Dis J. 2018 Jan;37(1):66-70. doi: 10.1097/INF.0000000000001684. PMID: 28719505. Excluded: wrong population.

13. Caniglia EC, Zash R, Jacobson DL, et al. Emulating a target trial of antiretroviral therapy regimens started before conception and risk of adverse birth outcomes. AIDS. 2018 Jan 02;32(1):113-20. doi: 10.1097/QAD.0000000000001673. PMID: 29112066. Excluded: wrong population.

14. Cecchini DM, Martinez MG, Morganti LM, et al. Antiretroviral therapy containing raltegravir to prevent mother-to-child transmission of HIV in infected pregnant women. Infect Dis Rep. 2017 May 31;9(2):7017. doi: 10.4081/idr.2017.7017. PMID: 28663779. Excluded: did not adjust for confounders and/or did not provide adequate data.

15. Centers for Disease Control and Prevention. HIV/AIDS HIV among pregnant women, infants, and children. 2016. http://www.cdc.gov/hiv/group/gender/pregnantwomen/index.html. Accessed October 28, 2016. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

16. Cha S, Malik T, Abara WE, et al. Screening for syphilis and other sexually transmitted infections in pregnant women - Guam, 2014. MMWR Morb Mortal Wkly Rep. 2017 Jun 23;66(24):644-8. doi: 10.15585/mmwr.mm6624a4. PMID: 28640799. Excluded: wrong outcome.

17. Chaiyachati KH, Ogbuoji O, Price M, et al. Interventions to improve adherence to antiretroviral therapy: a rapid systematic review. AIDS. 2014 Mar;28 Suppl 2:S187-204. doi: 10.1097/QAD.0000000000000252. PMID: 24849479. Excluded: wrong outcome.

18. Chaudhury S, Williams PL, Mayondi GK, et al. Neurodevelopment of HIV-exposed and HIV-unexposed uninfected children at 24 months. Pediatrics. 2017 Oct;140(4)doi: 10.1542/peds.2017-0988. PMID: 28912368. Excluded: wrong comparator.

19. Colbers AP, Hawkins DA, Gingelmaier A, et al. The pharmacokinetics, safety and efficacy of tenofovir and emtricitabine in HIV-1-infected pregnant women. AIDS. 2013 Mar 13;27(5):739-48. doi: 10.1097/QAD.0b013e32835c208b. PMID: 23169329. Excluded: sample size too small.

20. Coovadia HM, Brown ER, Fowler MG, et al. Efficacy and safety of an extended nevirapine regimen in infant children of breastfeeding mothers with HIV-1 infection for prevention of postnatal HIV-1 transmission (HPTN 046): a randomised, double-blind, placebo-controlled trial. Lancet. 2012 Jan 21;379(9812):221-8. doi: 10.1016/S0140-6736(11)61653-X. PMID: 22196945. Excluded: wrong population.

21. Currier J, et al. Randomized trial of stopping or continuing ART among postpartum women with pre-ART CD4 ≥400 cells/mm^3 (PROMISE 1077HS). 21st International AIDS Conference (AIDS 2016). 2016. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

22. da Silva KM, de Sa CD, Carvalho R. Evaluation of motor and cognitive development among infants exposed to HIV. Early Hum Dev. 2017 Feb;105:7-10. doi: 10.1016/j.earlhumdev.2016.12.013. PMID: 28088692. Excluded: wrong comparator.

23. d'Arminio Monforte A, Galli L, Lo Caputo S, et al. Pregnancy outcomes among ART-naive and ART-experienced HIV-positive women: data from the ICONA foundation study group, years 1997-2013. J Acquir Immune Defic Syndr. 2014 Nov 1;67(3):258-67. doi: 10.1097/QAI.0000000000000297. PMID: 25314248. Excluded: wrong outcome.

24. Davis NL, Miller WC, Hudgens MG, et al. Adherence to extended postpartum antiretrovirals is associated with decreased breast milk HIV-1 transmission. AIDS. 2014 Nov 28;28(18):2739-49. doi: 10.1097/QAD.0000000000000492. PMID: 25493600. Excluded: wrong intervention.

25. Decker S, Rempis E, Schnack A, et al. Prevention of mother-to-child transmission of HIV: Postpartum adherence to Option B+ until 18 months in Western Uganda. PLoS One. 2017;12(6):e0179448. doi: 10.1371/journal.pone.0179448. PMID: 28662036. Excluded: wrong outcome.

26. Del Bianco G, Bell CS, Benjamins LJ, et al. Persistently high perinatal transmission of HIV: assessment of risk factors. Pediatr Infect Dis J. 2014 Jun;33(6):e151-7. doi: 10.1097/INF.0000000000000199. PMID: 24836756. Excluded: did not adjust for confounders and/or did not provide adequate data.

27. Dinh TH, Delaney KP, Goga A, et al. Impact of maternal HIV seroconversion during pregnancy on early mother to child transmission of HIV (MTCT) measured at 4-8 weeks postpartum in South Africa 2011-2012: A national population-based evaluation. PLoS One. 2015;10(5):e0125525. doi: 10.1371/journal.pone.0125525. PMID: 25942423. Excluded: wrong country.

28. Domingues R, Saraceni V, Leal MDC. Mother to child transmission of HIV in Brazil: Data from the "Birth in Brazil study", a national hospital-based study. PLoS ONE. 2018;13(2):e0192985. doi: 10.1371/journal.pone.0192985. PMID: 29438439. Excluded: wrong country.

29. Downie J, Mactier H, Bland RM. Should pregnant women with unknown HIV status be offered rapid HIV testing in labour? Arch Dis Child Fetal Neonatal Ed. 2016 Jan;101(1):F79-84. doi: 10.1136/archdischild-2014-307226. PMID: 26668051. Excluded: wrong intervention.

30. Drake AL, Wagner A, Richardson B, et al. Incident HIV during pregnancy and postpartum and risk of mother-to-child HIV transmission: a systematic review and meta-analysis. PLoS Med. 2014 Feb;11(2):e1001608. doi: 10.1371/journal.pmed.1001608. PMID: 24586123. Excluded: wrong study design for Key Question.

31. Eleje GU, Edokwe ES, Ikechebelu JI, et al. Mother-to-child transmission of human immunodeficiency virus (HIV) among HIV-infected pregnant women on highly active anti-retroviral therapy with premature rupture of membranes at term. J Matern Fetal Neonatal Med. 2018 Jan;31(2):184-90. doi: 10.1080/14767058.2017.1279600. PMID: 28064549. Excluded: wrong population.

32. Faghih S, Secord E. Increased adolescent HIV infection during pregnancy leads to increase in perinatal transmission at urban referral center. J Int Assoc Physicians AIDS Care (Chic). 2012 Sep-Oct;11(5):293-5. doi: 10.1177/1545109712446175. PMID: 22628370. Excluded: wrong study design for Key Question.

33. Fitz Harris LF, Taylor AW, Zhang F, et al. Factors associated with human immunodeficiency virus screening of women during pregnancy, labor and delivery, United States, 2005-2006. Matern Child Health J. 2014 Apr;18(3):648-56. doi: 10.1007/s10995-013-1289-7. PMID: 23836013. Excluded: wrong outcome.

34. Frederick T, Homans J, Spencer L, et al. The effect of prenatal highly active antiretroviral therapy on the transmission of congenital and perinatal/early postnatal cytomegalovirus among HIV-infected and HIV-exposed infants. Clin Infect Dis. 2012 Sep;55(6):877-84. doi: 10.1093/cid/cis535. PMID: 22675157. Excluded: wrong study design for Key Question.

35. Gertsch A, Michel O, Locatelli I, et al. Adherence to antiretroviral treatment decreases during postpartum compared to pregnancy: a longitudinal electronic monitoring study. Aids Patient Care STDS. 2013 Apr;27(4):208-10. doi: 10.1089/apc.2013.0005. PMID: 23506310. Excluded: wrong outcome.

36. Gibb DM, Kizito H, Russell EC, et al. Pregnancy and infant outcomes among HIV-infected women taking long-term ART with and without tenofovir in the DART trial. PLoS Med. 2012;9(5):e1001217. doi: 10.1371/journal.pmed.1001217. PMID: 22615543. Excluded: wrong country.

37. Gill MM, Hoffman HJ, Ndatimana D, et al. 24-month HIV-free survival among infants born to HIV-positive women enrolled in Option B+ program in Kigali, Rwanda: The Kabeho Study. Medicine (Baltimore). 2017 Dec;96(51):e9445. doi: 10.1097/MD.0000000000009445. PMID: 29390577. Excluded: wrong population.

38. Gonzalez R, Ruperez M, Sevene E, et al. Effects of HIV infection on maternal and neonatal health in southern Mozambique: A prospective cohort study after a decade of antiretroviral drugs roll out. PLoS One. 2017;12(6):e0178134. doi: 10.1371/journal.pone.0178134. PMID: 28575010. Excluded: wrong comparator.

39. Harmsen MJ, Browne JL, Venter F, et al. The association between HIV (treatment), pregnancy serum lipid concentrations and pregnancy outcomes: a systematic review. BMC Infect Dis. 2017 Jul 11;17(1):489. doi: 10.1186/s12879-017-2581-8. PMID: 28697741. Excluded: wrong outcome.

40. Heemelaar S, Habets N, Makukula Z, et al. Repeat HIV testing during pregnancy and delivery: missed opportunities in a rural district hospital in Zambia. Trop Med Int Health. 2015 Mar;20(3):277-83. doi: 10.1111/tmi.12432. PMID: 25418130. Excluded: did not adjust for confounders and/or did not provide adequate data.

41. Hernandez S, Catalan-Garcia M, Moren C, et al. Placental mitochondrial toxicity, oxidative stress, apoptosis, and adverse perinatal outcomes in HIV pregnancies under antiretroviral treatment containing zidovudine. J Acquir Immune Defic Syndr. 2017 Aug 01;75(4):e113-e9. doi: 10.1097/QAI.0000000000001334. PMID: 28234688. Excluded: wrong comparator.

42. Huang X, Xu Y, Yang Q, et al. Efficacy and biological safety of lopinavir/ritonavir based anti-retroviral therapy in HIV-1-infected patients: a meta-analysis of randomized controlled trials. Sci Rep. 2015;5 PMID: 25704206. Excluded: wrong study design for Key Question.

43. Inzaule SC, Osi SJ, Akinbiyi G, et al. High prevalence of HIV drug resistance among newly diagnosed infants aged <18 months: results from a nationwide surveillance in Nigeria. J Acquir Immune Defic Syndr. 2018 01 01;77(1):e1-e7. doi: 10.1097/QAI.0000000000001553. PMID: 28961680. Excluded: wrong outcome.

44. Jao J, Abrams EJ. Metabolic complications of in utero maternal HIV and antiretroviral exposure in HIV-exposed infants. Pediatr Infect Dis J. 2014 Jul;33(7):734-40. doi: 10.1097/INF.0000000000000224. PMID: 24378947. Excluded: wrong study design for Key Question.

45. Johnson M, Afonina L, Haanyama O. The challenges of testing for HIV in women: experience from the UK and other European countries. Antivir Ther. 2013;18 Suppl 2:19-25. doi: 10.3851/IMP2637. PMID: 23784671. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

46. Kakkar FW, Samson L, Vaudry W, et al. Safety of combination antiretroviral prophylaxis in high-risk HIV-exposed newborns: a retrospective review of the Canadian experience. J Int AIDS Soc. 2016;19(1):20520. doi: 10.7448/IAS.19.1.20520. PMID: 26880241. Excluded: wrong population.

47. Kim LH, Cohan DL, Sparks TN, et al. The cost-effectiveness of repeat HIV testing during pregnancy in a resource-limited setting. JAIDS. 2013 Jun 1;63(2):195-200. doi: 10.1097/QAI.0b013e3182895565. PMID: 23392461. Excluded: wrong country.

48. Koss CA, Natureeba P, Plenty A, et al. Risk factors for preterm birth among HIV-infected pregnant Ugandan women randomized to lopinavir/ritonavir- or efavirenz-based antiretroviral therapy. J Acquir Immune Defic Syndr. 2014 Oct 01;67(2):128-35. doi: 10.1097/qai.0000000000000281. PMID: 25072616. Excluded: did not adjust for confounders and/or did not provide adequate data.

49. Lassi ZS, Imam AM, Dean SV, et al. Preconception care: preventing and treating infections. Reprod Health. 2014 Sep 26;11 Suppl 3:S4. doi: 10.1186/1742-4755-11-S3-S4. PMID: 25415557. Excluded: wrong outcome.

50. le Roux SM, Jao J, Brittain K, et al. Tenofovir exposure in utero and linear growth in HIV-exposed, uninfected infants. AIDS. 2017 Jan 02;31(1):97-104. doi: 10.1097/QAD.0000000000001302. PMID: 27898591. Excluded: wrong outcome.

51. Liao C, Golden WC, Anderson JR, et al. Missed opportunities for repeat HIV testing in pregnancy: Implications for elimination of mother-to-child transmission in the United States. Aids Patient Care STDS. 2017 Jan;31(1):20-6. doi: 10.1089/apc.2016.0204. PMID: 27936863. Excluded: wrong study design for Key Question.

52. Lin AW, Wong KH, Chan K, et al. Accelerating prevention of mother-to-child transmission of HIV: ten-year experience of universal antenatal HIV testing programme in a low HIV prevalence setting in Hong Kong. AIDS Care. 2014 Feb;26(2):169-75. doi: 10.1080/09540121.2013.819402. PMID: 23869699. Excluded: wrong outcome.

53. Liotta G, Mancinelli S, Nielsen-Saines K, et al. Reduction of maternal mortality with highly active antiretroviral therapy in a large cohort of HIV-infected pregnant women in Malawi and Mozambique. PLoS One. 2013;8(8):e71653. doi: 10.1371/journal.pone.0071653. PMID: 23990966. Excluded: wrong comparator.

54. Little KM, Taylor AW, Borkowf CB, et al. Perinatal antiretroviral exposure and prevented mother-to-child HIV infections in the era of antiretroviral prophylaxis in the United States, 1994-2010. Pediatr Infect Dis J. 2017 Jan;36(1):66-71. doi: 10.1097/INF.0000000000001355. PMID: 27749662. Excluded: wrong study design for Key Question.

55. Liu KC, Chibwesha CJ. Intrapartum management for prevention of mother-to-child transmission of HIV in resource-limited settings: a review of the literature. Afr J Reprod Health. 2013 Dec;17(4 Spec No):107-17. PMID: 24689322. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

56. Malaba TR, Phillips T, Le Roux S, et al. Antiretroviral therapy use during pregnancy and adverse birth outcomes in South African women. Int J Epidemiol. 2017 Oct 01;46(5):1678-89. doi: 10.1093/ije/dyx136. PMID: 29040569. Excluded: wrong comparator.

57. Mesfin YM, Kibret KT, Taye A. Is protease inhibitors based antiretroviral therapy during pregnancy associated with an increased risk of preterm birth? Systematic review and a meta-analysis. Reprod Health. 2016 Apr 5;13:30. doi: 10.1186/s12978-016-0149-5. PMID: 27048501. Excluded: systematic review or meta-analysis used as a source document only to identify individual studies.

