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 to 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 ≤200 cells/mm³) 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{12} and 99 cases in 2016.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{16} Most intrauterine transmission is thought to occur shortly before delivery.\textsuperscript{17} HIV is present in and transmitted through breast milk\textsuperscript{18} and breastfeeding is thought to be the only important mode for postpartum transmission to newborns and infants.\textsuperscript{19,20} In resource-poor settings in which women breastfeed for prolonged periods, postpartum transmission accounts for about 44 percent of infant cases.\textsuperscript{21} Antiretroviral treatment of the mother and infant does not completely eliminate breastfeeding transmission risk.\textsuperscript{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.\textsuperscript{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%).\textsuperscript{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).\textsuperscript{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).\textsuperscript{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.\textsuperscript{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. 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, which could result in unnecessary exposure to antiretroviral or other therapies.

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

In the United States, ~85 percent of HIV-infected women receive ART during pregnancy, with about 40 percent undergoing elective Cesarean section. 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), the American Academy of Pediatrics (AAP), the American College of Physicians (ACP), and the CDC, recommend voluntary “opt out” testing for HIV in all pregnant women as part of routine prenatal care. The CDC and ACOG 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. The American Academy of Family Physicians (AAFP) follows the 2013 USPSTF recommendation.
Chapter 2. Methods

Key Questions and Analytic Framework

Using the methods developed by the USPSTF,\textsuperscript{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\textsuperscript{®} 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\textsuperscript{®} 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, 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. 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 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.

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). 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. 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.

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. 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.

**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. 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. 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%). 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. 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\(^3\) 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 (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) 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 and three new cohort studies 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 or no difference in risk 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. 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), one study found no association between ART versus no ART and low birth weight (1 study, N=2,599), and two studies found no difference between tenofovir-containing versus nontenofovir-containing ART in risk of low birth weight (two studies, N=3,650).
Ten new cohort studies (in 11 publications) evaluated the association between ART and risk of being small for gestational age (SGA).\textsuperscript{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),\textsuperscript{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).\textsuperscript{56} Other studies found no effect between different ART regimens on risk of SGA,\textsuperscript{55,70,73,80,81} or no effect of ART versus no ART on SGA.\textsuperscript{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),\textsuperscript{56} while two other studies reported no difference between ART and zidovudine monotherapy.\textsuperscript{61,79}

Five studies evaluated the association between ART and risk of stillbirth.\textsuperscript{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),\textsuperscript{56} while two studies reported a significantly decreased risk of still birth compared with no ART.\textsuperscript{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),\textsuperscript{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).\textsuperscript{76} Two new cohort studies (N=4,381) reported no increase in risk of neonatal death with tenofovir-based ART\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{89-91} Five new cohort studies (N=40,436),\textsuperscript{57,59,64,71} including the Antiretroviral Pregnancy Registry,\textsuperscript{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.\textsuperscript{57} One study found an association between atazanavir, ritonavir, or any protease inhibitor and increased risk of congenital abnormalities versus nonexposure,\textsuperscript{71} one study found an association between lamivudine, first trimester abacavir, and first trimester exposure to zidovudine and risk of congenital abnormalities,\textsuperscript{64} one study found an association between first trimester efavirenz and risk of congenital abnormalities,\textsuperscript{59} and one study found emtricitabine associated with decreased risk of congenital anomalies.\textsuperscript{64} The Antiretroviral Pregnancy Registry
found zidovudine associated with increased risk of overall birth defects, but ritonavir associated with decreased risk.\textsuperscript{83}

One of the cohort studies (n=2,580) also reported specific categories of birth defects in children exposed in utero to ART.\textsuperscript{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)\textsuperscript{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\textsuperscript{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\textsuperscript{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.\textsuperscript{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). 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).\textsuperscript{63,64} The most common condition was ventricular septal defect. A second analysis of 400 HIV-uninfected children exposed to ART in utero\textsuperscript{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).\textsuperscript{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).\textsuperscript{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.\textsuperscript{94-96} We identified two publications of a U.S. surveillance cohort (the SMARTT study) of HIV-exposed, uninfected infants and children (Appendix B2).\textsuperscript{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).\textsuperscript{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).\textsuperscript{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.\textsuperscript{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\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{100}

New evidence identified for this update\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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 or neonatal death. 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 and echocardiographic changes, 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.

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. 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.

**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.
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.
References


13. Centers for Disease Control and Prevention. HIV Among Pregnant Women, Infants, and


Screening for HIV in Pregnant Women


29351561.


94. HIV-infected pregnant women and vertical transmission in Europe since 1986. European


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

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Setting</th>
<th>Intervention</th>
<th>Sample</th>
<th>Mother-to-child transmission rates by treatment group</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garcia-Tejedor et al, 2009&lt;sup&gt;105&lt;/sup&gt; Included in prior report</td>
<td>Spain Maternity hospitals</td>
<td>ART A: No treatment B: Mono/dual therapy C: ART</td>
<td>489 mother-infant pairs analyzed Rate of Cesarean section 51% No infants breastfed Followup NR Timing of infant HIV testing: NR</td>
<td>A: 18% (39/214) B: 8.6% (10/116) C: 0.6% (1/159) p&lt;0.001</td>
<td>Fair</td>
</tr>
<tr>
<td>Harris et al, 2007&lt;sup&gt;106&lt;/sup&gt; Enhanced Perinatal Surveillance project Included in prior report</td>
<td>United States Population surveillance data from areas reporting ≥60 HIV-positive women giving birth per year</td>
<td>ART A: No treatment B: Prenatal, intrapartum and neonatal ART*</td>
<td>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</td>
<td>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 &amp; other drugs with PI: AOR 0.4, 95% CI 0.3 to 0.7 ZDV &amp; 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</td>
<td>Fair</td>
</tr>
<tr>
<td>Townsend et al, 2008&lt;sup&gt;107&lt;/sup&gt; Included in prior report</td>
<td>Ireland, United Kingdom Population surveillance data from National Study of HIV in Pregnancy and Childhood</td>
<td>Antepartum treatment A: ART therapy B: Dual therapy C: Monotherapy D: No therapy</td>
<td>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</td>
<td>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</td>
<td>Fair</td>
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<td>Tariq et al, 2011&lt;sup&gt;108&lt;/sup&gt; Included in prior report</td>
<td>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</td>
<td>ART A: ZDV-containing B: ZDV-sparing</td>
<td>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</td>
<td>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</td>
<td>Fair</td>
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<tr>
<td>Author, Year</td>
<td>Setting</td>
<td>Intervention</td>
<td>Sample</td>
<td>Mother-to-child transmission rates by treatment group</td>
<td>Quality rating</td>
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| Chiappini et al, 2013<sup>47</sup> | 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<sup>46</sup> | 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<sup>45</sup> | 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)  
1<sup>st</sup> trimester 0.4%; AOR 2.9 (95% CI 0.6 to 17.7)  
2<sup>nd</sup> trimester 0.9%; AOR 6.0 (95% CI 1.7 to 29.7)  
3<sup>rd</sup> trimester 2.2% AOR 7.8 (95% CI 2.1 to 28.8) | Fair |
| Mor et al, 2017<sup>49</sup> | 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 |
<table>
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<tr>
<th>Author, Year</th>
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<th>Sample</th>
<th>Mother-to-child transmission rates by treatment group</th>
<th>Quality rating</th>
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</thead>
<tbody>
<tr>
<td>Tookey et al, 2016&lt;sup&gt;46&lt;/sup&gt;</td>
<td>UK and Ireland, National Study of HIV in Pregnancy and Childhood (NSHPC)</td>
<td>A. LPV/r + ZDF + 3TC</td>
<td>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</td>
<td>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%)</td>
<td>Fair</td>
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<td>B. LPV/r + FTC + TDF</td>
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<td>C. LPV/r + ABC + 3TC</td>
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<td>D. LPV/r + other or missing NRTIs</td>
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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