58. Minniear TD, Girde S, Angira F, et al. Outcomes in a cohort of women who discontinued maternal triple-antiretroviral regimens initially used to prevent mother-to-child transmission during pregnancy and breastfeeding--Kenya, 2003-2009. PLoS One. 2014;9(4):e93556. doi: 10.1371/journal.pone.0093556. PMID: 24733021. Excluded: wrong study design for Key Question.

59. Moodley D, Esterhuizen TM, Pather T, et al. High HIV incidence during pregnancy: compelling reason for repeat HIV testing. AIDS. 2009 Jun 19;23(10):1255-9. doi: 10.1097/QAD.0b013e32832a5934. PMID: 19455017. Excluded: wrong country.

60. Mora S, Diceglie C, Vigano A, et al. Antiretroviral therapy and pregnancy: effect on cortical bone status of human immunodeficiency virus-infected Caucasian women as assessed by quantitative ultrasonography. Calcif Tissue Int. 2013 Apr;92(4):394-8. doi: 10.1007/s00223-013-9696-8. PMID: 23307187. Excluded: wrong comparator.

61. Mora S, Giacomet V, Vigano A, et al. Exposure to antiretroviral agents during pregnancy does not alter bone status in infants. Bone. 2012 Jan;50(1):255-8. doi: 10.1016/j.bone.2011.10.030. PMID: 22080170. Excluded: wrong comparator.

62. Myer L, Zulliger R, Bekker LG, et al. Systemic delays in the initiation of antiretroviral therapy during pregnancy do not improve outcomes of HIV-positive mothers: a cohort study. BMC Pregnancy Childbirth. 2012;12:94. doi: 10.1186/1471-2393-12-94. PMID: 22963318. Excluded: wrong country.

63. Nachega JB, Uthman OA, Mofenson LM, et al. Safety of tenofovir disoproxil fumarate-based antiretroviral therapy regimens in pregnancy for HIV-infected women and their Infants: a systematic review and meta-analysis. J Acquir Immune Defic Syndr. 2017 Sep 01;76(1):1-12. doi: 10.1097/QAI.0000000000001359. PMID: 28291053. Excluded: systematic review or meta-analysis used as a source document only to identify individual studies.

64. Nesheim SR, Wiener J, Fitz Harris LF, et al. Brief report: estimated incidence of perinatally acquired HIV infection in the United States, 1978-2013. J Acquir Immune Defic Syndr. 2017 Dec 15;76(5):461-4. doi: 10.1097/QAI.0000000000001552. PMID: 28991886. Excluded: wrong study design for Key Question.

65. Ngoma MS, Hunter JA, Harper JA, et al. Cognitive and language outcomes in HIV-uninfected infants exposed to combined antiretroviral therapy in utero and through extended breast-feeding. AIDS. 2014 Jul;28 Suppl 3:S323-30. doi: 10.1097/QAD.0000000000000357. PMID: 24991905. Excluded: wrong intervention.

66. Nielsen-Saines K, Watts DH, Veloso VG, et al. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. N Engl J Med. 2012;366(25):2368-79. PMID: 22716975. Excluded: wrong intervention.

67. Parekh N, Ribaudo H, Souda S, et al. Risk factors for very preterm delivery and delivery of very-small-for-gestational-age infants among HIV-exposed and HIV-unexposed infants in Botswana. Int J Gynaecol Obstet. 2011 Oct;115(1):20-5. doi: 10.1016/j.ijgo.2011.04.008. PMID: 21767835. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

68. Patel K, Van Dyke RB, Mittleman MA, et al. The impact of HAART on cardiomyopathy among children and adolescents perinatally infected with HIV-1. AIDS. 2012 Oct 23;26(16):2027-37. doi: 10.1097/QAD.0b013e3283578bfa. PMID: 22781228. Excluded: wrong intervention.

69. Perry ME, Taylor GP, Sabin CA, et al. Lopinavir and atazanavir in pregnancy: comparable infant outcomes, virological efficacies and preterm delivery rates. HIV Med. 2016 Jan;17(1):28-35. doi: 10.1111/hiv.12277. PMID: 26200570. Excluded: did not adjust for confounders and/or did not provide adequate data.

70. Poliquin V, Yudin MH, Murphy KE, et al. Antepartum screening for maternal infection and immune status: is it time to broaden our routine? J Obstet Gynaecol Can. 2015 Dec;37(12):1118-21. PMID: 26637086. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

71. Prieto LM, Fernandez McPhee C, Rojas P, et al. Pregnancy outcomes in perinatally HIV-infected young women in Madrid, Spain: 2000-2015. PLoS One. 2017;12(8):e0183558. doi: 10.1371/journal.pone.0183558. PMID: 28841701. Excluded: wrong population.

72. Prosperi MC, Fabbiani M, Fanti I, et al. Predictors of first-line antiretroviral therapy discontinuation due to drug-related adverse events in HIV-infected patients: a retrospective cohort study. BMC Infect Dis. 2012;12:296. doi: 10.1186/1471-2334-12-296. PMID: 23145925. Excluded: wrong outcome.

73. Radon-Pokracka M, Piasecki M, Lachowska A, et al. Assessment of the implementation of the infectious diseases screening programmes among pregnant women in the Lesser Poland region and comparison with similar programmes conducted in other European Union countries. Ginekol Pol. 2017;88(3):151-5. doi: 10.5603/GP.a2017.0029. PMID: 28397205. Excluded: wrong outcome.

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Appendix A5. Criteria for Assessing Internal Validity of Individual Studies

Systematic Reviews

Criteria:

- Comprehensiveness of sources considered/search strategy used
- Standard appraisal of included studies
- Validity of conclusions
- Recency and relevance (especially important for systematic reviews)

Definition of ratings based on above criteria:

Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions

Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies

Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies

Case-Control Studies

Criteria:

- Accurate ascertainment of cases
- Nonbiased selection of cases/controls, with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variables

Definition of ratings based on above criteria:

Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80 percent; accurate diagnostic procedures and measurements applied equally to cases and controls; and appropriate attention to confounding variables

Fair: Recent, relevant, and without major apparent selection or diagnostic workup bias, but response rate less than

80 percent or attention to some but not all important confounding variables
Poor: Major selection or diagnostic workup bias, response rate less than 50 percent, or inattention to confounding variables

RCTs and Cohort Studies

Criteria:

- Initial assembly of comparable groups:
  - For RCTs: Adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
  - For 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
- All important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies or intention-to treat analysis for RCTs

Definition of ratings based on above criteria:
Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to all groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.
Fair: Studies are graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially, but some question remains whether some (although not major) differences occurred with 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. Intention-to-treat analysis is used for RCTs.
Poor: Studies are graded "poor" if any of the following fatal flaws 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 equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Diagnostic Accuracy Studies

Criteria:

- Screening test relevant, available for primary care, and adequately described
- Credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Indeterminate results handled in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Reliable screening test

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; assesses reliability of test; has few or handles indeterminate results in a reasonable manner; includes large number (>100) of broad-spectrum patients with and without disease
Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; has moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients
Poor: Has a fatal flaw, such as: Uses inappropriate reference standard; improperly administers screening test; biased ascertainment of reference standard; has very small sample size or very narrow selected spectrum of patients

Source: U.S. Preventive Services Task Force Procedure Manual. December 2015. Accessed at https://www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes

Appendix A7. Expert Reviewers of the Draft Report

- Maggie Czarnogorski, MD, MPH, Deputy Director, Comprehensive Women's Health, Department of Veterans Affairs
- Brenna Hughes, MD, Duke University
- Margaret Lampe, RN, MPH, Centers for Disease Control and Prevention
- Lynne Mofenson, MD, Elizabeth Glaser Pediatric AIDS Foundation
- Brandy Peaker, MD, MPH, Centers for Disease Control and Prevention
- George Siberry, MD, Pediatric Technical Advisor for PEPFAR, State Department

Note: Reviewers provided comments on a prior version of the draft report and may or may not agree with the report findings.

Appendix Table B1a. Preferred, Recommended Initial Antiretroviral Therapy for HIV in Pregnant Women

Two-NRTI Backbones	Protease Inhibitor regimens	Integrase Inhibitor regimens	NNRTI regimens	Notes
ABC/3TC	ATV/r	-	-	No HLA-B5701 due to hypersensitivity (ABC); No HIV RNA> 100,000 copies/mL at baseline (ABC/3TC with ATV/r); maternal hyperbilirubinemia (ATV/r); cannot be administered with a proton-pump inhibitor (ATV/r)
ABC/3TC	DRV/r	-	-	No HLA-B5701 due to hypersensitivity (ABC)
ABC/3TC	-	RAL	-	No HLA-B5701 due to hypersensitivity (ABC); Rapid viral load reduction (RAL)
TDF/FTC	ATV/r	-	-	Caution in renal insufficiency (TDF); maternal hyperbilirubinemia (ATV/r); cannot be administered with a proton-pump inhibitor (ATV/r)
TDF/FTC	DRV/r	-	-	Caution in renal toxicity (TDF)
TDF/FTC	-	RAL		Caution in renal insufficiency (TDF); rapid viral load reduction (RAL)
TDF/3TC	ATV/r	-	-	Caution in renal insufficiency (TDF); cannot be administered with a proton-pump inhibitor (ATV/r)
TDF/3TC	DRV/r	-	-	Caution in renal insufficiency (TDF)
TDF/3TC	-	RAL		Caution in renal insufficiency (TDF); rapid viral load reduction (RAL)

Appendix Table B1b. Alternative, Recommended Initial Antiretroviral Therapy for HIV in Pregnant Women

Two-NRTI Backbones	Protease Inhibitor regimens	Integrase Inhibitor regimens	NNRTI regimens	Notes
ZDV/3TC	ATV/r	-	-	Increase in hematologic toxicities (ZDV); maternal hyperbilirubinemia (ATV/r); cannot be administered with a proton-pump inhibitor (ATV/r)
ZDV/3TC	DRV/r	-	-	Increase in hematologic toxicities (ZDV)
ZDV/3TC	-	RAL		Increase in hematologic toxicities (ZDV); rapid viral load reduction (RAL)
ABC/3TC	LPV/r	-	-	No HLA-B5701 due to hypersensitivity (ABC); more nausea than preferred agents (LPV/r); increase LPV/r dose in third trimester
TDF/FTC	LPV/r	-	-	Caution in renal insufficiency (TDF); more nausea than preferred agents (LPV/r); increase LPV/r dose in third trimester
TDF/3TC	LPV/r	-	-	Caution in renal insufficiency (TDF); more nausea than preferred agents (LPV/r); increase LPV/r dose in third trimester
ABC/3TC	-	-	EFV	No HLA-B5701 due to hypersensitivity (ABC); screen for depression (EFV); birth defects in primate study (EFV)
TDF/FTC	-	-	EFV	Caution in renal insufficiency (TDF); screen for depression (EFV); birth defects in primate study (EFV)
TDF/3TC	-	-	EFV	Caution in renal insufficiency (TDF); screen for depression (EFV); birth defects in primate study (EFV)
TDF/FTC	-	-	RPV	Caution in renal insufficiency (TDF); No HIV RNA> 100,000 copies/mL at baseline (RPV); No CD4 cell counts < 200 cells/mm^3 (RPV); No proton pump inhibitors (RPV); little experience in pregnancy (RPV)
ABC/3TC	-	-	RPV	No HLA-B5701 due to hypersensitivity (ABC); No HIV RNA> 100,000 copies/mL at baseline (RPV); No CD4 cell counts < 200 cells/mm^3 (RPV); No proton pump inhibitors (RPV); little experience in pregnancy (RPV)
TDF/3TC	-	-	RPV	Caution in renal insufficiency (TDF); No HIV RNA> 100,000 copies/mL at baseline (RPV); No CD4 cell counts < 200 cells/mm3 (RPV); No proton pump inhibitors (RPV); little experience in pregnancy (RPV)
ABC/3TC	-	DTG	-	No HLA-B5701 due to hypersensitivity (ABC)
TDF/FTC	-	DTG	-	Caution in renal insufficiency (TDF)
TDF/3TC	-	DTG	-	Caution in renal insufficiency (TDF)

Abbreviations: 3TC=lamivudine; ABC=abacavir; ATV/r=atazanavir/ritonavir; DRV/r=darunavir/ritonavir; DTG= dolutegravir; EFV=efavirenz; FTC=emtricitabine; LPV/r=lopinavir/ritonavir; RAL=raltegravir; RPV=rilpivirine; TDF= tenofovir disoproxil fumarate; ZDV=zidovudine.

Source: Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Transmission in the United States. Version May 2018. aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. Accessed July 26, 2018.

Appendix B2a. Evidence Table of Included Studies – Study Characteristics

Study Author, year	Study design	No. of centers, Country	Study duration Mean followup	Intervention	Inclusion criteria	Patient characteristics	N	Quality rating	Funding source
Aaron, 2012[55]	Prospective cohort	1 site United States (Philadelphia, Pennsylvania)	Through birth January 2000 through January 2011	A. Any ART initiation during pregnancy (n=137) B. NNRTI use (n=39) C. PI use (n=117)	HIV-infected, pregnant, and more than 17 years of age	Maternal age: mean 28 years Race/ethnicity: 74.7% African American; 25.3% other Started medication in pregnancy: 74.9%	183	Fair	Not reported
Antiretroviral Pregnancy Registry, 2018[83]	Cohort (approx.. 1000 women prospectively included)	Multinational (69 countries), 75% USA and its territories	January 1989 through January 2018	Preferred initial treatment drugs in US: A. ABC (1131; 12%) B. 3TC (5008; 54%) C. TDF (3535; 38%) D. FTC (2785; 30%) E. ATV (1279; 14%) F. Ritonavir (3155; 34%) G. Darunavir (456; 5%) H. Raltegravir (291; 3%) Alternative initial treatment drugs in US: I. ZDV (4178; 45%) J. LPV (1418; 15%) K. EFV (1023; 11%) L. RPV (297; 3%)	Pregnant women exposed to antiretroviral drug for the treatment of HIV and hepatitis B virus infection and prevention of HIV infection (pre or post exposure prophylaxis)	Pregnancies enrolled in database (n=19,449): Maternal age: median 28 years Indication for ART at start of pregnancy: 89.4% HIV infected, 1.7% prophylaxis (HIV uninfected), 4.1% hepatitis B mono-infected, 2.3% unknown, 2.4% missing CD4 count at start of pregnancy: 30.9% $\geq$500 cells/mm^3, 39.4% 200-499 cells/mm^3, 14.1% <200 cells/mm^3	9,336	Fair	Co-sponsored and co-funded by 26 pharma-ceutical companies that manufacture drugs used in ART
Berard, 2017[77] Quebec Pregnancy Cohort	Prospective cohort	Database study (Quebec Drug Plan) Canada	Through birth 1998 to 2015	A. No ART exposure (n=214,042) B. First trimester ART exposure (n=198)	Age 15 and 45 years of age on the first day of gestation, continuously insured by the RAMQ drug plan for at least 6 months before the first day of gestation and during pregnancy, and have a singleton live birth.	A vs B Maternal age: 31.5 vs 28.3 years (p<0.0001) Welfare recipient: 54% vs 23% (p<0.0001) Infant gestational age: 38.2 vs 38.8 weeks	214,240	Fair	Canadian Institutes of Health Research, Fonds de Antiretroviral la recherche du Que´bec – Sante

Study Author, year	Study design	No. of centers, Country	Study duration Mean followup	Intervention	Inclusion criteria	Patient characteristics	N	Quality rating	Funding source
Chagomerana, 2017[74]	Retrospective cohort	1 hospital Malawi	Through birth Period April 2012 to November 2015	A. ART (n=2,909) B. No ART (n=165)	HIV+ pregnant women who initiated ART before 27 weeks gestation or did not receive ART and who delivered after 27 weeks	A vs. B Maternal age: 27 to 30 vs. 26 years Gestation at delivery: 38 vs. 38 weeks	3.074	Fair	National Institutes of Health and a Gilead Training Fellowship
Chen, 2012[56]	Prospective cohort	6 sites Botswana	May (1 site) or November (5 sites) 2009 through April 2011 28 days after delivery	A. Continued HAART during pregnancy (n=2,189) B. Initiated HAART during pregnancy (n=1,101) C. Initiated zidovudine during pregnancy (n=4,625) D. No ART (n=1,234)	All women who delivered live births or stillbirths at a gestational age ≥20 weeks at 6 government facilities in Botswana	A vs. B vs. C vs. D Maternal age: median 32 vs. 29 vs. 27 vs. 27 Botswana nationality: 99% vs. 98% vs. 97% vs. 64% Received antenatal care: 97% vs. 99% vs. 99% vs. 78%	9,504	Fair	CDC, NIH, Harvard University, Doris Duke Charitable Research Foundation
Chiappini, 2013[47] European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)	Analysis from 8 cohort studies	8 cohorts from 7 countries in Europe: UK and Ireland's National Study of HIV in Pregnancy and Childhood (NSHPC) and Collaborative HIV Paediatric Study (CHIPS); Italian Register for HIV infection in children (ITLR); Madrid Cohort of HIV-infected Children; Catalan Cohort of HIV-infected Children (CoRISPE-Cat); 'Victor Babes' Hospital Cohort, Bucharest, Romania; Swiss Mother and Child HIV Cohort Study	Up to 18 months Period 1996-2010	A. 3 or more drugs (n=2,355) B. 2 drugs (n=255) C. 1 drug (n=681) D. No therapy (n=1,933)	Children born to diagnosed HIV- infected mothers between 1 January 1996 and 30 June 2010 at high risk for acquiring HIV infection born to mothers who received antenatal and intrapartum antiretroviral drugs but had suboptimal viral suppression at delivery (defined as a detectable viral load (>50 copies/ml) documented in the last 8 weeks of pregnancy and/or at delivery), received only intrapartum antiretroviral drugs, and received no antenatal or intrapartum antiretroviral drugs	Maternal age: mean NR; 70% age ≥20 years Race/ethnicity: 29% white; 40% Black; 3% other Region or country: 37% Europe; 42% Africa Maternal CD4 count: mean NR; 53% ≥200 cells/mm^3 Maternal viral load: mean NR; 27% ≥1,000 copies/ml Gestational age: mean NR; 6% ≤32 weeks; 16% 33 to 36 weeks; 76% ≥37 weeks	5,285 mother-infant pairs	Fair	European Union Seventh Framework Programme; PENTA Foundation

Study Author, year	Study design	No. of centers, Country	Study duration Mean followup	Intervention	Inclusion criteria	Patient characteristics	N	Quality rating	Funding source
		(MoCHiV); European Collaborative Study (ECS) on HIV- infected pregnant women and their children; ECS was considered as 2 studies							
Duryea, 2015[80]	Retrospective cohort	Single site Texas, US	Through birth Period January 1984 to April 2014	A. ART with PI (n=597) B. ART without PI (n=230) C. No ART (n=177)	All HIV+ women who delivered at the institution (University of Texas Southwestern Medical Center, Dallas) during the study period	Maternal age at delivery: 25-28 years (p<0.001) Race/ethnicity: black 64-69%, Hispanic 19%, white 11-16% Gestational age at presentation for prenatal care: 12-24 weeks (p<0.001) CD4 count at presentation: 456-557 cells/mm^3 (p<0.001) CD4 count at delivery: 505-565 cells/mm3 (p=0.349) Duration of diagnosis: 1-2 years (p<0.001)	1,004	Fair	Not reported
Floridia, 2013[57] Italian Group on Surveillance on Antiretroviral Treatment in Pregnancy	Prospective cohort	Unclear Italy	Through birth Period 2001-2011	Various cART regimens	HIV-positive pregnant women with data from the Italian National Programme on Surveillance on Antiretroviral Treatment in Pregnancy	Mean maternal age at conception: 32.3 years Ethnicity: 66% white, 29% African, 4% 0ther CD4 count at first trimester: 464 cells/mm^3 HIV RNA at first trimester: 3.0 copies/mL, log10 HCV coinfection: 22% HBV coinfection: 11% Treatment-naive before pregnancy: 36% Diagnosis of HIV during current pregnancy: 24.6% Week of first antiretroviral therapy in pregnancy: 10.4 Mode of HIV acquisition: 73.1% sexual, 13.6% PWID Maternal ART at first trimester: 55.3% NRTI, 20.4% NNRTI, 27.8% PI	1,257	Fair	Italian Medicines Agency

Study Author, year	Study design	No. of centers, Country	Study duration Mean followup	Intervention	Inclusion criteria	Patient characteristics	N	Quality rating	Funding source
French Perinatal Cohort (ANRS-EPF) study Mandelbrot, 2015[45]	Prospective cohort, no control	90 sites France (but majority from sub-Sahara Africa)	Pre-conception to postpartum Period 2000-2011	cART comparing starting at different times and viral loads A. preconception B. 1st trimester C. 2nd trimester D. 3rd trimester Other interventions: Intrapartum zidovudine 96.0% Neonatal antiretroviral prophylaxis: 91.6% zidovudine monotherapy, 7.5% other Neonatal single dose nevirapine: 4.2%	All HIV-1+ women enrolled in the French Perinatal Cohort delivering in metropolitan France between 2000 and 2011 that received highly active ART (regimen containing ≥3 drugs or 1 drug other than a NRTI) during pregnancy. Women wo received only reverse-transcriptase inhibitor monotherapy or dual therapy were excluded. However, women who switched from a combination therapy to monotherapy or dual therapy were included, as were the small number of women who received monotherapy with ritonavir-boosted protease inhibitors Breastfeeding women were excluded	N=8,678 Age: <25 years 8.7%, 25 to 34 years 56.5%, >34 years 34.8% Geographic origin: metropolitan France 16.6%, sub-Sahara Africa 71.6%, Other 11.8% HIV diagnosis before conception: 80.4% Timing of ART initiation: before conception 47.2% (n=4,095), 1st trimester 8.2% (n=713), 2nd trimester 32.3% (n=2,803), 3rd trimester 12.3% (n=1,067) Initial ART regimen during pregnancy: triple NRTI 5.9%, PI-based 76.1%, NNRTI-based 15.8%, 3 classes 1.2%, other 1.0% Last ART regimen during pregnancy: Zidovudine monotherapy 0.4%, dual NRTI 1.1%, triple NRTI 3.1%, PI-based 81.2%, NNRTI-based 10.9%, 3 classes 1.3%, other 2.0% Maintained initial ART regimen throughout pregnancy: 71.4% Last viral load before delivery (copies/mL): <50 68.0%, undetectable 50 to 400 5.9%, 50 to 399 15.2%, ≥400 10.9% CD4 count before delivery (cells/mm^3): <200 9.0%, 200 to 349 21.0%, 350 to 499 28.0%, ≥500 42.0% Delivery mode: vaginal 42.7%, emergency Cesarean 22.0%, planned Cesarean 35.3%	Eligible: 8,678 mother-infant pairs HIV status of child determined: 8,075 mother-infant pairs	Fair	Agence Nationale de Recherche sur le Sida et les Hepatites Virales
French Perinatal Cohort Study (EPF, ANRS C01/C011) Sibiude, 2012[65]	See above	See above	See Period 1990-2009	A. Zidovudine monotherapy (n=2,975) B. NRTI dual therapy (n=1,664) C. cARV therapy (n=6,738) Substudy: D. Boosted PI	All HIV-1+ women enrolled in the French Perinatal Cohort between 1990 and 2009 Substudy cohort: Singleton births from 2005 through 2009 for mothers enrolled in the EPF- CO1 component of the cohort, which recorded more detailed	A vs. B vs. C Maternal age: median NR; 65% vs. 63% vs. 57% age 25 to 34 Maternal geographic origin - France: 28% vs. 31% vs. 19% Africa: 51% vs. 53% vs. 63% other: 21% vs. 16% vs. 17% D vs. E	13,271	See above	French Agence Nationale de Recherche sur le SIDA (ANRS)

Study Author, year	Study design	No. of centers, Country	Study duration Mean followup	Intervention	Inclusion criteria	Patient characteristics	N	Quality rating	Funding source
				(n=1,066) E. Nonboosted PI (n=187)	data	Maternal age: median NR; 83% vs. 84% age 25 to 39 Maternal geographic origin: Europe: 11% vs. 14% Africa or Caribbean: 88% vs. 83% other: 1% vs. 3%			
French Perinatal Cohort Study (EPF, ANRS C01/C011) Sibiude, 2014[64]	Prospective cohort	90 centers France (but majority from sub-Sahara Africa)	2 years Period 1994-2010	cART	Same as Sibiude 2012	Same as Sibiude 2012 Median maternal age: 31 years Origin sub-Sahara Africa: 61% PWID: 2% Exposed to ART in the first trimester: 42% (5,388)	13,124	See above	See above
French Perinatal Cohort Study (EPF, ANRS C01/C011) and nested PRIMEVA ANRS 135 RCT Sibiude, 2015[63]	Cohort combining prospectively collected observational data and retrospective analysis of data from an RCT	Same as Sibiude 2014	Up to 24 months Period 1994-2010	A. Zidovudine exposure (n=3,262) B. No zidovudine exposure (n=9,626)	Same as Sibiude 2014	Maternal age: mean NR; 60% age 25 to 34 years Race/ethnicity: NR Maternal geographic origin: 22% France; 61% Africa	12,888	See above	French National Agency for Research on AIDS and Viral Hepatitis
Fowler, 2017[52] PROMISE (Promoting Maternal and Infant Survival Everywhere) trial	RCT, open label	14 sites in 7 countries (India, Malawi, South Africa, Tanzania, Uganda, Zambia, Zimbabwe)	Through 6 to 14 days postpartum (antepartum period) Period 2011 to 2014.	A. Zidovudine-based ART (Zidovudine, lamivudine, lopinavir/ritonavir) B. Tenofovir-based ART (tenofovir, emtricitabine, lopinavir/ritonavir) C. Zidovudine alone (zidovudine plus intrapartum single-dose nevirapine with 6 to 14 days of tenofovir and emtricitabine post partum) All infants received nevirapine from birth. During period 1 (April 2011 to September 2012),	Eligibility criteria included a CD4 count of at least 350 cells/mm^3 (or a country-specific threshold for initiating triple- drug ART, if that threshold was higher), gestation of at least 14 weeks and not in labor, no previous use of triple-drug ART, no clinical or immune-related indication for triple-drug ART, a hemoglobin level of at least 7.5 g/dL, an absolute neutrophil count of at least 750 cells/mm^3, an alanine aminotransferase level of less than 2.5 times the upper limit of the normal range, an estimated creatinine clearance of more than 60 ml/min, and no serious pregnancy complications. Receipt of 1	Median age: 26 years Race or ethnic group: 97% black African, 3% Indian, <0.5% other Median CD4 count: 530 cells/mm^3 Median viral load: 3.9 log$_{10}$ copies/ml WHO clinical stage 1: 97% Gestational age: 26 weeks Region or country: 47% East Africa, 33% South Africa, 17% Southern Africa 3% India	Enrolled 3,529 mother-infant pairs Analyzed: 3.490 mother-infant pairs	Fair	The National Institute of Allergy and Infectious Diseases of the NIH, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the National Institute of Mental Health and some study drugs were donated by pharmaceutical

Study Author, year	Study design	No. of centers, Country	Study duration Mean followup	Intervention	Inclusion criteria	Patient characteristics	N	Quality rating	Funding source
				women without HBV were assigned only to zidovudine alone or zidovudine-based ART, but starting in October 2012 due to additional data on tenofovir, women were assigned to any regimen regardless of HBV status (period 2 = October 2012 to October 2014)	or 2 antiretroviral agents for the prevention of mother-to-child transmission in previous pregnancies and for 30 days or fewer during the current pregnancy before enrollment was permitted. Key exclusion criteria were active tuberculosis or receipt of tuberculosis treatment within 30 days before trial entry, HBV infection requiring HBV treatment (patients who did not require HBV treatment could enroll), a structural or conduction heart defect, or a fetus with a serious congenital malformation				companies
Kakkar, 2015[58] Centre Maternel et Infantile sure le SIDA mother-infant cohort	Retrospective cohort	Canada (Montreal)	Period 1988 to 2011	A. Boosted protease inhibitors (PI; n=144) Unboosted PI (n=220) Other treatment (n=166) No treatment (n=59)	Centre Maternel et Infantile sur le SIDA (CMIS) mother child cohort of all HIV positive pregnant women presenting to Centre Hospitalier Universitaire (CHU) Sainte-Justine with attendance for at least two antenatal obstetric visits and singleton live births, at 24 weeks of gestational age or older	A vs. B vs. C vs. D Maternal age: median NR; 60% vs. 63% vs. 66% vs. 62% age 25 to 35 years Race/ethnicity: 79% vs. 63% vs. 66% vs. 64% Black; 15% vs. 28% vs. 26% vs. 34% Caucasian; 5% vs. 9% vs. 9% vs. 2% other	525 mother-infant pairs	Fair	Fonds de Recherche du Quebec-Sante´ (FRQ-S)
Knapp, 2012[59] International Maternal Pediatric Adolescent AIDS Clinical Trials Groups (IMPAACT) protocol P1025	Case-control	Multiple sites International	Through birth Period 2002-2007	Various cART regimens A. Congenital anomaly (n=61) B. No congenital anomaly (n=1,051)	Singleton children born to HIV-infected mothers enrolled in P1025 trial	Maternal age at enrollment, ≤24 years: 33% Maternal age at enrollment, 25 to 34 years: 53% Maternal age an enrollment, ≥35 years: 15% HIV diagnosis prior to pregnancy: 69% Earliest ART use during pregnancy: 47% first trimester, 52% second trimester HIV RNA near labor and delivery <400 copies/mL: 76%	1,112	Fair	NIH, NIAID