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<tr>
<th>Author, year</th>
<th>Setting</th>
<th>Prenatal intervention</th>
<th>Peripartum intervention</th>
<th>Postpartum intervention</th>
<th>Sample</th>
<th>Mother-to-child transmission rates by treatment group</th>
<th>Quality rating</th>
</tr>
</thead>
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<tr>
<td>Chi et al, 2008&lt;sup&gt;101&lt;/sup&gt; Other publication: Chi, 2007&lt;sup&gt;109&lt;/sup&gt; Included in prior report</td>
<td>Zambia</td>
<td>From 32 weeks: ZDV to all groups</td>
<td>A: TDF/FTC + NVP B: NVP</td>
<td>All neonates: NVP dose in hospital + ZDV for one week</td>
<td>355 mother-infant pairs analyzed 92% of infants breastfed in both groups</td>
<td>6 weeks postpartum A: 6% B: 8% p=0.4</td>
<td>Fair</td>
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<td>de Vincenzi et al, 2011&lt;sup&gt;111&lt;/sup&gt; Other publication: Kesho Bora Study Group, 2010&lt;sup&gt;110&lt;/sup&gt; Included in prior report</td>
<td>Burkina Faso, Kenya, South Africa</td>
<td>From 28 weeks: A: ZDV + 3TC + LPV/r B: ZDV</td>
<td>A: 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</td>
<td>805 live born infants 77% of infants in group A and 78% in group B were ever breastfed</td>
<td>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</td>
<td>Good</td>
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<td>Gray et al, 2006&lt;sup&gt;102&lt;/sup&gt; Included in prior report</td>
<td>South Africa</td>
<td>From 34 weeks gestation: A: d4T B: ddl C: d4T + ddl D: ZDV</td>
<td>A: d4T B: ddl C: d4T + ddl D: ZDV</td>
<td>Infants received same ART regime as mother until 6 weeks of age</td>
<td>362 mother-infant pairs analyzed No infants breastfed</td>
<td>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</td>
<td>Fair</td>
</tr>
<tr>
<td>Author, year</td>
<td>Setting</td>
<td>Prenatal intervention</td>
<td>Peripartum intervention</td>
<td>Postpartum intervention</td>
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<td>Shapiro et al, 2010&lt;sup&gt;10&lt;/sup&gt; Included in prior report</td>
<td>Botswana</td>
<td>Randomization groups† From 26 weeks: A: ABC + ZDV + 3TC B: LPV/r + ZDV + 3TC Observational group‡ From 18 weeks: C: NVP + ZDV + 3TC</td>
<td>A: ABC + ZDV + 3TC B: LPV/r + ZDV + 3TC C: NVP + ZDV + 3TC</td>
<td>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</td>
<td>709 live born infants (including n=156 in the observational group) 97% of live born infants breastfed and 71% continued for &gt;5 months</td>
<td>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</td>
<td>Fair</td>
</tr>
<tr>
<td>Shapiro et al, 2006&lt;sup&gt;103&lt;/sup&gt; Included in prior report</td>
<td>Botswana</td>
<td>From 34 weeks: ZDV to all groups</td>
<td></td>
<td>A: sdNVP B: placebo</td>
<td>All neonates: NVP at birth and ZDV from birth to one month of age¶</td>
<td>694 live first born infants 50% of infants in both groups were breastfed Infant followup until one month of age</td>
<td>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)</td>
</tr>
<tr>
<td>Thistle et al, 2007&lt;sup&gt;111&lt;/sup&gt; Included in prior report</td>
<td>Zimbabwe</td>
<td>None</td>
<td>A: ZDV/sdNVP B: sdNVP</td>
<td>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)</td>
<td>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</td>
<td>Fair</td>
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<tr>
<td>Fowler et al, 2016&lt;sup&gt;50&lt;/sup&gt;</td>
<td>India, Malawi, South Africa, Tanzania, Uganda, Zambia, Zimbabwe</td>
<td>Randomized From 14 weeks: A. ZDV B. ZDV + 3TC + LPVr C. TDF + FTC + LPVr</td>
<td>A. sdNVP (ZDV only group)</td>
<td>A. TDF + FTC (6-14 days; ZVD only group) B.ZDV + 3TC + LPV/r C. TDF + FTC + LPV/r</td>
<td>3202 live born infants; mothers primarily black African; 92% breastfed; % screen-detected HIV during pregnancy NR</td>
<td>A. 1.8% (25/1386) B. 0.5% (7/1385) C. 0.6% (2/325) B + C vs. A. A difference in percentage points -1.3, 95% CI -2.1 to -0.4</td>
<td>Fair</td>
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</table>