Study Author, year	Study design	No. of centers, Country	Study duration Mean followup	Intervention	Inclusion criteria	Patient characteristics	N	Quality rating	Funding source
Kreitchmann, 2014[60] Perinatal and Longitudinal Study in Latin American Countries (LILAC)	Prospective cohort	Multi-site Latin America and Caribbean	Through birth Period 2002-2011	At least 28 days 3rd trimester: A. HAART + PI (888; 59%) B. HAART no PI (410; 27%) Non-HAART (134; 9%) D. No ARV (80; 5%) Total N=1,512	Pregnant women who were enrolled in the NISDI Perinatal and LILAC protocols with first pregnancy after study enrollment, and either a live birth or a stillbirth	Maternal age: mean 28.2 years Maternal education: mean 8.0 years Race/ethnicity: 91.4% Hispanic/Latino; 70% non-Hispanic/Latino; 58% white; 20.4% Black; 21.6% other races.	1,563	Fair	NICHD
Li, 2016[61]	Prospective cohort	10 sites Tanzania	18 months November 2004 to September 2011	A. Initiated ZDV during pregnancy (1768; 53%) B. Initiated HAART during pregnancy (512; 15%) C. Continued HAART from before pregnancy (582; 18%) D. No ART (452; 14%)	HIV-infected pregnant women who had uninfected HIV-exposed infants at birth	Maternal age: median 30 years Race/ethnicity: NR	3,314	Fair	US President's Emergency Plan for AIDS Relief (PEPFAR)
Lopez, 2012[62]	Retrospective cohort (case control)	1 site Spain (Barcelona)	January 1986 to June 2010 Through birth	A. HAART entire pregnancy (n=226) B. HAART 2nd half of pregnancy only (n=72) C. PI during pregnancy (n=178) D. No HAART (n=221)	HIV-infected pregnant women who consecutively attended and delivered in a university referral hospital in Barcelona, Spain, covering an urban area of about a million inhabitants between January 1986 and June 2010 Inclusion criteria were singleton pregnancy and delivery beyond 22 weeks Women with active PWID during pregnancy were excluded	HIV infected only: Maternal age: mean 30 years 8% Black; other race/ethnicity NR Low education level: 50% Prior preterm delivery: 8%	519	Fair	Not reported

Study Author, year	Study design	No. of centers, Country	Study duration Mean followup	Intervention	Inclusion criteria	Patient characteristics	N	Quality rating	Funding source
Lu, 2014[46] Canadian Perinatal HIV Surveillance Program (CPHSP)	Retrospective cohort, no control	Canada (Ontario)	Through birth Period 1996-2008	A. Complete antiretroviral prophylaxis (n=251) B. Incomplete antiretroviral prophylaxis (n=336) A. No antiretroviral prophylaxis (n=58)	Data from women delivering 1996 to 2008 in the Ontaria group of the Canadian Perinatal HIV Surveillance Program	Maternal age: NR Maternal race/ethnicity: 63% Black; 26% white Maternal region or country: 52% Africa; 30% Canada Cesarean section: 43% Screen-detected HIV during pregnancy: NR; 13% were considered late diagnoses (diagnosed at or after delivery)	645 mother-child pairs	Fair	None reported
Moodley, 2016[66]	Respective cross sectional analysis	Single center South Africa	July to December 2011 and January to June 2014	B. Dual ART (AZT/NVP; n=974) C. Triple ART (D4T/3TC/NVP; n=907) D. Fixed-dose ART (EFV/TDF/FTC; n=1,666) No ART (n=148)	Women with viable pregnancies delivering a neonate greater than or equal to 500 g and whose birth outcomes were recorded in the maternity register	Not reported	3,695	Fair	Not reported
Mor, 2017[49]	Cohort	Multi-site Israel	Through birth Period 1985-2011	A. Infants born before 1996 (n=80) B. Infant born after 1997 (HAART introduced; n=716)	All HIV-infected women who delivered in Israel and were local citizens between January 1988 and December 2011	A vs. B Maternal age: 27.6 vs. 30.4 years (p=0.001) Mother born in Ethiopia: 87.5% vs. 81.7% HIV transmission route: endemic country 88.6% vs. 82.6%, drug use 1.3% vs. 5.3%, heterosexual 10.1% vs. 12.1% Previous HIV infected child(ren): 12.0% vs. 9.9% Mother did not receive HAART during pregnancy: 90.0% vs. 46.8% (p=0.001) Caesarian delivery: 11.2% vs. 44.4% (p=0.001) Mother did not receive ART during labor: 95.0% vs. 55.8% Infant did not receive ART after birth: 80.0% vs. 19.9% (p=0.001) Breastfed: 1.3% vs. 1.0%	796 infants born to HIV-infected mothers	Fair	No funding received

Study Author, year	Study design	No. of centers, Country	Study duration Mean followup	Intervention	Inclusion criteria	Patient characteristics	N	Quality rating	Funding source
Pintye, 2017[78] Partners PrEP Study and Partners Demonstration Project	Cohort	Kenya and Uganda	Partners PrEP: 2008 through 2012 Partners Demonstration Project: 2012-2016	A. TDF-containing 3-drug ART (n=208) B. NonTDF-containing 3-drug ART (n=214)	Women who were HIV-infected at enrollment in Partners PrEP or Partners Demonstration Projects and became pregnant during the study period.	A vs B Maternal age 24.7 vs 26.6 years Years of education: 8 vs 7 years Timing of ART initiation: 39.2% vs 26.4% before pregnancy; 20.6% vs 13.0% first trimester; 40.2% vs 60.6% second or third trimester	422 pregnancies	Fair	National Institutes of Health, University of Washington Center for AIDS Research, University of Washington Global Center for Integrated Health of Women Adolescents and Children
Ramokolo, 2017[79] Prevention of Mother to Child Transmission (PWTCT) Program	Cross-sectional cohort	580 sites South Africa	Through 4-8 weeks postpartum Period October 2012 to May 2013	A. Postconception ART (n=780) B. Preconception ART (n=616) C. Zidovudine prophylaxis (n=873) D. No ART (n=330)	Mother-infant pairs attending immunization services at one of 580 primary health facilities offering immunization services consecutively or systematically enrolled, regardless of maternal HIV status	A vs B vs C vs D Maternal age: 3.1% vs 1.8% vs 7.0% vs 5.2% <20 years; 28.5% vs 10.0% vs 36.2% vs 34.9% age 20-25 years; 27.2% vs 23.3% vs 26.1% vs 24.5% age 26-29 years; 29.8% vs 35.2% vs 19.1% vs 20.7% age 30-35 years; 14.6% vs 29.8% vs 11.6% vs 14.7% >35 years Education, <7th grade: 15.1% vs 16.9% vs 21.8% vs 22.1% Black race: 98.2% vs 97.3% vs 96.2% vs 97.5%	2,599 (HIV exposed infants only)	Fair	CDC; South African National Health Scholarship Programme
Sartorius, 2013[54] Kesho Bora Trial	RCT	Africa (3 countries)	January 2005 and August 2008 Duration: 28 weeks of pregnancy until 12 to 24 months after delivery	A. Triple ART, CD4 < 200 (n=118) B. Zidovudine plus single- dose nevirapine, CD4 > 500 (n=128) C. Triple ART, CD4 200 to 500 (n=412) D. Zidovudine plus single-dose nevirapine, CD4 200 to 500 (n=412) Note: >70% breastfed	HIV-infected women had to reside and plan to continue living in the study area until two years post-delivery, have no contraindication to receive ARVs, and no evidence of clinically significant conditions (obstetric, cardiac, respiratory including active tuberculosis, hepatic, gastrointestinal, endocrine, renal, hematologic, psychiatric, neurologic, or allergic) which may interfere with	A vs. B vs. C vs. D Maternal age: 28 vs. 26 vs. 27 vs. 27 years Secondary education or higher: 36% vs. 40% vs. 52% vs. 49%	1,072	Fair	Not reported

Study Author, year	Study design	No. of centers, Country	Study duration Mean followup	Intervention	Inclusion criteria	Patient characteristics	N	Quality rating	Funding source
					study interventions				
Short, 2013[67]	Retro-spective analysis	1 site United Kingdom (London)	Period 1996 to 2010	A. Zidovudine (n=65) Dual NRTI (n=7) Triple NRTI (n=5) Short-term cART (n=59) E. Preconception cART (n=131) New continuous cART (n=56)	HIV-positive pregnant women managed by a single, multidisciplinary team at St Mary's Hospital	Maternal age: median 32 years Race: 78% Black African; other races NR Maternal history of any AIDS-defining illness: 11.5% Median gestational age: 13 weeks	331	Fair	Not reported
Surveillance Monitoring for Antiretroviral Treatment Toxicities (SMARTT) study and Pediatric HIV/AIDS Cohort Study (PHACS) Nozyce, 2014[69]	Prospective cohort	Multi-site United States	Up to 13 years Period 2007-2012	Any maternal cART regimen containing at least 3 antiretroviral drugs from at least 2 drug classes, analyzed by assessment scale: WPPSI-III (Wechsler Preschool and Primary Scale of Intelligence, 3rd Edition; n=369) WASI (Wechsler Abbreviated Scale of Intelligence; n=452) WIAT-II-A (Wechsler Individual Achievement Test, 2nd Edition; n=451) Other intervention: Neonatal prophylaxis defined as antiretroviral drugs used during the first 8 weeks of life	All children enrolled in the SMARTT Static cohort (HIV-exposed) that completed a valid, age-appropriate measure of cognition and/or academic achievement in English and had information regarding in utero and neonatal ARV exposure	Male: 49 to 52% Ethnicity: 75 to 77% black, 19 to 25% Hispanic Preterm births (<37 weeks): 17 to 21% Low birth weight (<2,500 grams): 18 to 20% Households ≤$20,000 annual income: 59 to 69% Caregivers with less than a high school education: 32 to 34% First viral load during pregnancy > 400: 60 to 72% Last viral load prior to delivery >400: 19 to 33%	739	Fair	Eunice Kennedy Shriver National Institute of Child Health and Human Development; National Institute on Drug Abuse, the National Institute of Allergy and Infectious Diseases, the Office of AIDS Research, the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, the National Institute on Deafness and Other Communicatio n Disorders, the National Heart Lung and Blood Institute, the National Institute of Dental and Craniofacial

Study Author, year	Study design	No. of centers, Country	Study duration Mean followup	Intervention	Inclusion criteria	Patient characteristics	N	Quality rating	Funding source
									Research, and the National Institute on Alcohol Abuse and Alcoholism, Harvard University and Tulane University and NIH
Pediatric HIV/AIDS Cohort Study (PHACS) Lipshultz, 2015[68]	Same as Nozyce 2014	Same as Nozyce 2014	Mean 4 years Period 2007-2012	A. HIV-exposed uninfected (HEU; n=417) B. HIV unexposed controls (n=98)	SMARTT enrolled children with echocardiogram and unexposed controls	A vs. B Maternal age: 28 vs. 26 years Race: 62% vs. 70% Black; 30% vs. 26% white; 9% vs. 4% other; 39% vs. 22% Hispanic Child age at time of echocardiogram: 4.0 vs. 4.8 years	515	Same as Nozyce 2014	NIH
Surveillance Monitoring for Antiretroviral Treatment Toxicities (SMARTT) study of the Pediatric HIV/AIDS Cohort Study (PHACS) and P1025 study of the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) cohort Rough, 2018[82]	Cohort	2 multisite cohorts USA	Period 2007-2016 for Dynamic cohort of the SMARTT study and 2002-2013 for the P1025 study	A. TDF + FTC + LPV/r (128; 8%) B. ZDV + 3TC + LPV/r (954; 59%) C. TDF + FTC + ATV/r (539; 33%)	All infants with an observed birth outcome in the SMARTT or P1025 study, when the first ART regimen that their mothers used during pregnancy was one of the following: TDF + FTC + LPV/r, ZDV + 3TC + LPV/r, or TDF + FTC + ATV/r	A vs. B vs. C Maternal age: 39.1% vs. 37.2% vs. 25.2% ≤24 years, 52.3% vs. 49.6% vs. 54.4% 25-34 years, 8.6% vs. 13.1% 20.2% ≥35 years Race: 11.7% vs. 7.1% vs. 8.2% non-Hispanic white, 63.3% vs. 64.0% vs. 67.7% non-Hispanic black, 23.4% vs. 27.0% vs. 22.3% Hispanic, 0.8% vs. 1.2% vs. 1.7% other First CD4 count in pregnancy: 23.4% vs. 20.3% vs. 18.6% <250 cells/mm^3, 36.7% vs. 39.9% vs. 38.0% 250-500 cells/mm^3, 36.7% vs/ 38.3% vs/ 41.7% >500 cells/mm^3 First viral RNA in pregnancy: 47.7% vs. 29.5% vs. 51.4% <400 copies/ml, 25.8% vs. 37.8% vs. 25.4% 400-10,000 copies/ml, 25.8% vs. 32.0% vs. 22.6% >10,000 copies/ml Timing of regimen initiation: 45.3% vs. 11.6% vs. 49.2% before pregnancy, 14.1% vs. 12.1% vs. 15.2% first trimester, 40.6% vs. 76.3%	1,621	Fair	Same as Nozyce 2014

Study Author, year	Study design	No. of centers, Country	Study duration Mean followup	Intervention	Inclusion criteria	Patient characteristics	N	Quality rating	Funding source
						35.6% second or third trimester			
Surveillance Monitoring for Antiretroviral Treatment Toxicities (SMARTT) study and Pediatric HIV/AIDS Cohort Study (PHACS) Siberry, 2012[73]	Prospective cohort	Multi-site United States	Through infant growth at 1 year Period through January 2011	A. TDF-containing ART (n=449) B. nonTDF-containing ART (n=1,580)	Data collected in the SMARTT study of the PHACS network, restricted primary models to consider only those exposed in utero to combination antiretroviral regimens with vs without TDF	Race/ethnicity: black 66%, Latino 33% Caesarian delivery: 54% Gestational age: <32 weeks 3%, 32-37 weeks 17%, 37+ weeks 76% Maternal CD4 count <250 cells/mm^3 at delivery: 15% HBV+: 2%	2,029	Same as Nozyce 2014	Same as Nozyce 2014
Surveillance Monitoring for Antiretroviral Treatment Toxicities (SMARTT) study and Pediatric HIV/AIDS Cohort Study (PHACS) Watts, 2013[70]	Prospective cohort	22 sites United States	Unclear Period 2007-2010	Various maternal cART regimens	HIV-infected mothers and their children enrolled in SMARTT study of the PHACS network. This analysis limited to singleton gestations with maternal enrollment on or before October 2010	Mean maternal age at delivery: 27 years Ethnicity: 65% black, 28% white, 7% other [34% Hispanic] Annual household income <$20,000: 63% CD4 count <200: 13% CD4 count 200 to 500: 46% CD4 count >500: 36% Antiretroviral regimen: 3% none, 7% monotherapy or dual therapy, 71% combination with PI (with or without NNRTI), 10% combination with >or=3 NRTIs, 9% combination with NNRTI (no PI) First trimester use of cART: 40% Second trimester use of cART: 63% Third trimester use of cART: 76%	1,869	Same as Nozyce 2014	Same as Nozyce 2014
Surveillance Monitoring for Antiretroviral Treatment Toxicities (SMARTT) study and Pediatric HIV/AIDS Cohort Study (PHACS)	Combined data from prospective and retrospective cohorts	Same as Nozyce 2014	Period 2007-2012	A. Any ART (n=1,219) Any HAART (n=1,025) C. NNTRI (n=214) D. NRTI (n=1,211) E. Protease inhibitor (n=887) F. No ART exposure of any kind (n=1,298 to	Static (retrospective) cohort: Mothers or caregivers and their children younger than 12 years who had detailed information on ARV use during pregnancy and pregnancy outcomes Dynamic (prospective) cohort: Pregnant women and their infants between	Maternal age: mean NR; 13% >35 years Race/ethnicity: 66% Black; 27% white; 0.5% other; 33% Latino/Hispanic Caregiver not a HS graduate: 5%	2,580	Same as Nozyce 2014	Same as Nozyce 2014