*Began after protocol change in December 2006 (enrollment commenced June 2005). †Women with CD4 count >200 cells/mm³.
‡Women with CD4 count <200 cells/mm³ 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/mm³ 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>
<thead>
<tr>
<th>Harm category</th>
<th>Study, year Country Study Name</th>
<th>ART regimen (n;%)</th>
<th>Birth Outcome Definition</th>
<th>Birth Outcome Distribution</th>
<th>Magnitude of Risk: Adjusted OR (95% CI), p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm Delivery</td>
<td>Cotter et al, 2006 USA University of Miami study Included in prior report</td>
<td>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</td>
<td>Preterm delivery &lt;37 weeks; Very preterm &lt;32 weeks</td>
<td>Median at delivery 39 weeks</td>
<td>Combination with vs. without PI: &lt;37 weeks: 1.8 (1.1 to 3.0), p=0.03 Combination + PI: &lt;37 weeks: 36.6% of women (p&lt;0.05) &lt;32 weeks: 2.2% of women (NS)</td>
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<tr>
<td>Preterm Delivery</td>
<td>Grosch-Warner et al, 2008 Germany, Austria Included in prior report</td>
<td>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</td>
<td>Preterm delivery &lt;36 weeks</td>
<td>&lt;36 weeks 34%* (crude rate)</td>
<td>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</td>
</tr>
<tr>
<td>Preterm Delivery</td>
<td>Powis et al, 2011 Botswana Included in prior report</td>
<td>A: PI group (lopinavir/ritonavir/zidovudine/lamivudine) (n=275; 49%) B: NRTI group, TZV (abacavir/zidovudine/lamivudine) (n=285; 51%) Total N=560</td>
<td>Preterm delivery &lt;37 weeks</td>
<td>&lt;37 weeks 11.8%* Triple NRTI; 21.4% PI based &lt;32 weeks 2.6% (n=12); 8/12 associated with ART + PI; 4/12 triple NRTI</td>
<td>A. ART (+) PI: 2.03 (1.26 to 3.27), p=0.004 B. ART (-) PI (NRTI-based): 1.0</td>
</tr>
<tr>
<td>Preterm Delivery</td>
<td>Schulte et al, 2007 USA Pediatric Spectrum of HIV Disease cohort Included in prior report</td>
<td>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</td>
<td>Preterm delivery &lt;37 weeks</td>
<td>Mean 37 weeks (range 26-42)</td>
<td>C. 1 reference E. 1.21 (1.04 to 1.48), p-value NR</td>
</tr>
<tr>
<td>Preterm Delivery</td>
<td>Townsend et al, 2007 UK, Ireland Included in prior report</td>
<td>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</td>
<td>Preterm delivery &lt;37 weeks</td>
<td>&lt;37 weeks 14.1%* &lt;35 weeks 7.8% &lt;32 weeks 1.4%</td>
<td>A. &lt;37 weeks: 1.39 (1.05 to1.83) p=0.02 A. &lt;35 weeks: 2.02 (1.35 to 3.04), p=0.001 A. &lt;32 weeks: 2.63 (1.3 to 5.33), p=0.007 B. 1 reference all comparisons</td>
</tr>
<tr>
<td>Harm category</td>
<td>Study, year Country Study Name</td>
<td>ART regimen (n;%)</td>
<td>Birth Outcome Definition</td>
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<tr>
<td>Preterm Delivery</td>
<td>Chagomerana et al, 2017&lt;sup&gt;44&lt;/sup&gt; Malawi</td>
<td>Started ART before 27 weeks or not at all A. ART (2,909; 95%) B. no ART (165; 5%) Total N=3,074</td>
<td>Preterm delivery 27 weeks to 37 weeks</td>
<td>24%</td>
<td>Deliveries after 27 weeks: A. 1 reference B. aRR 1.14 (0.84 to 1.55)</td>
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<tr>
<td>Preterm Delivery</td>
<td>Chen et al, 2012&lt;sup&gt;96&lt;/sup&gt; Botswana Approx. 87% received ZDV/3TC/NVP</td>
<td>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</td>
<td>Preterm delivery &lt;37 weeks</td>
<td>24%*</td>
<td>Initiated HAART vs. initiated ZDV: 1.4 (1.2 to 1.8) Continued HAART vs. all others: 1.2 (1.1 to 1.4)</td>
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<tr>
<td>Preterm Delivery</td>
<td>Duryea, 2015&lt;sup&gt;40&lt;/sup&gt; USA University of Texas study</td>
<td>A. ART with PI (597; 59%) B. ART without PI (230; 23%) C. No ART (177; 18%) Total N=1,004</td>
<td>Preterm delivery &lt;37 weeks</td>
<td>13% to 21% depending on ART regimen</td>
<td>A. 1 reference B. 0.9 (0.5 to 1.5) C. 1.0 (0.5 to 2.0)</td>
</tr>
<tr>
<td>Preterm Delivery</td>
<td>Kakkar et al, 2015&lt;sup&gt;58&lt;/sup&gt; Canada</td>
<td>A. NRTI/NNRTI (159; 30%) B. Boosted PI (119; 23%) C. Unboosted PI (195; 37%) D. No treatment (52; 10%) Total N=525</td>
<td>Preterm delivery &lt;37 weeks</td>
<td>14%*</td>
<td>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</td>
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<tr>
<td>Preterm Delivery</td>
<td>Kreitchmann et al, 2014&lt;sup&gt;10&lt;/sup&gt; Latin America Caribbean At least 28 days 3&lt;sup&gt;rd&lt;/sup&gt; 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</td>
<td>Preterm delivery &lt;37 weeks</td>
<td>&lt;37 weeks 21%*</td>
<td>Receiving ART at conception vs. no ART at conception: 1.53 (1.11 to 2.09)</td>
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<tr>
<td>Preterm Delivery</td>
<td>Li et al, 2016&lt;sup&gt;61&lt;/sup&gt; Tanzania</td>
<td>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</td>
<td>Preterm delivery &lt;37 weeks Very preterm &lt;34 weeks</td>
<td>No infants had HIV &lt;37 weeks 29%* &lt;34 weeks 10%*</td>
<td>HAART vs. ZDV started during pregnancy: &lt;37 weeks: 0.85 (0.70 to 1.02), p=0.14 &lt;34 weeks: 0.87 (0.60 to 1.25), p=0.45</td>
</tr>
<tr>
<td>Harm category</td>
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| Preterm Delivery | Lopez et al, 2012 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 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 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 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 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) | |
<table>
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<tr>
<th>Harm category</th>
<th>Study, year Country Study Name</th>
<th>ART regimen (n;%)</th>
<th>Birth Outcome Definition</th>
<th>Birth Outcome Distribution</th>
<th>Magnitude of Risk: Adjusted OR (95% CI), p-value</th>
</tr>
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<tbody>
<tr>
<td>Preterm Delivery</td>
<td>Short et al, 2013 (^7) UK</td>
<td>A. ZDV (66; 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%)</td>
<td>Preterm delivery &lt;37 weeks</td>
<td>13%*</td>
<td>Short-term combination ART vs. ZVD: 5.00 (1.49 to 16.79)</td>
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<tr>
<td>Preterm Delivery</td>
<td>Sibiude et al, 2012 (^5) France</td>
<td>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%)</td>
<td>Preterm delivery &lt;37 weeks</td>
<td>14%*</td>
<td>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</td>
</tr>
<tr>
<td>Preterm Delivery</td>
<td>Snijdewind et al, 2018 (^4) The Netherlands</td>
<td>A. PI-based (928; 67%) B. NNRTI-based (438; 31%) C. Both or NRTI (12; 1%)</td>
<td>Preterm delivery &lt;37 weeks</td>
<td>15%</td>
<td>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</td>
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<td>Preterm Delivery</td>
<td>Watts et al, 2013 (^6) USA PHACS/SMARTT</td>
<td>A. Combination, with PI (1319; 74%) B. Combination, with NNRTI, no PI (160; 9%) C. Combination, with ≥3 NRTIs (193; 10%)</td>
<td>Preterm delivery &lt;37 weeks</td>
<td>Any preterm birth: &lt;37 weeks 19%* Spontaneous preterm birth: &lt;37 weeks 10%*</td>
<td>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)</td>
</tr>
<tr>
<td>Preterm Delivery</td>
<td>Zash et al, 2016 (^6) Botswana</td>
<td>All CD4 counts: A. TDF/FTC/EFV (1054; 33%) B. other ART (2172; 64%) Total N=3226 CD4 counts &gt;350 A. TDF/FTC/EFV (335; 31%) B. ZDF (752; 69%) Total N=1,087</td>
<td>Preterm delivery &lt;37 weeks</td>
<td>27%</td>
<td>A vs. B (all CD4 counts): 0.7 (0.5 to 1.1) A vs. B (CD4 &gt;350): 1.1 (0.6 to 2.1)</td>
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<td>Harm category</td>
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<td>Preterm Delivery</td>
<td>Zash et al, 2017 Botswana</td>
<td>A. TDF/FTC/EFV (2472; 49%)&lt;br&gt;B. TDF/FTC/NVP (760; 15%)&lt;br&gt;C. TDF/FTC/LPV/r (231; 5%)&lt;br&gt;D. ZDV/3TC/NVP (1365; 27%)&lt;br&gt;E. ZDV/3TC/LPV/r (167; 3%)&lt;br&gt;Total N=4,995</td>
<td>Preterm delivery &lt;37 weeks&lt;br&gt;Very preterm delivery &lt;32 weeks</td>
<td>22%&lt;br&gt;5%</td>
<td>Adjusted Relative Risks:&lt;br&gt;A. 1 reference&lt;br&gt;B. 0.88 (0.75 to 1.05) preterm delivery&lt;br&gt;C. 1.23 (0.84 to 1.80) very preterm delivery&lt;br&gt;D. 1.12 (0.88 to 1.43) preterm delivery&lt;br&gt;E. 1.36 (0.76 to 2.45) very preterm delivery&lt;br&gt;D. 1.14 (1.01 to 1.29) preterm delivery&lt;br&gt;D. 1.44 (1.07 to 1.95) very preterm delivery&lt;br&gt;E. 1.36 (1.06 to 1.75) preterm delivery&lt;br&gt;E. 2.21 (1.29 to 3.79) very preterm delivery</td>