Study Author, year	Study design	No. of centers, Country	Study duration Mean followup	Intervention	Inclusion criteria	Patient characteristics	N	Quality rating	Funding source
Williams, 2015[71]				2,303 depending on comparison) All exposure was during first trimester	22 weeks of gestation and 1 week after delivery				
Surveillance Monitoring for Antiretroviral Treatment Toxicities (SMARTT) study and Pediatric HIV/AIDS Cohort Study (PHACS) Williams, 2016[72]	Same as Nozyce 2014	Same as Nozyce 2014	Period 2007-2012	A. Any HAART exposure (n=2,211) B. NNTRI exposed (n=395) C. NRTI (n=1,907) D. Protease inhibitor (n not reported) E. No ART exposure of any kind (n=469)	SMARTT cohort children with adverse event trigger cases, defined as language impairment, metabolic abnormality, impaired growth, neurologic diagnosis, neurodevelopmental impairment, elevated blood lactate, chemistry or hematology toxicity, or hearing impairment	No adverse event vs. adverse event Maternal age: mean NR; 33% vs. 33% <25 years Infant characteristics- 49% vs. 47% female Race/ethnicity: 68% vs. 61% Black; 26% vs. 32% white; 4% vs. 4% Puerto Rican; 1% vs. 1% other; 32% vs. 37% Hispanic 17% vs. 25% low birth weight 19% vs. 24% preterm birth (<37 weeks gestation) 55% vs. 56% C-section	2,680	Same as Nozyce 2014	Same as Nozyce 2014
Snijdewind, 2018[81] ATHENA cohort	Retro-spective cohort	26 centers The Netherlands	Period 1997-2015	A. PI-based (928; 67%) B. NNRTI-based (438; 31%) C. Both or NRTI (12; 1%)	ATHENA cohort database; HIV-positive women >18 years of age who gave birth to HEU infants after a minimum 24 weeks pregnancy; singleton births; includes women who started cART pre-conception as well as those who began post-conception	Maternal age: median 29 Region of origin: 61.3% sub-Sahara Africa, 20.7% Western Europe, 16.5% other Mode of delivery: 44.5% spontaneous labor, 13.6% elective C-section, 6.8% emergency C-section, 27.7% unknown CD4 count: median 520 cells/mm^3) HIV RNA: 79.1% $\leq$500 copies/ml Infant birth weight: median 3.090 kg Duration of pregnancy: 85.3% >37 weeks, 11.9% <37 weeks	1,378	Fair	Dutch Health Ministry

Study Author, year	Study design	No. of centers, Country	Study duration Mean followup	Intervention	Inclusion criteria	Patient characteristics	N	Quality rating	Funding source
Tookey, 2016[48] National Study of HIV in Pregnancy and Childhood (NSHPC)	Retro-spective cohort, no control	United Kingdom and Ireland	Through birth Period 2003-2012	LPV/r	National Study of HIV in Pregnancy and Childhood participants with pregnancies that were due to deliver	Maternal age: median 30 years Maternal race/ethnicity: 15% white; 77% Black; 8% other Maternal region/country: 14% UK/Ireland; 77% Africa; 10% other	4,118 mothers, 4,864 pregnancies	Fair	Health Protection Agency, National Screening Committee and the Welton Foundation, Medical Research Council, National Institute for Health Research Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London
Zash, 2016[76]	Cohort	2 hospitals Botswana	Through birth Period May 2009 to April 2011 and April 2013 to April 2014	A. TDF-FTC-EFV at conception (n=165) B. Other 3 drug ART at conception (n=2,006) C. TDF-FTC-EFV during pregnancy (n=1,054) D. Other 3 drug ART during pregnancy (n=2,172)	All women who delivered live-born or still-born infants at 8 government maternity wards in Botswana Excluded births that occurred before arrival at hospital and at gestational age <24 weeks	HIV infected, years 2009-2011 vs. 2013-2014: Maternal age: 28.9 vs. 30.2 years Any medical history: 17.4% vs. 19.5% Hypertension in pregnancy: 19.1% vs. 17.5% Anemia in pregnancy: 59.0% vs. 48.1% Primiparous 20.6% vs. 15.9% No prenatal care: 5.7% vs. 4.8% Unknown HIV status: 4.7% vs. 1.2% No ARVs during pregnancy: 16.1% vs. 12.3% Initiated ARVs <4 weeks prior to delivery: 24.7% vs. 17.0% Initiated ARVs <28 weeks	32,583 births, 9,445 HIV infected women	Fair	Centers for Disease Control and National Institutes of Health/ National Institute of Allergy and Infectious Diseases

Study Author, year	Study design	No. of centers, Country	Study duration Mean followup	Intervention	Inclusion criteria	Patient characteristics	N	Quality rating	Funding source
						gestational age: 22.0% vs. 59.8% Median CD4 count: 388 vs. 415			
Zash, 2017[75]	Surveillance cohort	8 government hospitals Botswana	Through birth Period August 2014 to August 2016	A. TDF-FTC-EFV (n=2,472) B. TDF-FTC-NVP (n=760) C. TDF-FTC-LPV-R (n=231) D. ZDV-3TC-NVP (n=1,365) E. ZDV-3TC-LPV-R (n=167)	All women who delivered live-born or still-born infants at 8 government maternity wards in Botswana Excluded births that occurred before arrival at hospital and at gestational age <24 weeks, and HIV positive mothers with no ART exposure, unknown ART timing, or unknown ART exposure	Maternal age: median 31 years Primiparous: 14.8% Gestational age at antenatal care presentation: median 17 weeks Received no prenatal care: 3.3% Alcohol consumption or smoking during pregnancy: 8.1% Cesarean delivery: 23.7% ART prior to conception: 5,780 infants, breakdown below: TDF-FTC-EFV: 2,503 ZDV-3TC-NVP: 1,403 TDF-FTC-NVP: 775 Unspecified ART: 547 TDF-FTC-LPV-R: 237 ZDV-3TC-LPV-R: 169 Other 3-drug ART: 104 Nonstandard ART: 21 Changed or terminated ART: 21 ART after conception: 4,812 infants, breakdown below: TDF-FTC-EFV: 4,569 Other ART regimen: 129 Unspecified ART: 94 Changed or terminated ART: 14 ZDV monotherapy: 3 Nonstandard ART: 3	47,124 total births 11,932 HIV exposed births 10,592 included in analysis	Fair	National Institutes of Health

Abbreviations: 3TC=lamivudine; ANRS=French Agence Nationale de Recherche sur le SIDA; ART=antiretroviral therapy; ARV=antiretroviral drug; AZT=zidovudine (Retrovir); cART=combination antiretroviral therapy; CD4=cluster of differentiation 4; CDC=centers for disease control; CHIPs=collaborative HIV paediatric study; CHU=centre Hospitalier Universitaire; CMIS=centre maternal et infantile sur le SIDA; CoRISPE-Cat=Catalan cohort of HIV-infected children; D4T=stavudine (Zerit); ECS=European Collaborative Study; EFV=efavirenz;EPF-CO1; FRQ-S=fonds de recherche du quebec-sante; FTC = emtricitabine; g/dL=grams per deciliter; g=gram; HAART=highly active antiretroviral therapy; HBV=hepatitis B virus; HCV=herpes simplex virus; HEU=HIV-exposed uninfected; HIV=human immunodeficiency syndrome; HIV RNA=human immunodeficiency syndrome ribonucleic acid; ITLR=Italian register for HIV infection in children; LPV/r=lopinavir/ritonavir; ml=milliliter; ml/min = milliliter per minute; mm=millimeter; MoCHiV=Swiss mother and child HIV cohort study; NIAID=national institute of allergy and infectious diseases; NICHD=national institute of child health and human development; NIH=national institutes of health; NISDI=NICHD international site development initiative; NNRTI=nonnucleoside reverse transcriptase inhibitors; NR=not reported; NRTI=nucleoside reverse transcriptase inhibitors; NSHPC=national study of HIV in pregnancy and childhood; NVP=nevirapine; p=probability; PEPFAR=U.S. president's emergency plan for AIDS relief; PI=protease inhibitor; PWID=people who inject drugs; RCT=randomized controlled trial; SMARTT=science moving towards research translation and therapy; TDF=tenofovir disoproxil fumarate;

vs=versus; WASI=wechsler abbreviated scale of intelligence; WHO=world health organization; WIAT-II-A=wechsler individual achievement test; WPPSI-III=wechsler preschool and primary scale of intelligence, 3d edition; ZDV=zidovudine.

Appendix B2b. Evidence Table of Included Studies – Results

Study Author, year	Intervention	HIV transmission	Adverse events
Aaron, 2012[55]	A. Any ART initiation during pregnancy (n=137) B. NNRTI use (n=39) C. PI use (n=117)	Not reported	A. Small for gestational age, 10th percentile: aOR 1.47 (95% CI 0.60 to 3.58); 3rd percentile: aOR 4.64 (95% CI 0.81 to 26) B. Small for gestational age, 10th percentile: aOR 0.28 (95% CI 0.10 to 0.75); 3rd percentile: 0.16 (95% CI 0.03 to 0.91) C. Small for gestational age, 10th percentile: aOR 1.68 (95% CI 0.79 to 3.55); 3rd percentile: aOR 2.73 (95% CI 0.83 to 9.00)
Antiretroviral Pregnancy Registry, 2018[83]	Preferred initial treatment drugs in US: A. ABC (1131; 12%) B. 3TC (5008; 54%) C. TDF (3535; 38%) D. FTC (2785; 30%) E. ATV (1279; 14%) F. Ritonavir (3155; 34%) G. Darunavir (456; 5%) H. Raltegravir (291; 3%) Alternative initial treatment drugs in US: I. ZDV (4178; 45%) J. LPV (1418; 15%) K. EFV (1023; 11%) L. RPV (297; 3%)	Not reported	Congenital abnormalities First-trimester exposed vs. unexposed, unadjusted OR (our analysis): A. 1.04 (0.72 to 1.52) B. 1.26 (0.98 to 1.63) C. 0.77 (0.59 to 1.01) D. 0.85 (0.64 to 1.13) E. 0.77 (0.52 to 1.15) F. 0.74 (0.56 to 0.97) G. 0.88 (0.48 to 1.61) H. 1.14 (0.58 to 2.24) I. 1.38 (1.08 to 1.77) J. 0.74 (0.50 to 1.09) K. 0.84 (0.55 to 1.29) L. 0.36 (0.11 to 1.12)
Berard, 2017[77] Quebec Pregnancy Cohort	A. No ART exposure (n=214,042) B. First trimester ART exposure (n=198)	Not reported	A vs B Any major congenital malformation: aOR 0.59 (95% CI 0.33–1.06) Nervous system major malformation: aOR 0.21 (95% CI 0.03–1.83) Circulatory system major malformation: aOR 0.75 (95% CI 0.31–1.85) Digestive system major malformation: aOR 0.80 (95% CI 0.14–4.40) Urinary system major malformation: aOR 0.14 (95% CI 0.02–1.12) Musculoskeletal major malformation: aOR 0.59 (95% CI 0.21–1.68) Specific malformations for which there was a statistically significant difference between groups - Small intestine: aOR 10.32 (95% CI 2.85–37.38) Other digestive congenital malformations (excluding tongue, mouth, pharynx, esophagus, intestines, gall bladder, bile ducts, liver): aOR 6.83 (95% CI 2.18–21.35) *OR adjusted for HIV diagnosis in the 6 months prior to and during pregnancy, maternal age, place of residence and welfare status, hospitalizations and emergency department visits, physician and specialist visits, number of other medication use and number of prescribers, maternal diabetes, hypertension and asthma.*
Chagomerana, 2017[74]	A. ART (n=2,909) B. No ART (n=165)	Not reported	Overall preterm birth: 24% (731/3,074) A vs. B Preterm birth: 31% (690/2,219) vs. 33% (41/124), aRR 1.14, 95% CI 0.84 to 1.55 Extremely to very preterm (27-32 weeks) birth: 6% (133/2,219) vs. 13% (16/124), aRR 2.33, 95% CI 1.39 t0 3.92

Study Author, year	Intervention	HIV transmission	Adverse events
Chen, 2012[56]	A. Continued HAART during pregnancy (n=2,189) B. Initiated HAART during pregnancy (n=1,101) C. Initiated zidovudine during pregnancy (n=4,625) D. No ART (n=1,234)	Not reported	A vs. (B or C or D) Preterm delivery: 26.5% (543/2,050) vs. 22.7% (1,515/6,676); aOR 1.2 (95% CI 1.1 to 1.4) Small for gestational age: 26.1% (562/2,151) vs .15.6% (1,067/6,840); aOR 1.8 (95% CI 1.6 to 2.1) Stillbirth: 6.3% (1,38/2,189) vs 4.1% (283/6,960); qOR 1.5 (95% CI 1.2 to 1.8) A vs. B Small for gestational age: 26.1% (562/2,151) vs 21.6% (237/1,095); aOR 1.3 (95% CI 1.0 to1.5) B vs. C Preterm delivery: 19.8% (177/892) vs 14.2% (533/3,762); aOR 1.4 (95% CI 1.2 to 1.8) Small for gestational age: 21.5% (200/930) vs. 14.2% (542/3,811); aOR 1.5 (95% CI 1.2 to 1.9) Stillbirth: 4.7% (44/936) vs. 1.7% (64/3,827); aOR 2.5 (95% CI 1.6 to 3.9)
Chiappini, 2013[47] European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)	A. 3 or more drugs (n=2,355) B. 2 drugs (n=255) C. 1 drug (n=681) D. No therapy (n=1,933)	A. 2.8% (65/2355); AOR 0.36 (95% CI 0.23 to 0.57), p<0.001 B. 1.2% (3/255); AOR 0.12 (95% CI 0.04 to 0.40), p<0.001 C. 3.1% (21/681); AOR 0.33 (95% CI 0.19 to 0.55), p<0.005 D. 14.3% (158/1,107); AOR 1 reference	Not reported
Duryea, 2015[80]	A. ART with PI (n=597) B. ART without PI (n=230) C. No ART (n=177)	Not reported	Preterm birth (<37 weeks): A. 14% (82/597), 1 reference B. 13% (31/230), 0.9 (0.5 to 1.5) C. 21% (37/177), 1.0 (0.5 to 2.0) SGA (<10th percentile): 4% to 10% depending on ART regimen: A. 19% (116/597), 1 reference B. 23% (54/230), 1.3 (0.8 to 1.9) C. 22% (39/177) 1.1 (0.6 to 2.0)
Floridia, 2013[57] Italian Group on Surveillance on Antiretroviral Treatment in Pregnancy	Various cART regimens	Data on transmission available for 868 infants, of which 4 were HIV positive, 0.5%, 95% CI 0.0 to 0.9	Birth defects (Antiretroviral Pregnancy Registry criteria): Overall: 3.3% (42/1,257) for exposure at any time to ART during pregnancy Exposure to any antiretroviral drug during the first trimester: prevalence 3.2%, 95% CI 1.9 to 4.5 (23 cases with defects) vs. initial exposure to ART after the first trimester: prevalence 3.4%, 95% CI 1.9 to 4.9 (19 cases) By drug: No associations found between major birth defects and first trimester exposure to any ART: OR 0.94, 95% CI 0.51 to 1.75 NRTI: OR 0.95, 95% CI 0.51 to 1.76 NNRTI: OR 1.20, 95% CI 0.56 to 2.55 PI: OR 0.92, 95% CI 0.43 to 1.95 Also, no associations found for individual drugs