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<td>Low Birthweight</td>
<td>Kreitchmann et al, 2014 Latin America Caribbean</td>
<td>At least 28 days 3rd trimester:&lt;br&gt;A. HAART + PI (888; 59%)&lt;br&gt;B. HAART no PI (410; 27%)&lt;br&gt;C. Non-HAART (134; 9%)&lt;br&gt;D. No ARV (80; 5%)&lt;br&gt;Total N=1,512</td>
<td>Low birthweight &lt;2500 g</td>
<td>16%*</td>
<td>HAART w/PI vs. no ART: 0.59 (0.28 to 1.26)&lt;br&gt;HAART no PI vs. no ART: 0.33 (0.14 to 0.74)&lt;br&gt;Non-HAART 0.40 (0.15 to 1.05) vs. no ART</td>
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<td>Low Birthweight</td>
<td>Moodley et al, 2016 South Africa</td>
<td>A. No ART (148; 4%)&lt;br&gt;B. AZT + NVP (974; 26%)&lt;br&gt;C. D4T +3TC + NVP (907; 25%)&lt;br&gt;D. EFV + TDF + FTC (1666; 45%)&lt;br&gt;Total N=3,695</td>
<td>Low birthweight &lt;2500 g</td>
<td>13.5%</td>
<td>A. 1 reference&lt;br&gt;B. 0.06 (0.02 to 0.18), p&lt;0.001&lt;br&gt;C. 0.09 (0.03 to 0.24), p&lt;0.001&lt;br&gt;D. 0.12 (0.04 to 0.37), p&lt;0.001</td>
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<td>Low Birthweight</td>
<td>Ramokolo et al, 2017 South Africa</td>
<td>A. Postconception ART (780; 30%)&lt;br&gt;B. No ART (330; 13%)&lt;br&gt;C. Preconception ART (616; 24%)&lt;br&gt;Total =2,599</td>
<td>Low birthweight &lt;2500 g</td>
<td>10.7%</td>
<td>A. 1 reference&lt;br&gt;B. 0.8 (0.6 to 1.1), p=0.14&lt;br&gt;C. 1.1 (0.8 to 1.6), p=0.47&lt;br&gt;D. 0.9 (0.6 to 1.3), p=0.54</td>
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<td>Low Birthweight</td>
<td>Rough et al, 2018 USA PHACS and IMPAACT</td>
<td>A. TDF + FTC + LPV/r (128; 8%)&lt;br&gt;B. ZDV + 3TC + LPV/r (954; 59%)&lt;br&gt;C. TDF + FTC + ATV/r (539; 33%)&lt;br&gt;Total=1,621</td>
<td>Low birthweight &lt;2500 g&lt;br&gt;Very Low birthweight &lt;1500 g</td>
<td>18% Low birth weight&lt;br&gt;2% Very low birth weight</td>
<td>Low birth weight, adjusted OR:&lt;br&gt;A vs. B: 1.13 (0.78 to 1.64)&lt;br&gt;C vs. B: 0.80 (0.60 to 1.09)&lt;br&gt;A vs. C: 1.45 (0.96 to 2.17)&lt;br&gt;Very Low birth weight, unadjusted OR:&lt;br&gt;A vs. B: 0.41 (0.06 to 3.06)&lt;br&gt;C vs. B: 0.89 (0.40 to 2.00)&lt;br&gt;A vs. C: 0.49 (0.07 to 3.57)</td>
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<td>Low Birthweight</td>
<td>Siberry et al, 2012 USA PHACS/SMARTT</td>
<td>A. TDF-containing ART (449; 22%)&lt;br&gt;B. nonTDF-containing ART (1580; 78%)&lt;br&gt;Total=2,029</td>
<td>Low birthweight &lt;2500 g</td>
<td>19%</td>
<td>A vs B: 0.73 (0.48 to 1.11), p=0.14</td>
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<td>Low Birthweight</td>
<td>Snijdewind et al, 2018 The Netherlands</td>
<td>A. PI-based (928; 67%)&lt;br&gt;B. NNRTI-based (438; 31%)&lt;br&gt;C. Both or NRTI (12; 1%)&lt;br&gt;Total=1,378</td>
<td>Low birthweight &lt;2500 g</td>
<td>16%</td>
<td>Unadjusted OR:&lt;br&gt;A. 1 (reference)&lt;br&gt;B. 1.19 (0.88 to 1.60), p=0.26&lt;br&gt;C. 1.47 (0.54 to 3.97), p=0.45</td>
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<td>Small for Gestational Age</td>
<td>Aaron et al, 2012 USA Drexel University study</td>
<td>A. NRTIs + NNRTI (39; 21%) B. NRTI + PI (117; 64%) C. NRTIs alone (27; 15%) Total N=183</td>
<td>SGA &lt;10&lt;sup&gt;th&lt;/sup&gt; percentile of birth weight by gestational age (based on infant gender and mother’s parity)</td>
<td>&lt;10&lt;sup&gt;th&lt;/sup&gt; percentile 31%* &lt;3&lt;sup&gt;rd&lt;/sup&gt; percentile 13%*</td>
<td>&lt;10&lt;sup&gt;th&lt;/sup&gt; percentile: A. 0.28 (0.10 to 0.75), p&lt;0.05 vs. others B. 1.68 (0.79 to 3.55), p&lt;0.05 vs. others &lt;3&lt;sup&gt;rd&lt;/sup&gt; percentile: A. 0.16 (0.03 to 0.91), p&lt;0.05 vs. others B. 2.73 (0.83 to 9.00), p&gt;0.05 vs. others</td>
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<td>Small for Gestational Age</td>
<td>Chen et al, 2012 Botswana</td>
<td>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</td>
<td>SGA &lt;10&lt;sup&gt;th&lt;/sup&gt; percentile</td>
<td>13.5%*</td>
<td>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)</td>
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<td>Small for Gestational Age</td>
<td>Duryea, 2015 USA University of Texas study</td>
<td>A. ART with PI (597; 59%) B. ART without PI (230; 23%) C. No ART (177; 18%) Total N=1,004</td>
<td>SGA &lt;10&lt;sup&gt;th&lt;/sup&gt; percentile of birth weight by gestational age</td>
<td>4% to 10% depending on ART regimen</td>
<td>A. 1 reference B. 1.3 (0.8 to 1.9) C. 1.1 (0.6 to 2.0)</td>
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<tr>
<td>Small for Gestational Age</td>
<td>Li et al, 2016 Tanzania</td>
<td>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</td>
<td>SGA &lt;10&lt;sup&gt;th&lt;/sup&gt; percentile of birth weight by gestational age; &lt;3&lt;sup&gt;rd&lt;/sup&gt; percentile for severe SGA</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; to 10&lt;sup&gt;th&lt;/sup&gt; percentile 9%* &lt;3&lt;sup&gt;rd&lt;/sup&gt; percentile 11%*</td>
<td>HAART vs. ZDV started during pregnancy: 3-10&lt;sup&gt;th&lt;/sup&gt; %: 1.09 (0.88 to 1.35), p=0.41 &lt;3&lt;sup&gt;rd&lt;/sup&gt; %: 1.47 (1.09 to 1.98), p=0.01</td>
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<td>Small for Gestational Age</td>
<td>Moodley et al, 2016 South Africa</td>
<td>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</td>
<td>SGA</td>
<td>8.2%</td>
<td>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</td>
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<td>Small for Gestational Age</td>
<td>Ramokolo et al, 2017 South Africa</td>
<td>A. Postconception ART (780; 30%) B. ZDV (873; 34%) C. No ART (330; 13%) D. Preconception ART (616; 24%) Total =2,599</td>
<td>SGA &lt;10&lt;sup&gt;th&lt;/sup&gt; percentile of birth weight by gestational age</td>
<td>14.9%</td>
<td>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</td>
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<td>Small for Gestational Age</td>
<td>Siberry et al, 2012 USA PHACS/SMARTT</td>
<td>A. TDF-containing ART (449; 27%) B. nonTDF-containing ART (1580; Total=2,029</td>
<td>SGA</td>
<td>8.6%</td>
<td>A vs B: 0.96 (0.60 to 1.52), p=0.85</td>
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| Small for Gestational Age | Snijdewind et al, 2018<sup>11</sup> The Netherlands | A. PI-based (928; 67%)  
B. NNRTI-based (438; 31%)  
C. Both or NRTI (12; 1%)  
Total=1,378 | SGA <10<sup>th</sup> 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<sup>10</sup> 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 <10<sup>th</sup> percentile of birth weight by gestational age | 7%<sup>*</sup> | All vs. no ARV 1<sup>st</sup> 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<sup>16</sup> 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 <10<sup>th</sup> 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<sup>73</sup> 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 <10<sup>th</sup> percentile of birth weight by gestational age  
Very SGA <3<sup>rd</sup> percentile | 22% | 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 |
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<td>Stillbirth</td>
<td>Chen et al, 2012&lt;sup&gt;16&lt;/sup&gt; Botswana</td>
<td>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</td>
<td>Stillbirth (Fetal death with APGAR of 0)</td>
<td>3.3%*</td>
<td>HAART initiation vs. ZDV initiation: 2.5 (1.6 to 3.9) Continued HAART vs. all others: 1.5 (1.2 to 1.8)</td>
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<td>Stillbirth</td>
<td>Kreitchmann et al, 2014&lt;sup&gt;40&lt;/sup&gt; Latin America Caribbean</td>
<td>At least 28 days 3&lt;sup&gt;rd&lt;/sup&gt; 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</td>
<td>Stillbirth Birth at 20 weeks gestation or later with no signs of life</td>
<td>2%*</td>
<td>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)</td>
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<td>Stillbirth</td>
<td>Moodley et al, 2016&lt;sup&gt;40&lt;/sup&gt; South Africa</td>
<td>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</td>
<td>Stillbirth</td>
<td>3.1%</td>
<td>A. 1 reference B. 0.08 (0.04 to 0.16), p&lt;0.001 C. 0.20 (0.11 to 0.38), p&lt;0.001 D. 0.18 (0.10 to 0.34), p&lt;0.001</td>
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<td>Stillbirth</td>
<td>Rough et al, 2018&lt;sup&gt;52&lt;/sup&gt; USA PHACS and IMPAACT</td>
<td>A. TDF + FTC + LPV/r (128; 8%) B. ZDV + 3TC + LPV/r (954; 59%) C. TDF + FTC + ATV/r (539; 33%) Total=1,621</td>
<td>Fetal loss was undefined, included stillbirth (likely also included spontaneous abortion and fetal demise)</td>
<td>0.6%</td>
<td>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)</td>
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<td>Stillbirth</td>
<td>Zash et al, 2016&lt;sup&gt;16&lt;/sup&gt; Botswana</td>
<td>All CD4 counts: A. TDF/FTC/EFV (1054; 33%) B. other ART (2172; 64%) Total N=3226 CD4 counts &gt;350 A. TDF/FTC/EFV (335; 31%) B. ZDF (752; 69%) Total N=1,087</td>
<td>Stillbirth</td>
<td>3%</td>
<td>A vs. B (all CD4 counts): 0.6 (0.3 to 1.3) A vs. B (CD4 &gt;350): 0.9 (0.4 to 2.1)</td>
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<td>Stillbirth</td>
<td>Zash et al, 2017&lt;sup&gt;53&lt;/sup&gt; Botswana</td>
<td>A. TDF/FTC/NVP (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</td>
<td>Stillbirth</td>
<td>3.6%</td>
<td>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)</td>
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<td>Study Name</td>
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<td>Birth Outcome Definition</td>
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<td>Neonatal Death</td>
<td>Pintye et al, 2017&lt;sup&gt;76&lt;/sup&gt;</td>
<td>Kenya and Uganda</td>
<td>ART regimen (n;%)</td>
<td>Birth Outcome Definition</td>
<td>Birth Outcome Distribution</td>
</tr>
<tr>
<td>Neonatal Death</td>
<td>Rough et al, 2018&lt;sup&gt;82&lt;/sup&gt;</td>
<td>USA</td>
<td>PHACS and IMPAACT</td>
<td>Neonatal death within 3 days of live birth</td>
<td>2%</td>
</tr>
<tr>
<td>Neonatal Death</td>
<td>Zash et al, 2017&lt;sup&gt;73&lt;/sup&gt;</td>
<td>Botswana</td>
<td>Neonatal death within 14 days of live birth</td>
<td>0.1% (2 events)</td>
<td>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)</td>
</tr>
<tr>
<td>Congenital Abnormalities</td>
<td>Antiretroviral Pregnancy Registry Interim Report (1989 through 2018)&lt;sup&gt;93&lt;/sup&gt;</td>
<td>Multinational (69 countries), 75% USA and its territories</td>
<td>Preferred initial treatment drugs in US:</td>
<td>Follows Centers for Disease Control and Prevention guidelines</td>
<td>2.73% First trimester exposure</td>
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<td>A. ABC (1131; 12%)</td>
<td>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)</td>
<td>2.77% Any trimester exposure</td>
</tr>
<tr>
<td>Harm category</td>
<td>Study, year Country Study Name</td>
<td>ART regimen (n;%)</td>
<td>Birth Outcome Definition</td>
<td>Birth Outcome Distribution</td>
<td>Magnitude of Risk: Adjusted OR (95% CI), p-value</td>
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<tr>
<td>Congenital Abnormalities</td>
<td>Floridia et al, 2013 Italy</td>
<td>Preferred initial treatment drugs in US:&lt;br&gt;A. ABC (88; 7%)&lt;br&gt;B. 3TC (544; 43%)&lt;br&gt;C. TDF (173; 14%)&lt;br&gt;D. FTC (87; 7%)&lt;br&gt;E. ATV (63; 5%)&lt;br&gt;F. Ritonavir (231; 18%)&lt;br&gt;Alternative initial treatment drugs in US:&lt;br&gt;G. ZDV (358; 28%)&lt;br&gt;H. LPV (140; 11%)&lt;br&gt;I. EFV (80; 6%)&lt;br&gt;J. Any NRTI (716; 56%)&lt;br&gt;K. Any PI (353; 28%)&lt;br&gt;L. Any NNRTI (273; 21%)&lt;br&gt;Total N=1,257</td>
<td>Birth Defects Not defined</td>
<td>3.4%*</td>
<td>Not clear if ORs are adjusted; 1st Trimester exposure vs. unexposed:&lt;br&gt;ABC 1.01 (0.29 to 3.47), p=0.99&lt;br&gt;3TC 1.14 (0.61 to 2.15), p=0.67&lt;br&gt;TDF 0.85 (0.31 to 2.31), p=0.75&lt;br&gt;FTC 0.67 (0.15 to 2.93), p=0.60&lt;br&gt;ATV 0.93 (0.21 to 4.11), p=0.93&lt;br&gt;Ritonavir 1.02 (0.44 to 2.37), p=0.96&lt;br&gt;ZDV 0.65 (0.28 to 1.51), p=0.32&lt;br&gt;LPV 1.28 (0.50 to 3.26), p=0.61&lt;br&gt;EFV 0.73 (0.17 to 3.20), p=0.68&lt;br&gt;Any NRTI 0.95 (0.51 to 1.76), p=0.86&lt;br&gt;Any PI 0.92 (0.43 to 1.95), p=0.82&lt;br&gt;Any NNRTI 1.20 (0.56 to 2.55), p=0.64</td>
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<td>Congenital Abnormalities</td>
<td>Knapp et al, 2012 USA (IMPAACT) These patients may also be represented in the Antiretroviral Pregnancy Registry</td>
<td>Preferred initial treatment drugs in US:&lt;br&gt;A. ABC (312; 28%)&lt;br&gt;B. 3TC (979; 88%)&lt;br&gt;C. TDF (235; 21%)&lt;br&gt;D. FTC (121; 11%)&lt;br&gt;E. ATV (104; 9%)&lt;br&gt;F. Ritonavir (131; 12%)&lt;br&gt;Alternative initial treatment drugs in US:&lt;br&gt;G. ZDV (358; 28%)&lt;br&gt;H. LPVr (306; 28%)&lt;br&gt;I. EFV (56; 5%)&lt;br&gt;J. Any NRTI (1097; 99%)&lt;br&gt;K. Any PI (804; 72%)&lt;br&gt;L. Any NNRTI (205; 18%)&lt;br&gt;Total N=1,112</td>
<td>Birth Defects Metropolitan Atlanta Congenital Defects Program (MACDP)</td>
<td>5%*</td>
<td>All vs. unexposed:&lt;br&gt;ABC 1st T 1.45 (0.68 to 3.10)&lt;br&gt;ABC 2-3 T 1.25 (0.62 to 2.51)&lt;br&gt;3TC 1st T 1.68 (0.61 to 4.58)&lt;br&gt;3TC 2-3 T 1.52 (0.56 to 4.08)&lt;br&gt;TDF 1st T 1.69 (0.83 to 3.44)&lt;br&gt;TDF 2-3 T 1.01 (0.38 to 2.65)&lt;br&gt;FTC 1st T 1.33 (0.49 to 3.60)&lt;br&gt;FTC 2-3 T 0.56 (0.06 to 2.31)&lt;br&gt;ATV 1st T 1.83 (0.73 to 4.58)&lt;br&gt;ATV 2-3 T 0.87 (0.10 to 3.65)&lt;br&gt;Ritonavir 1st T 1.60 (0.64 to 3.99)&lt;br&gt;Ritonavir 2-3 T 1.18 (0.29 to 3.54)&lt;br&gt;ZDV 1st T 1.02 (0.45 to 2.28)&lt;br&gt;ZDV 2-3 T 1.02 (0.48 to 2.17)&lt;br&gt;LPVr 1st T 1.66 (0.81 to 3.38)&lt;br&gt;LPVr 2-3 T 0.80 (0.35 to 1.82)&lt;br&gt;<strong>EFV 1st T 2.84 (1.13 to 7.16)</strong>&lt;br&gt;EFV 2-3 T NA (0 to 9.05)&lt;br&gt;Any NRTI 1st T 0.84 (0.11 to 39.45)&lt;br&gt;Any NRTI 2-3 T 0.62 (0.08 to 29.05)&lt;br&gt;Any PI 1st T 1.32 (0.64 to 2.71)&lt;br&gt;Any PI 2-3 T 1.15 (0.58 to 2.29)&lt;br&gt;Any NNRTI 1st T 1.53 (0.72 to 3.25)&lt;br&gt;Any NNRTI 2-3 T 0.77 (0.14 to 2.69)</td>
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<td>Harm category</td>
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</table>
| Congenital Abnormalities | Sibiude et al, 2014 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)  
FDC 1st T 0.52 (0.30 to 0.90)  
FDC 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 14.2)  
Any NRTI 1st T 2.36 (0.96 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 T 0.94 (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) |
<table>
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<tr>
<th>Harm category</th>
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</tr>
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<tbody>
<tr>
<td>Congenital Abnormalities</td>
<td>Williams, 2015 USA PHACS/SMARTT</td>
<td>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%)</td>
<td>Antiretroviral Pregnancy Registry modification to MACDP</td>
<td>6.8%</td>
<td>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)</td>
</tr>
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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; 1\textsuperscript{st} T=first trimester; 2-3 T=second and third trimester; TDF=tenofovir; ZDV=zidovudine.
<table>
<thead>
<tr>
<th>Key Question</th>
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<th>Reporting Bias</th>
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<th>Body of Evidence Limitations</th>
<th>EPC Assessment of SOE for Key Question</th>
<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ 1. Benefits of screening</td>
<td>No studies</td>
<td>No studies</td>
<td>No studies</td>
<td>No studies</td>
<td>No studies</td>
<td>No studies</td>
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<td>KQ 2. Yield of repeat HIV screening at different intervals</td>
<td>No studies</td>
<td>No studies</td>
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<td>KQ 3. Harms of screening</td>
<td>No studies</td>
<td>No studies</td>
<td>No studies</td>
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<tr>
<td>KQ 4. Effectiveness of currently recommended antiretroviral therapy regimens</td>
<td>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)</td>
<td>The prior USPSTF review included 8 cohort studies that found full-course combination ART associated with rates of mother-to-child transmission of &lt;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 &lt;1% to 2.8%. One African RCT reported a rate of mother-to-child transmission of 0.5%.</td>
<td>Consistent</td>
<td>No imprecision</td>
<td>No reporting bias detected</td>
<td>Moderate</td>
<td>Most evidence observational, with no RCT conducted in the U.S. or other high-income setting</td>
<td>High</td>
<td>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.</td>
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</table>