Study Author, year	Intervention	HIV transmission	Adverse events
			Still birth: 0.8% (10/1,257) Death within 2 weeks of delivery: 4 (different from the 4 with HIV, and none had birth defects. Reasons: 2 complications from prematurity and 2 neonatal sepsis Preterm delivery (<37 weeks): 20.9% Very preterm delivery (<32 weeks): 2.5% Low birthweight (2,500 grams): 22.1% Very low birthweight (<1,500 grams): 2.5%
French Perinatal Cohort (ANRS-EPF) study Mandelbrot, 2015[45]	ART comparing starting at different times and viral loads A. preconception B. 1st trimester C. 2nd trimester D. 3rd trimester Other interventions: Intrapartum zidovudine 96.0% Neonatal antiretroviral prophylaxis: 91.6% zidovudine monotherapy, 7.5% other Neonatal single dose nevirapine: 4.2%	Overall mother-to-child HIV transmission: 0.7%, 95% CI 0.5 to 0.9 (56/8,075) A vs. B vs. C vs. D Mother-to-child HIV transmission based on timing of ART initiation: 0.2% (6/3,505) vs. 0.4% (3/709) vs. 0.9% (24/2,810) vs. 2.2% (23/1,051), p<0.001 Mother-to-child HIV transmission based on viral load (copies/mL) near delivery: <50 0.3 (95% CI 0.1 to 0.4), undetectable >50 0.2 (95% CI <0.1 to 1.2), 50 to 399 1.5 (95% CI 0.9 to 2.4), ≥400 2.8 (95% CI 1.8 to 4.2), p<0.001, adjusted OR 4.0, 95% CI 1.9 to 8.2	A vs. B vs. C vs. D Live born: 99.1% (4,055/4,095) vs. 99.2% (707/713) vs. 99.1% (2,772/2,803) vs. 99.6% (1,062/1,067) Median birth weight (grams): 3,020 vs. 3,065 vs. 3,018 vs. 3,040 Median length at birth (cm): 48.0 vs. 48.0 vs. 48.0 vs. 49.0 Median head circumference (cm): 34.0 vs. 34.0 vs. 34.0 vs. 34.0 5 minute Apgar score 8-10: 96.4% (3,776/4,095) vs. 97.3% (659/713) vs.97.3% (2,618/2,803) vs. 97.7% (1,017/1,067) Gestational age at delivery: <32 weeks: 4.0% (164/4,095) vs. 3.2% (23/713) vs. 3.6% (100/2,803) vs. 0.7% (7/1,067) 32 to 36 weeks: 13.4% (549/4,095) vs. 12.8% (91/713) vs. 12.0% (336/2,803) vs. 11.6% (124/1,067) ≥37 weeks: 82.6% (3,382/4,095) vs. 84.0% (599/713) vs. 84.4% (2,367/2,803) vs. 87.7% (936/1,067) Stillbirth: 1.0% (38/4,095) vs. 0.8% (6/713) vs. 0.9% (25/2,803) vs. 0.4% (4/1,067) Death before HIV diagnosis: 0.5% (22/4,095) vs. 0.6% (4/713) vs. 0.5% (15/2,803) vs. 0.3% (3/1,067)
French Perinatal Cohort Study (EPF, ANRS C01/C011) Sibiude, 2012[65]	A. Zidovudine monotherapy (n=2,975) B. NRTI dual therapy (n=1,664) C. cARV therapy (n=6,738) Substudy: D. Boosted PI (n=1,066) E. Nonboosted PI (n=187)	Not reported	<u>Full cohort, A vs. B vs. C</u> Premature birth: 9.6% vs.11.3% vs. 14.7%; B vs. A: aOR 1.24 (95% CI 0.96 to1.60); C vs. A: aOR 1.69 (95% CI 1.38 to 2.07) <u>Substudy, D vs. E</u> Premature birth: 14.4% vs. 9.1%; aHR 2.03 (95% CI 1.06 to 3.89) Gestational diabetes: 2.9% vs. 1.6%; p=0.46
French Perinatal Cohort Study (EPF, ANRS C01/C011) Sibiude, 2014[64]	cART	Not reported	Overall birth defects prevalence (EUROCAT classification): 4.4% (575/13,124), 95% CI 4.0 to 4.7 Overall birth defects prevalence (MACDP classification): 7.0% (914/13,124), 95% CI 6.5 to 7.4 Premature delivery (<37 weeks): 14.5% (1,901/13,124) Low birth weight (<2,500 grams): 16.2% (2,127/13,124) After adjustment for potential confounders, and by drug Significant association found between exposure to zidovudine in the first trimester and congenital heart defects: 2.3%, (74/3,267), aOR 2.2, 95% CI 1.3 to 3.7 Significant association found between exposure to didanosine and head and neck defects: 0.5%, aOR 3.4, 95% CI 1.1 to 10.4 Significant association found between exposure to indinavir and head and

Study Author, year	Intervention	HIV transmission	Adverse events
			neck defects: 0.9%, aOR 3.8, 95% CI 1.1 to 13.8 Significant association found between exposure to efavirenz and neurological defects (MACDP classification): n=4, aOR 3.0, 95% CI 1.1 to 8.5; but it was not significant using the EUROCAT classification: aOR 2.1, 95% CI 0.7 to 5.9 No association found between birth defects and lopinavir or ritonavir (with a power >85%) nor for nevirapine, tenofovir, stavudine, abacavir (with a power >70%)
French Perinatal Cohort Study (EPF, ANRS C01/C011) and nested PRIMEVA ANRS 135 RCT Sibiude, 2015[63]	A. Zidovudine exposure (n=3,262) B. No zidovudine exposure (n=9,626)	Overall mother-to-child transmission: 1.3% (169/12,888)	A vs. B Congenital heart defect (CHD): 1.5% vs. 0.77%; aOR 2.2 (95% CI 1.5 to 3.2) -CHD, boys: aOR 2.1 (95% CI 1.2 to 3.7 -CHD, girls: aOR 2.0 (95% CI 1.2 to 3.2); p for interaction=0.89 Echocardiography (based on RCT data only): girls more likely than boys to show left ventricular shortening fraction at one month (p for interaction=0.3); no significant differences for other measures at 1 month or 1 year
Fowler, 2017[52] PROMISE (Promoting Maternal and Infant Survival Everywhere) trial	A. Zidovudine-based ART (Zidovudine, lamivudine, lopinavir/ritonavir) vs. B. Tenofovir-based ART (tenofovir, emtricitabine, lopinavir/ritonavir) vs. C. Zidovudine alone (zidovudine plus intrapartum single-dose nevirapine with 6 to 14 days of tenofovir and emtricitabine post partum) All infants received nevirapine from birth. During period 1 (April 2011 to September 2012), women without HBV were assigned only to zidovudine alone or zidovudine-based ART, but starting in October 2012 due to additional data on tenofovir, women were assigned to any regimen regardless of HBV status (period 2 = October 2012 to October 2014)	Periods 1 and 2 A vs. B vs. C Rate of transmission: 0.5% (7/1,385) vs. 0.6% (2/325) vs. 1.8% (25/1,386), difference A and B vs. C: -1.3 percentage points (repeated CI - 2.1 to -0.4) Gestational age at trial entry <34 weeks: 0.5% (6/1230) vs. 0.4% (1/274) vs. 1.3% (16/1,229), difference A and B vs. C: -0.8 percentage points (repeated CI -1.6 to -0.1) Gestational age at trial entry ≥34 weeks: 0.6% (1/154) vs. 2.0% (1/51) vs. 5.7% (9/157), difference A and B vs. C: -4.8 percentage points (repeated CI -8.9 to -0.6) CD4 count at trial entry, 350-499 cells/mm^3: 0.7% (4/592) vs. 0.7% (1/136) vs. 2.8% (16/577), difference A and B vs. C: -2.1 percentage points (repeated CI -3.7 to -0.5) CD4 count at trial entry, ≥500 cells/mm^3: 0.4% (3/793) vs. 0.5% (1/189) vs. 1.1% (9/809), difference A and B vs. C: -0.7 percentage points (repeated CI -1.6 to 0.2) Viral load at trial entry, <1,000 copies/ml: 0.4% (1/253) vs. 0% (0/57) vs. 0% (0/299), difference A and B vs. C: 0.3 percentage points (repeated CI -0.4 to 1.0) Viral load at trial entry, ≥1,000 copies/ml:	Periods 1 and 2 A vs. C Maternal any grade ≥2 adverse event: 21.1% (318/1,505) vs. 17.3% (261/1,510), p=0.008 Maternal grade ≥2 abnormal blood chemical value: 5.8% (88/1,505) vs. 1.3% (19/1,505), p<0.001 Any adverse pregnancy outcome: 40.0% (563/1,407) vs. 27.5% (389/1,414), p<0.001 Low birth weight, <2,500g: 23.0% (306/1,332) vs. 12.0% (161/1,347), p<0.001 Preterm delivery, <37 weeks: 20.5% (288/1,406) vs. 13.1% (185/1,411), p<0.001 Any severe adverse pregnancy outcome: 7.1% (99/1,385) vs. 5.9% (83/1,399), p=0.22 Very preterm delivery, <34 weeks: 3.1% (44/1,406) vs. 2.6% (37/1,411), p=0.43 Infant death through week 1: 1.2% (17/1,419) vs. 2.0% (28/1,532), p=0.13 Period 2 A vs. B Maternal any grade ≥adverse event: 15.8% (61/385) vs. 15.8% (60/380), p>0.99 Maternal grade ≥abnormal blood chemical value: 4.7% (18/385) vs. 2.9% (11/380), p=0.26 Any adverse pregnancy outcome: 37.5% (123/328) vs. 34.7% (111/320), p=0.46 Low birth weight, <2,500g: 20.4% (65/319) vs. 16.9% (51/301), p=0.30 Preterm delivery, <37 weeks: 19.7% (68/346) vs. 18.5% (62/335), p=0.77 Any severe adverse pregnancy outcome: 4.3% (14/322) vs. 9.2% (29/314), p=0.02 Very preterm delivery, <34 weeks: 2.6% (9/346) vs. 6.0% (20/335), p=0.04 Infant death through week 1: 0.6% (2/346) vs. 4.4% (15/341), p=0.001 Period 2 B vs. C

Study Author, year	Intervention	HIV transmission	Adverse events
		0.5% (6/1,129) vs. 0.7% (2/268) vs. 2.3% (25/1,083), difference A and B vs. C: -1.7 percentage points (repeated CI -2.8 to -0.7)	Maternal any grade ≥adverse event: 15.8% (60/380) vs. 15.0% (59/393), p=0.77 Maternal grade ≥abnormal blood chemical value: 2.9% (11/380) vs. 0.8% (3/392), p=0.03 Any adverse pregnancy outcome: 34.7% (111/320) vs. 27.2% (91/334), p=0.04 Low birth weight, <2,500g: 16.9% (51/301) vs. 8.9% (28/315), p=0.004 Preterm delivery, <37 weeks: 18.5% (62/335) vs. 13.5% (46/341), p=0.09 Any severe adverse pregnancy outcome: 9.2% (29/314) vs. 6.7% (22/329), p=0.25 Very preterm delivery, <34 weeks: 6.0% (20/335) vs. 3.2% (11/341), p=0.10 Infant death through week 1: 4.4% (15/341) vs. 3.2% (11/349), p=0.43
Kakkar, 2015[58] Centre Maternel et Infantile sure le SIDA mother-infant cohort	A. Boosted protease inhibitors (PI; n=144) B. Unboosted PI (n=220) C. Other treatment (n=166) D. No treatment (n=59)	Not reported	A vs. B Preterm delivery: 19.3% vs. 10.8%; aOR 2.17 (95% CI 1.05 to 4.51) C vs. B Preterm delivery: 8.8% vs. 10.8%; aOR 0.67 (95% CI 0.27 to 1.63) D vs. B Preterm delivery: 25% vs. 10.8%; aOR 1.50 (95% CI 0.33 to 6.78)
Knapp, 2012[59] International Maternal Pediatric Adolescent AIDS Clinical Trials Groups (IMPAACT) protocol P1025	Various cART regimens A. Congenital anomaly (n=61) B. No congenital anomaly (n=1,051)	0.63% (7/1,112)	Congenital anomalies (MACDP guidelines): Overall: 5.5% (61/1,112 infants), prevalence 5.49/100 live births, 95% CI 4.22 to 6.99, including 80 anomalies: cardiovascular (n=33), musculoskeletal (n=15), renal (n=9), genitourinary (n=6), craniofacial (n-4), and central nervous system (n=2) Preterm birth (<37 weeks): 17% (191/1,112) Low birth weight (<2,500 grams): 14% (153/1,112) Efavirenz, 1st trimester exposure: OR 2.84 (1.13-7.16) No other significant adjusted ORs for other drugs or timing of exposure
Kreitchmann, 2014[60] Perinatal and Longitudinal Study in Latin American Countries (LILAC)	At least 28 days 3rd trimester: A. HAART + PI (888; 59%) B. HAART no PI (410; 27%) C. Non-HAART (134; 9%) D. No ARV (80; 5%) Total N=1,512	Not reported	Receiving ART at conception vs. no ART at conception, preterm delivery <37 weeks: 1.53 (1.11 to 2.09)
Li, 2016[61]	A. Initiated ZDV during pregnancy (1768; 53%) B. Initiated HAART during pregnancy (512; 15%) C. Continued HAART from before pregnancy (582; 18%) D. No ART (452; 14%)	Not reported	HAART vs. ZDV started during pregnancy, preterm delivery: 34 to 37 weeks: 0.85 (0.70 to 1.02), p=0.14 <34 weeks: 0.87 (0.60 to 1.25), p=0.45
Lopez, 2012[62]	A. HAART entire pregnancy (n=226) B. HAART 2nd half of pregnancy only (n=72) C. PI during pregnancy (n=178) D. No HAART (n=221)	Not reported	Spontaneous preterm birth: A vs. D: aOR 0.55 (95% CI 0.20 to 1.51) B vs. D: aOR 0.55 (95% CI 0.18 to 1.68) C vs. D: aOR 1.95 (95% CI 0.87 to 4.38) Iatrogenic preterm birth: A vs. D: aOR 3.42 (95% CI 0.80 to 14.63) B vs. D: aOR 6.16 (95% CI 1.42 to 26.8)