Table 4. Summary of Evidence
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<tr>
<th>Key Question</th>
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<tbody>
<tr>
<td>KQ 5. Harms of currently recommended antiretroviral therapy regimens</td>
<td>Preterm Birth</td>
<td>2012 USPSTF review: 1 RCT (n=560), 5 cohort studies (15,812) New: 1 RCT (3,490) and 17 cohort studies (48,452)</td>
<td>Preterm Birth</td>
<td>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</td>
<td>Inconsistent No imprecision</td>
<td>No reporting bias detected</td>
<td>Moderate</td>
<td>No US RCTs or trials from non-resource-poor countries</td>
<td>Low</td>
<td>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.</td>
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<td>Overall Birth Defects</td>
<td>2012 USPSTF review: 3 cohort studies (13,730) New: 5 cohort studies (27,409)</td>
<td>Overall Birth Defects</td>
<td>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</td>
<td>Consistent Precise</td>
<td>No reporting bias detected</td>
<td>Moderate</td>
<td>No RCTs</td>
<td>Moderate</td>
<td>Cohort studies conducted in high-resource settings. Individual ART drugs specified.</td>
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<tr>
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<td>KQ 5 cont.</td>
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<td>Low</td>
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<td>Low Birth Weight</td>
<td>2012 USPSTF review: 7 cohort studies (n=352 to 8,192) New: 1 RCT (n=3,490) and 5 cohort studies (n=11,213)</td>
<td>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</td>
<td>Consistent Imprecise</td>
<td>No reporting bias detected</td>
<td>Moderate</td>
<td>No US RCTs or trials from non-resource-poor countries; Variability in timing of ART initiation.</td>
<td>Low</td>
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<td>SGA</td>
<td>2012 USPSTF review: none New: 10 cohort studies (n=37,670)</td>
<td>SGA 9 new cohort studies found no clear association between ART and SGA</td>
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<td>Low</td>
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<td>Stillbirth</td>
<td>2012 USPSTF review: none New: 6 cohort studies (n=30,417)</td>
<td>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</td>
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<td>Low</td>
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<td>Neonatal Death</td>
<td>2012 USPSTF review: none New: 1 RCT (n=3,490) and 3 cohort studies (7,038)</td>
<td>Neonatal Death 1 new RCT and 3 cohort studies found mixed results for neonatal death</td>
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<td>KQ 5 cont.</td>
<td>Infant Cardiac Harms</td>
<td>2012 USPSTF review: 1 cohort study (n=352) New: 3 cohort studies (n=15,888)</td>
<td>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</td>
<td>Consistent Imprecise</td>
<td>No reporting bias detected</td>
<td>Moderate</td>
<td>No RCTs; no studies of in utero exposed, HIV-uninfected children beyond age 7</td>
<td>Low</td>
<td>Cohort studies conducted in high-resource settings. Variability in timing of ART initiation.</td>
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<tr>
<td>KQ 5 cont.</td>
<td>Infant Neuro-developmental Harms</td>
<td>2012 USPSTF review: 3 cohort studies (n=2,590) New: SMARTT cohort (n=3,542)</td>
<td>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</td>
<td>Consistent Precise</td>
<td>No reporting bias detected</td>
<td>Moderate</td>
<td>No RCT; drug regimens often not provided</td>
<td>Low</td>
<td>Cohort studies conducted in high-income settings. Variability in timing of ART initiation.</td>
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<td>KQ 5 cont.</td>
<td>Maternal Harms</td>
<td>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)</td>
<td>Maternal Harms</td>
<td>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</td>
<td>Inconsistent</td>
<td>No reporting bias detected</td>
<td>Moderate</td>
<td>No US RCTs or trials from non-resource-poor countries</td>
<td>Low</td>
<td>Cohort studies conducted in all settings; RCTs conducted in Africa. Exact ART regimen not specified in most studies. Variability in timing of ART initiation.</td>
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</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Category</th>
<th>Include</th>
<th>Exclude</th>
</tr>
</thead>
</table>
| **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

Abstracts of potentially relevant articles identified through searches and other sources: 1,229

Excluded abstracts and background articles: 1,102

Full-text articles reviewed: 127

Articles excluded: 91
Wrong population: 13
Wrong intervention: 5
Wrong outcome: 16
Wrong comparator: 8
Wrong study design for key question: 11
Not a study (letter, editorial, non-systematic review article, no original data): 9
Inadequate duration: 1
Sample size too small: 1
Systematic review or meta-analysis used as a source document only to identify individual studies: 6
Wrong country: 6
Did not adjust for confounders and/or did not provide adequate data: 15

Included studies: 29 in 38 publications

Key Question 1: 0
Key Question 2: 0
Key Question 3: 0
Key Question 4: 1 trial and 5 cohort studies
Key Question 5: 2 trials and 21 cohort studies (in 30 publications)

* 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


<table>
<thead>
<tr>
<th></th>
<th>Reference</th>
<th>Excluded:</th>
<th>Notes</th>
</tr>
</thead>
</table>


89. Villatoro CM, Luarte ME, Natareno GV, et al. Highly active antiretroviral treatment (HAART) for the prevention of HIV mother to child transmission (PMTCT) at Roosevelt Hospital's Infectious Diseases Clinic in Guatemala: the role of (LPV/r) standard dose. World J AIDS. 2012;2(03):259. Excluded: did not adjust for confounders and/or did not provide adequate data.


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 independently 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


- 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

<table>
<thead>
<tr>
<th>Two-NRTI Backbones</th>
<th>Protease Inhibitor regimens</th>
<th>Integrase Inhibitor regimens</th>
<th>NNRTI regimens</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC/3TC</td>
<td>ATV/r</td>
<td>-</td>
<td>-</td>
<td>No HLA-B5701 due to hypersensitivity (ABC); No HIV RNA&gt; 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)</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>DRV/r</td>
<td>-</td>
<td>-</td>
<td>No HLA-B5701 due to hypersensitivity (ABC)</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>-</td>
<td>RAL</td>
<td>-</td>
<td>No HLA-B5701 due to hypersensitivity (ABC); Rapid viral load reduction (RAL)</td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>ATV/r</td>
<td>-</td>
<td>-</td>
<td>Caution in renal insufficiency (TDF); maternal hyperbilirubinemia (ATV/r); cannot be administered with a proton-pump inhibitor (ATV/r)</td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>DRV/r</td>
<td>-</td>
<td>-</td>
<td>Caution in renal toxicity (TDF)</td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>-</td>
<td>RAL</td>
<td>-</td>
<td>Caution in renal insufficiency (TDF); rapid viral load reduction (RAL)</td>
</tr>
<tr>
<td>TDF/3TC</td>
<td>ATV/r</td>
<td>-</td>
<td>-</td>
<td>Caution in renal insufficiency (TDF); cannot be administered with a proton-pump inhibitor (ATV/r)</td>
</tr>
<tr>
<td>TDF/3TC</td>
<td>DRV/r</td>
<td>-</td>
<td>-</td>
<td>Caution in renal insufficiency (TDF); rapid viral load reduction (RAL)</td>
</tr>
</tbody>
</table>

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

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

Abbreviations: 3TC=lamivudine; ABC=abacavir; ATV/r=atazanavir/ritonavir; DRV/r=darunavir/ritonavir; RAL=raltegravir; RPV=rilpivirine; TDF= tenofovir disoproxil fumarate; ZDV=zidovudine.