Study Author, year	Intervention	HIV transmission	Adverse events
			C vs. D: aOR 0.44 (95% CI 0.18 to 1.10)
Lu, 2014[46] Canadian Perinatal HIV Surveillance Program (CPHSP)	A. Complete antiretroviral prophylaxis (n=251) B. Incomplete antiretroviral prophylaxis (n=336) C. No antiretroviral prophylaxis (n=58)	A. 1% (3/251) B. 2% (8/336) C. 67% (39/58)	Not reported
Moodley, 2016[66]	A. Dual ART (AZT/NVP; n=974) B. Triple ART (D4T/3TC/NVP; n=907) C. Fixed-dose ART (EFV/TDF/FTC; n=1,666) D. No ART (n=148)	Not reported	Stillbirth: A vs. D: aOR 0.08 (95% CI 0.04 to 0.16) B vs. D: aOR 0.20 (95% CI 0.11 to 0.38) C vs. D: aOR 0.18 (95% CI 0.10 to 0.34) Preterm birth: A vs. D: aOR 0.20 (95% CI 0.08 to 0.51) B vs. D: aOR 0.21 (95% CI 0.08 to 0.55) C vs. D: aOR 0.31 (95% CI 0.11 to 0.90) Low birth weight: A vs. D: aOR 0.06 (95% CI 0.02 to 0.18) B vs. D: aOR 0.09 (95% CI 0.03 to 0.24) C vs. D: aOR 0.12 (95% CI 0.04 to 0.37) Small for gestational age: A vs. D: aOR 0.37 (95% CI 0.10 to 1.45) B vs. D: aOR 0.29 (95% CI 0.08 to 1.07) C vs. D: aOR 0.35 (95% CI 0.07 to 0.87)
Mor, 2017[49]	A. Infants born before 1996 (n=80) B. Infant born after 1997 (HAART introduced; n=716)	MTCT Overall: 3.1% (25/796) A vs. B: 16.3% (13/80) vs. 1.7% (12/716), p<0.01 Transmission with HAART and vaginal delivery: 1.5% Transmission with HAART and C-section: 0.6% Variables on MTCT HAART vs no HAART during pregnancy: aOR 0.4, 95% CI 0.1 to 0.8 Infant ART prophylaxis: aOR 0.2, 95% CI 0.1 to 0.5	Not reported
Pintye, 2017[78] Partners PrEP Study and Partners Demonstration Project	A. TDF-containing 3-drug ART (n=208) B. NonTDF-containing 3-drug ART (n=214)	Not reported	A vs B Pregnancy loss: 14% (17/208) vs 9% (7/214); aOR 1.05 (0.75–1.46) Pregnancy loss, <20 weeks: 11% (13/208) vs 7% (6/214); aOR 1.02 (0.73–1.40) Pregnancy loss, >20 weeks: 2% (4/208) vs 1% (1/214); aOR 1.04 (0.95–1.13) Neonatal death: 1% (3/208) vs 2% (4/214); aOR 1.01 (0.96–1.06) Preterm birth: 6% (10/208) vs 10% (20/214); aOR 0.85 (0.74–1.02) *OR adjusted for study cohort, maternal age, time since HIV diagnosis, and HIV RNA at first pregnancy visit, and year pregnancy occurred*

Study Author, year	Intervention	HIV transmission	Adverse events
Ramokolo, 2017[79] Prevention of Mother to Child Transmission (PWTCT) Program	A. Postconception ART (n=780) B. Preconception ART (n=616) C. Zidovudine prophylaxis (n=873) D. No ART (n=330)	Not reported	A vs B vs C vs D Preterm delivery: A vs B: aOR 1.7 (95% CI 1.1–2.5); A vs C: aOR 1.4 (95% CI 0.9–2.0); A vs D: aOR 1.9 (95% CI 1.1–3.1) Low birth weight: A vs B: aOR 0.9 (95% CI 0.6–1.3); A vs C: aOR 0.8 (95% CI 0.6–1.1); A vs D: aOR 1.1 (95% CI 0.8–1.6) Small for gestational age: A vs B: aOR 0.9 (95% CI 0.6–1.3); A vs C: aOR 0.7 (95% CI 0.5–1.0); A vs D: 0.7 (95% CI 0.4–1.1) Underweight for age: A vs B: aOR 1.1 (95% CI 0.7–1.6); A vs C: aOR 1.1 (95% CI 0.8–1.6); A vs D: aOR 1.4 (95% CI 0.9–2.2)
Sartorius, 2013[54] Kesho Bora Trial	A. Triple ART, CD4 < 200 (n=118) B. Zidovudine plus single- dose nevirapine, CD4 > 500 (n=128) C. Triple ART, CD4 200 to 500 (n=412) D. Zidovudine plus single- dose nevirapine, CD4 200 to 500 (n=412) Note: >70% breastfed	Not reported	A vs. B vs. C vs. D Severe maternal anemia (Hb < 8 g/dL), cumulative incidence - At delivery 0.14 (95% CI 0.09 to 0.22) vs. 0.05 (95% CI 0.03 to 0.11) vs. 0.09 (95% CI 0.06 to 0.12) vs. 0.08 (95% CI 0.06 to 0.11); p=0.51 6 months postpartum: 0.30 (95% CI 0.23 to 0.39) vs. 0.10 (95% CI 0.06 to 0.16) vs. 0.16 (95% CI 0.13 to 0.20) vs. 0.17 (95% CI 0.14 to 0.21); p=0.44 12 months postpartum: 0.33 (95% CI 0.26 to 0.41) vs. 0.11 (95% CI 0.06 to 0.17) vs. 0.18 (0.14 to 0.21) vs. 0.19 (0.16 to 0.23); p=0.71 18 months postpartum: 0.34 (95% CI 0.27 to 0.42) vs. 0.11 (95% CI 0.06 to 0.17) vs. 0.18 (95% CI 0.15 to 0.22) vs. 0.21 (95% CI 0.17 to 0.25); p=0.36 C vs. D: aHR 0.78 (95% CI 0.54 to 1.11)
Short, 2013[67]	A. Zidovudine (n=65) B. Dual NRTI (n=7) C. Triple NRTI (n=5) D. Short-term cART (n=59) E. Preconception cART (n=131) F. New continuous cART (n=56)	Not reported	A vs. B vs. C vs. D vs. E vs. F Preterm delivery rate: 6.2% vs. 0% vs. 0% vs. 25.4% vs. 9.9% vs. 17.9% D vs. A: aOR 5.00 (95% CI 1.49 to 16.79)
Surveillance Monitoring for Antiretroviral Treatment Toxicities (SMARTT) study and Pediatric HIV/AIDS Cohort Study (PHACS) Nozyce, 2014[69]	Any maternal cART regimen containing at least 3 antiretroviral drugs from at least 2 drug classes, analyzed by assessment scale: WPPSI-III (Wechsler Preschool and Primary Scale of Intelligence, 3rd Edition; n=369) WASI (Wechsler Abbreviated Scale of Intelligence; n=452) WIAT-II-A (Wechsler Individual Achievement Test, 2nd Edition; n=451) Other intervention: Neonatal prophylaxis defined as antiretroviral drugs used during the first 8 weeks of life	Not reported	Mean cognitive and academic scores were significantly below population norms (p=0.01 to p<0.001), with the exception of the WASI VIQ (p=0.48) - data in figure There were no significant differences in adjusted mean scores for any cognitive or academic outcome when comparing different cART regimens or specific drugs or cumulative duration of prenatal cART exposure
Pediatric HIV/AIDS Cohort Study (PHACS) Lipshultz, 2015[68]	A. HIV-exposed uninfected (HEU; n=417) B. HIV unexposed controls (n=98)	Not reported	A vs. B, adjusted mean difference Z-score LV ejection fraction: 0.04 (95% CI 0.14 to 0.21) LV M-mode shortening fraction: 0.06 (95% CI 0.26 to 0.15) LV stress–velocity index: 0.12 (95% CI 0.11 to 0.35) LV M-mode ED short axis dimension: 0.07 (95% CI 0.15 to 0.29) LV M-mode ED postwall thickness: 0.05 (95% CI 0.25 to 0.15) M-mode ED septal thickness: 0.06 (95% CI 0.25 to 0.13) LV M-mode mass: 0.02 (95% CI 0.23 to 0.19)

Study Author, year	Intervention	HIV transmission	Adverse events
			LV M-mode ES wall stress: 0.02 (95% CI 0.29 to 0.25) LV M-mode thickness-to-dimension ratio: 0.07 (95% CI 0.26 to 0.12)
Surveillance Monitoring for Antiretroviral Treatment Toxicities (SMARTT) study of the Pediatric HIV/AIDS Cohort Study (PHACS) and P1025 study of the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) cohort Rough, 2018[82]	A. TDF + FTC + LPV/r (128; 8%) B. ZDV + 3TC + LPV/r (954; 59%) C. TDF + FTC + ATV/r (539; 33%)	Not reported	Preterm delivery, adjusted OR: A vs. B: 0.90 (0.60 to 1.33) C vs. B: 0.69 (0.51 to 0.94) A vs. C: 1.14 (0.75 to 1.72) Very preterm delivery, unadjusted OR: A vs. B: 0.85 (0.34 to 2.13) C vs. B: 1.04 (0.60 to 1.83) A vs. C: 0.82 (0.31 to 2.17) Low birth weight, adjusted OR: A vs. B: 1.13 (0.78 to 1.64) C vs. B: 0.80 (0.60 to 1.09) A vs. C: 1.45 (0.96 to 2.17) Very low birth weight, unadjusted OR: A vs. B: 0.41 (0.06 to 3.06) C vs. B: 0.89 (0.40 to 2.00) A vs. C: 0.49 (0.07 to 3.57) Stillbirth - Fetal loss was undefined, included stillbirth (likely also included spontaneous abortion and fetal demise) Unadjusted odds ratio (our analysis) for initial drug regimen: A vs. B: 2.51 (0.50 to 13) A vs. C: 4.26 (0.60 to 31) B vs. C: 1.70 (0.34 to 8.45) Neonatal death – within 14 days of live birth Unadjusted odds ratio (our analysis) for initial drug regimen: A vs. B. 2.47 (0.10 to 61) A vs. C: 1.40 (0.06 to 34) B vs. C: 0.56 (0.04 to 9.04)
Surveillance Monitoring for Antiretroviral Treatment Toxicities (SMARTT) study and Pediatric HIV/AIDS Cohort Study (PHACS) Siberry, 2012[73]	A. TDF-containing ART (n=449) B. nonTDF-containing ART (n=1,580)	Not reported	A vs. B LBW (n=1,302)): 19.5 vs. 19,1%%, aOR 0.73, 95% CI 0.48 to 1.11 SGA (n=1,148): 8.3% vs. 8.6%, aOR 0.96, 95% CI 0.60 to 1.52

Study Author, year	Intervention	HIV transmission	Adverse events
Surveillance Monitoring for Antiretroviral Treatment Toxicities (SMARTT) study and Pediatric HIV/AIDS Cohort Study (PHACS) Watts, 2013[70]	Various maternal cART regimens	Not reported	Overall: Preterm birth (<37 weeks): 18.6% (346/1869) Spontaneous preterm birth (occurred after preterm labor or membrane rupture, without other complications): 10.2% (191/1869) Very preterm delivery: 2.1% (37/1799) Small for gestational age (SGA; birth weight <10% for gestational age): 7.3% (135/1,861) First trimester exposure: Association of first trimester exposure to PI-based cART and preterm birth: aOR 1.55, 95% CI 1.16 to 2.07 Association of first trimester exposure to PI-based cART and spontaneous preterm birth: aOR 1.59, 95% CI 1.10 to 2.30 No association of first trimester exposure to PI-based cART and SGA: aOR 0.79, 95% CI 0.49 to 1.26 No associations for regimens containing NNRTI or ≥3 NRTIs during the first trimester Exposure overall (no significant associations): PI-based cART and preterm birth: aOR 1.49, 95% CI 0.83 to 2.67 PI-based cART and spontaneous preterm birth: aOR 1.41, 95% CI 0.66 to 2.99 NNRTI-based cART and preterm birth: aOR 1.28, 95% CI 0.62 to 2.66 NNRTI-based cART and spontaneous preterm birth: aOR 1.53, 95% CI 0.62 to 3.81 ≥3 NRTIs based cART and preterm birth: aOR 1.04, 95% CI 0.50 to 2.14 ≥3 NRTIs based cART and spontaneous preterm birth: aOR 0.88, 95% CI 0.34 to 2.29
Surveillance Monitoring for Antiretroviral Treatment Toxicities (SMARTT) study and Pediatric HIV/AIDS Cohort Study (PHACS) Williams, 2015[71]	A. Any ART (n=1,219) B. Any HAART (n=1,025) C. NNTRI (n=214) D. NRTI (n=1,211) D. Protease inhibitor (n=887) E .No ART exposure of any kind (n=1,298 to 2,303 depending on comparison) All exposure was during first trimester	Not reported	Any congenital abnormality (CA): A vs. F: aOR 1.20 (95% CI 087 to 1.67) B vs. F: aOR 1.35 (95% CI 0.98 to 1.87) C vs. F: aOR 0.97 (95% CI 0.54 to 1.74) D vs. F: 1.19 (95% CI 0.86 to 1.65) E vs. F: 1.39 (95% CI 1.00 to 1.92) For specific drugs, there was no significant difference in risk of CA for exposed vs. unexposed except: -Didanosine plus stavudine: aOR 8.19 (95% CI 1.53 to 43) -Atazanavir sulfate: aOR 1.95 (95% CI 1.24 to 3.05) -Ritonavir when used as a booster: aOR 1.56 (95% CI 1.11 to 2.20)
Surveillance Monitoring for Antiretroviral Treatment Toxicities (SMARTT) study and Pediatric HIV/AIDS Cohort Study (PHACS)	A. Any HAART exposure (n=2,211) B. NNTRI exposed (n=395) C. NRTI (n=1,907) C. Protease inhibitor (n not reported) D. No ART exposure of any kind (n=469)	Not reported	Adverse event cases: A vs. E: aRR 0.98 (95% CI 0.82 to 1.16) B vs. E: aRR 0.98 (95% CI 0.81 to 1.18) C vs. E: aRR 1.15 (95% CI 0.73 to 1.82) D vs. E: aRR 1.01 (95% CI 0.86 to 1.17) Differences for specific drug/event combinations: HAART, metabolic cases: aRR 0.60 (95% CI 0.44 to 0.82) Protease inhibitors, metabolic cases: aRR 0.69 (95% CI 0.52 to 0.92) Zidovudine exposure, metabolic cases: aRR1.61 (95% CI: 1.01 to 2.58)

Study Author, year	Intervention	HIV transmission	Adverse events
Williams, 2016[72]			Lopinavir exposure, metabolic cases: aRR 0.46 (95% CI 0.31 to 0.69) Lopinavir (1st trimester), metabolic cases: aRR 0.39 (95% CI 0.20 to 0.78) Ritonavir (as booster), metabolic cases: aRR 0.59 (95% CI 0.43 to 0.81) Ritonavir (1st trimester), metabolic cases: aRR 0.61 (95% CI 0.40 to 0.95) NRTIs, impaired growth: aRR 0.48 (95% CI 0.24 to 0.96) Neurodevelopmental impairment: HAART: aRR 0.47 (95% CI 0.27 to 0.83) NNRTIs: aRR 0.38 (95% CI 0.14 to 1.04) Lamivudine: aRR 0.36 (95% CI 0.36 to 1.02) ZVD + 3TC: aRR 0.71 (95% CI 0.41 to 1.17) Lamivudine (1st trimester): aRR 0.64 (95% CI 0.35 to 1.18)
Snijdewind, 2018[81] ATHENA cohort	A. PI-based (928; 67%) B. NNRTI-based (438; 31%) C. Both or NRTI (12; 1%)	Not reported	Preterm delivery Unadjusted OR: A. 1 (reference) B. 1.30 (0.95 to 1.77), p=0.11 C. 1.15 (0.41 to 3.19), p=0.78 Low birthweight Unadjusted OR: A. 1 (reference) B. 1.19 (0.88 to 3.97), p=0.26 C. 1.47 (0.54 to 3.97), p=0.45 Small for gestational age Unadjusted OR: A. 1 (reference) B. 1.04 (0.80 to 1.16), p=0.76 C. 2.51 (1.16 to 5.53), p=0.02 Adjusted OR: A. 1 (reference) B. 0.95 (0.71 to 1.27), p=0.73 C. 2.11 (0.98 to 4.57), p=0.06
Tookey, 2016[48] National Study of HIV in Pregnancy and Childhood (NSHPC)	LPV/r	2003 to 2007 Overall: 18/1,633 (1.1%, 95% CI 0.6 to 1.6) LPV/r initiation - -Before conception: 2/6,333 (0.6%, 95% CI 0.2% to 2.2%) -First trimester: 0/33 (0%) -Second trimester: 8/858 (0.9%, 95% CI 0.5% to 4.1%) -Third trimester: 8/376 (2.1%, 1.1% to 4.1%) 2008 to 2012 Overall: 12/2,406 (0.5%, 95% CI 0.2% to 0.8%) LPV/r initiation - -Before conception: 2/635 (0.3%, 95% CI 0.1% to 1.1%)	Infant mortality: 0.5% (24/4,762) Gestational age - <32 weeks: 2.5% (112/4,762) 32 to 36 weeks: 10.4% (473/4,762) ≥37 weeks: 87% (3971/4,762) Birth weight - <1500 g: 2.3% (101/4,762) 1500 to 2499 g: 12.4% (545/4,762) ≥2500 g: 85.3% (3749/4,762) Any congenital abnormality: 2.9%

Study Author, year	Intervention	HIV transmission	Adverse events
		-First trimester: 0/77 (0%) -Second trimester: 5/1,397 (0.4%, 95% CI 0.2% to 0.8%) -Third trimester: 5/264 (1.9%, 0.8% to 4.4%)	
Zash, 2016[76]	A. TDF-FTC-EFV at conception (n=165) B. Other 3 drug ART at conception (n=2,006) C. TDF-FTC-EFV during pregnancy (n=1,054) D. Other 3 drug ART during pregnancy (n=2,172)	Not reported	Initiated ART at conception A vs. B Stillbirth: 4.9% (8/165) vs. 6.4% (128/2006), aOR 0.4, 95% CI 0.1 to 2.9 Preterm birth: 28% (47/165) vs. 31% (631/2006), aOR 0.9, 95% CI 0.3 to 2.9 Very preterm birth: 10% (17/165) vs. 12% (236/2006), aOR 0.9, 95% CI 0.1 to 8.0 SGA, Botswana norms: 8% (14/165) vs. 24% (476/2006), aOR 0.4, 95% CI 0.1 to 1.4 SGA, WHO norms: 13% (22/165) vs. 32% (636/2006), aOR 0.3, 95% CI 0.1 to 1.0 Any adverse outcome (any stillbirth, preterm birth, and/or small for gestational age): 33% (55/165) vs. 51% (1030/2006), aOR 0.5, 95% CI 0.1 to 1.2 Initiated ART during pregnancy C vs. D Stillbirth: 1.7% (18/1054) vs. 3.2% (70/2172), aOR 0.6, 95% CI 0.3 to 1.3 Preterm birth: 18.2% (192/1054) vs. 20.7% (450/2172), aOR 0.7, 95% CI 0.5 to 1.1 SGA, Botswana norms: 11.9% (125/1054) vs. 21.1% (459/2172), aOR 0.4, 95% CI 0.3 to 0.6 SGA, WHO norms: 19.2% (202/1054) vs. 27.7% (602/2172), aOR 0.5, 95% CI 0.4 to 0.7 Any adverse outcome (any stillbirth, preterm birth, and/or small for gestational age): 27% (287/1054) vs. 41% (880/2172), aOR 0.4, 95% CI 0.3 to 0.6
Zash, 2017[75]	A. TDF-FTC-EFV (n=2,472) B. TDF-FTC-NVP (n=760) C. TDF-FTC-LPV-R (n=231) D. ZDV-3TC-NVP (n=1,365) E. ZDV-3TC-LPV-R (n=167)	Not reported	Preterm birth A. 21.4% (529/2472), reference B. 19.1% (145/760), RR 0.88, 95% CI 0.75 to 1.04, ARR 0.88, 95% CI 0.75 to 1.05 C. 23.8% (55/231), RR 1.11, 95% CI 0.87 to 1.41, ARR 1.12, 95% CI 0.88 to 1.43 D. 24.8% (338/1365), RR 1.15, 95% CI 1.02 to 1.30, ARR 1.14, 95% CI 1.01 to 1.29 E. 29.3% (49/167), RR 1.36, 95% CI 1.07 to 1.74, ARR 1.36, 95% CI 1.06 to 1.75 Very preterm birth (<32 weeks) A. 4.1% (101/2472), reference B. 5.1% (39/760), RR 1.25, 95% CI 0.87 to 1.79, ARR 1.23, 95% CI 0.84 to 1.80 C. 5.2% (12/231), RR 1.26, 95% CI 0.71 to 2.27, ARR 1.36, 95% CI 0.76 to 2.45 D. 5.9% (80/1365), RR 1.43, 95% CI 1.07 to 1.90, ARR 1.44, 95% CI 1.07 to 1.95 E. 9.0% (15/167), RR 2.19, 95% CI 1.30 to 3.67, ARR 2.21, 95% CI 1.29 to 3.79 SGA (<10th percentile) A. 16.9% (419/2472), reference B. 24.9% (189/760), RR 1.44, 95% CI 1.24 to 1.68, ARR 1.44, 95% CI 1.24 to

Study Author, year	Intervention	HIV transmission	Adverse events
			1.68 C. 27.7% (64/231), RR 1.62, 95% CI 1.29 to 2.03, ARR 1.56, 95% CI 1.25 to 1.97 D. 28.2% (385/1365), RR 1.65, 95% CI 1.46 to 1.86, ARR 1.66, 95% CI 1.46 to 1.87 E. 20.4% (34/167), RR 1.19, 95% CI 0.87 to 1.63, ARR 1.13, 95% CI 0.82 to 1.56 Very SGA (<3rd percentile) A. 7.1% (176/2472), reference B. 11.2% (85/760), RR 1.55, 95% CI 1.21 to 1.98, ARR 1.52, 95% CI 1.18 to 1.94 C. 13.4% (31/231), RR 1.87, 95% CI 1.31 to 2.67, ARR 1.81, 95% CI 1.26 to 2.59 D. 12.9% (176/1365), RR 1.80, 95% CI 1.47 to 2.19, ARR 1.76, 95% CI 1.44 to 2.16 E. 12.6% (21/167), RR 1.75, 95% CI 1.15 to 2.67, ARR 1.70, 95% CI 1.10 to 2.62 Stillbirth A. 2.4% (59/2472), reference B. 2.9% (22/760), RR 1.21, 95% CI 0.75 to 1.97, ARR 1.15, 95% CI 0.70 to 1.89 C. 4.3% (10/231), RR 1.81, 95% CI 0.94 to 3.50, ARR 1.81, 95% CI 0.94 to 3.50 D. 6.1% (83/1365), RR 2.55, 95% CI 1.84 to 3.53, ARR 2.31, 95% CI 1.64 to 3.26 E. 3.6% (6/167), RR 1.51, 95% CI 0.66 to 3.44, ARR 1.53, 95% CI 0.67 to 3.49 Neonatal death A. 1.2% (29/2472), reference B. 1.7% (13/760), RR 1.46, 95% CI 0.77 to 2.80, ARR 1.57, 95% CI 0.81 to 3.06 C. 1.7% (4/231), RR 1.50, 95% CI 0.53 to 4.24, ARR 1.60, 95% CI 0.56 to 4.76 D. 2.1% (28/1365), RR 1.82, 95% CI 1.09 to 3.04, ARR 1.94, 95% CI 1.13 to 3.33 E. 4.2% (7/167), RR 3.64, 95% CI 1.62 to 8.17, ARR 4.01, 95% CI 1.78 to 9.11

Abbreviations: 3TC=lamivudine; aHR=adjusted hazard ratio; ANRS=French Agence Nationale de Recherche sur le SIDA; aRR=adjusted risk ratio; ART=antiretroviral therapy; ARV=antiretroviral drug; AZT=zidovudine (Retrovir); CA=congenital abnormality; cART=combination antiretroviral therapy; CD4=cluster of differentiation 4; CI=confidence interval; cm=centimeters; D4T=stavudine (Zerit); ED=end diastolic; EFV=efavirenz; EUROCAT=European surveillance of congenital anomalies; FTC = emtricitabine; g/dL=grams per deciliter; g=gram; HAART=highly active antiretroviral therapy; Hb=hemoglobin concentration; HBV=hepatitis B virus; HEU=HIV-exposed uninfected; HIV=human immunodeficiency syndrome; HIV RNA=human immunodeficiency syndrome ribonucleic acid; LPV/r=lopinavir/ritonavir; LV=left ventricle; MACDP=metropolitan Atlanta congenital defects program; ml=milliliter; mm=millimeter; NNRTI=nonnucleoside reverse transcriptase inhibitors; NR=not reported; NRTI=nucleoside reverse transcriptase inhibitors; NSHPC=national study of HIV in pregnancy and childhood; NVP=nevirapine; OR=odds ratio; p=probability; PI=protease inhibitor; PWID=people who inject drugs; RCT=randomized controlled trial; SGA=small for gestational age; SMARTT=science moving towards research translation and therapy; TDF=tenofovir disoproxil fumarate; vs=versus; WASI VIQ=wechsler abbreviated scale of intelligence verbal intelligence quotient; WIAT-II-A=wechsler individual achievement test; WPPSI-III=wechsler preschool and primary scale of intelligence, 3d edition; ZDV=zidovudine.

Appendix B3. Quality Assessment of Cohort Studies

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 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?	Is there high attrition?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Quality rating
Aaron, 2012[55]	Yes	Not relevant	Not relevant	Yes	Unclear	No	Unclear	Yes	Fair
Anteretroviral Pregnancy Registry Interim Report[83]	Not relevant (volunteer database); encourages participating MDs to enter all cases	Not relevant	Not relevant	Yes but no adjustment for confounding	Unclear	No	No	Yes	Fair
Berard, 2017[77]	Yes	No	Yes	Yes	Unclear	No	Unclear	Yes	Fair
Chagomerana, 2017[74]	Yes	No	Yes	Yes	Unclear	Yes	No	Yes	Fair
Chen, 2012[56]	Yes	Differences in age, past adverse pregnancy outcome, receipt of antenatal care, CD4 count, parity	Unclear	Yes	Unclear	No	Unclear	Yes	Fair
Chiappini, 2013[47]	Yes	Not relevant	Not relevant	Yes	Unclear	No	Unclear	Yes	Fair
Duryea, 2015[80]	Yes	No	Yes	Yes	Unclear	No	Unclear	Yes	Fair
Floridia, 2013[57]	Yes	Not relevant	Not relevant	Yes	Unclear	No	Unclear	Yes	Fair
French Perinatal Cohort (ANRS-EPF) study Mandelbrot, 2015[45] Sibiude, 2012[65] Sibiude, 2014[67] Sibiude, 2015[63]	Yes	Not relevant	Not relevant	Yes	Unclear	No	Unclear	Yes	Fair
Kakkar, 2015[58]	Yes	Differences in study time period, parity, ethnicity	Unclear	Yes	Unclear	No	Unclear	Yes	Fair
Knapp, 2012[59]	Yes	Not relevant	Not relevant	Yes	Yes	No	Unclear	Yes	Fair
Kreitchmann, 2014[60]	Yes	Not relevant	Not relevant	Yes	Unclear	No	Unclear	Yes	Fair
Li, 2016[61]	Yes	Differences in delivering prior to year 2007, CD4 count, nutritional status, and other diseases and symptoms	Unclear	Yes	Unclear	No	Unclear	Yes	Fair
Lopez, 2012[62]	Yes	Differences in nulliparity and prior preterm birth for case control analysis	Unclear	Yes	Unclear	No	Unclear	Yes	Fair
Lu, 2014[46]	Yes	Not relevant	Not relevant	Yes	Unclear	Yes	No	Yes	Fair
Mor, 2017[49]	Yes	No	Yes	Yes	Unclear	No	Unclear	Yes	Fair
Moodley, 2016[66]	Yes	Unclear	Unclear	Yes	Unclear	No	Unclear	Yes	Fair
Pintye, 2017[78]	Yes	No	Yes	Yes	Unclear	Yes	No	Yes	Fair
Ramokolo, 2017[79]	Yes	No	Yes	Yes	Unclear	No	Unclear	Yes	Fair

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 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?	Is there high attrition?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Quality rating
Rough, 2018[82] PHACS and IMPAACT P1025	Yes	Differences in age, timing of regimen initiation, viral load, and timing of HIV diagnosis	Yes	Yes	Unclear	No	Unclear	Yes	Fair
Short, 2013[67]	Yes	Not relevant	Not relevant	Yes	Unclear	No	Unclear	Yes	Fair
SMARTT/ PHACS studies Nozyce, 2014[69] Lipshultz, 2015[68] Siberry, 2012[73] Watts, 2013[70] Williams, 2015[71] Williams, 2016[72]	Yes	Not relevant	Not relevant	Yes	Unclear	No	Unclear	Yes	Fair
Snijdewind, 2018[81]	Yes	Not relevant	Not relevant	Yes	Unclear	No	Unclear	Yes	Fair
Tookey, 2016[48]	Yes	Not relevant	Not relevant	Yes	Unclear	No	Unclear	Yes	Fair
Zash, 2016[76]	Yes	Yes	Yes	Yes	Unclear	No	Unclear	Yes	Fair
Zash, 2017[75]	Yes	No	Yes	Yes	Unclear	No	Unclear	Yes	Fair

Abbreviations: PHACS=Pediatric HIV/AIDS Cohort Study; SMARTT=Surveillance Monitoring for Antiretroviral Treatment Toxicities study.

Appendix B4. Quality Assessment of Randomized Trials

Author, year	Random-ization 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 (>10%)/ high (>20%)?	Analyze people in the groups in which they were randomized?	Quality rating
Fowler, 2016[52]	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No, No	Yes	Fair
Sartorius, 2013[54]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No, No	Unclear	Fair