### Appendix B2a. Evidence Table of Included Studies – Study Characteristics

<table>
<thead>
<tr>
<th>Study Author, year</th>
<th>Study design</th>
<th>No. of centers/Country</th>
<th>Study duration, Mean followup</th>
<th>Intervention</th>
<th>Inclusion criteria</th>
<th>Patient characteristics</th>
<th>N</th>
<th>Quality rating</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aaron, 2012²¹</td>
<td>Prospective cohort</td>
<td>1 site United States (Philadelphia, Pennsylvania)</td>
<td>Through birth January 2000 through January 2011</td>
<td>A. Any ART initiation during pregnancy (n=137) B. NNRTI use (n=39) C. PI use (n=117)</td>
<td>HIV-infected, pregnant, and more than 17 years of age</td>
<td>Maternal age: mean 28 years Race/ethnicity: 74.7% African American; 25.3% other Started medication in pregnancy: 74.9%</td>
<td>183</td>
<td>Fair</td>
<td>Not reported</td>
</tr>
<tr>
<td>Antiretroviral Pregnancy Registry, 2018¹¹</td>
<td>Cohort (approx., 1000 women prospectively included)</td>
<td>Multinational (69 countries), 75% USA and its territories</td>
<td>January 1989 through January 2018</td>
<td>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%)</td>
<td>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)</td>
<td>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% &gt;=500 cells/mm³, 39.4% 200-499 cells/mm³, 14.1% &lt;200 cells/mm³</td>
<td>9,336</td>
<td>Fair</td>
<td>Co-sponsored and co-funded by 26 pharmaceutical companies that manufacture drugs used in ART</td>
</tr>
<tr>
<td>Berard, 2017²⁷</td>
<td>Prospective cohort</td>
<td>Database study (Quebec Drug Plan) Canada</td>
<td>Through birth 1998 to 2015</td>
<td>A. No ART exposure (n=214,042) B. First trimester ART exposure (n=198)</td>
<td>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.</td>
<td>A vs B Maternal age: 31.5 vs 28.3 years (p&lt;0.0001) Welfare recipient: 54% vs 23% (p&lt;0.0001) Infant gestational age: 38.2 vs 38.8 weeks</td>
<td>214,240</td>
<td>Fair</td>
<td>Canadian Institutes of Health Research, Fonds de l'Institut du Quebec – Santé</td>
</tr>
<tr>
<td>Study Author, year</td>
<td>Study design</td>
<td>No. of centers, Country</td>
<td>Study duration Mean followup</td>
<td>Intervention</td>
<td>Inclusion criteria</td>
<td>Patient characteristics</td>
<td>N</td>
<td>Quality rating</td>
<td>Funding source</td>
</tr>
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<tr>
<td>Chagomerana, 2017&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>1 hospital Malawi</td>
<td>Through birth Period April 2012 to November 2015</td>
<td>A. ART (n=2,909) B. No ART (n=165)</td>
<td>HIV+ pregnant women who initiated ART before 27 weeks gestation or did not receive ART and who delivered after 27 weeks</td>
<td>A vs. B Maternal age: 27 to 30 vs. 26 years Gestation at delivery: 38 vs. 38 weeks</td>
<td>3,074</td>
<td>Fair</td>
<td>National Institutes of Health and a Gilead Training Fellowship</td>
</tr>
<tr>
<td>Chen, 2012&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Prospective cohort</td>
<td>6 sites Botswana</td>
<td>May (1 site) or November (5 sites) 2009 through April 2011 28 days after delivery</td>
<td>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)</td>
<td>All women who delivered live births or stillbirths at a gestational age ≥20 weeks at 6 government facilities in Botswana</td>
<td>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%</td>
<td>9,504</td>
<td>Fair</td>
<td>CDC, NIH, Harvard University, Doris Duke Charitable Research Foundation</td>
</tr>
<tr>
<td>Chiappini, 2013&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Analysis from 8 cohort studies</td>
<td>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); &quot;Victor Babes&quot; Hospital Cohort, Bucharest, Romania; Swiss Mother and Child HIV Cohort Study</td>
<td>Up to 18 months Period 1996-2010</td>
<td>A. 3 or more drugs (n=2,355) B. 2 drugs (n=255) C. 1 drug (n=681) D. No therapy (n=1,933)</td>
<td>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 (&gt;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</td>
<td>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&lt;sup&gt;3&lt;/sup&gt; 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</td>
<td>5,285</td>
<td>Fair</td>
<td>European Union Seventh Framework Programme; PENTA Foundation</td>
</tr>
<tr>
<td>Study Author, year</td>
<td>Study design</td>
<td>No. of centers, Country</td>
<td>Study duration, Mean followup</td>
<td>Intervention</td>
<td>Inclusion criteria</td>
<td>Patient characteristics</td>
<td>N</td>
<td>Quality rating</td>
<td>Funding source</td>
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<tr>
<td>-------------------</td>
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<td>(MoCHiV); European Collaborative Study (ECS) on HIV-infected pregnant women and their children; ECS was considered as 2 studies</td>
<td>Retrospective cohort</td>
<td>Single site Texas, US</td>
<td>Through birth Period January 1984 to April 2014</td>
<td>A. ART with PI (n=597) B. ART without PI (n=230) C. No ART (n=177)</td>
<td>All HIV+ women who delivered at the institution (University of Texas Southwestern Medical Center, Dallas) during the study period</td>
<td>Maternal age at delivery: 25-28 years (p&lt;0.001) Race/ethnicity: black 64-69%, Hispanic 19%, white 11-16% Gestational age at presentation for prenatal care: 12-24 weeks (p&lt;0.001) CD4 count at presentation: 456-557 cells/mm³ (p&lt;0.001) CD4 count at delivery: 505-565 cells/mm³ (p=0.349) Duration of diagnosis: 1-2 years (p&lt;0.001)</td>
<td>1,004</td>
<td>Fair</td>
<td>Not reported</td>
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<tr>
<td>Floridia, 2013</td>
<td>Prospective cohort</td>
<td>Unclear Italy</td>
<td>Through birth Period 2001-2011</td>
<td>Various cART regimens</td>
<td>HIV-positive pregnant women with data from the Italian National Programme on Surveillance on Antiretroviral Treatment in Pregnancy</td>
<td>Mean maternal age at conception: 32.3 years Ethnicity: 66% white, 29% African, 4% Other CD4 count at first trimester: 464³ cells/mm³ HIV RNA at first trimester: 3.0 copies/mL, log10 HCV coinfection: 22% HBV coinfection: 11% Treatment-naïve 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</td>
<td>1,257</td>
<td>Fair</td>
<td>Italian Medicines Agency</td>
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<td>Study Author, year</td>
<td>Study design</td>
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<td>Study duration Mean followup</td>
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<td>French Perinatal Cohort (ANRS-EPF) study Mandelbrot, 2015&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Prospective cohort, no control</td>
<td>90 sites</td>
<td>France (but majority from sub-Saharan Africa)</td>
<td>Pre-conception to postpartum Period 2000-2011</td>
<td>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%</td>
<td>All HIV-1+ women enrolled in the French Perinatal Cohort delivering in metropolitan France between 2000 and 2011 that received highly active ART (regimens containing ≥3 drugs or 1 drug other than a NRTI) during pregnancy. Women who 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</td>
<td>N=8,678 Age: &lt;25 years 8.7%, 25 to 34 years 56.5%, &gt;34 years 34.8% Geographic origin: metropolitan France 16.6%, sub-Saharan 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 53.9%, 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 3.1%, other 2.0% Maintained initial ART regimen throughout pregnancy: 71.4% Last viral load before delivery (copies/mL): &lt;50 68.0%, undetectable 50 to 400 5.9%, 50 to 399 15.2%, ≥400 10.9% CD4 count before delivery (cells/mm&lt;sup&gt;3&lt;/sup&gt;): &lt;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</td>
<td>Fair</td>
<td>Agence Nationale de Recherche sur le Sida et les Hepatites Virales</td>
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<tr>
<td>French Perinatal Cohort Study (EPF, ANRS C01/C011) Sibiude, 2012&lt;sup&gt;55&lt;/sup&gt;</td>
<td>See above</td>
<td>See above</td>
<td>See Period 1990-2009</td>
<td>A. Zidovudine monotherapy (n=2,975) B. NRTI dual therapy (n=1,664) C. cARV therapy (n=6,738) Substudy: D. Boosted PI</td>
<td>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. 18% vs. 17% D vs. E</td>
<td>13,271</td>
<td>See above</td>
<td>French Agence Nationale de Recherche sur le SIDA (ANRS)</td>
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<td>Study Author, year</td>
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<td>French Perinatal Cohort Study (EPF, ANRS C01/C011) Sibiude, 2014&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Prospective cohort</td>
<td>90 centers France (but majority from sub-Saharan Africa)</td>
<td>2 years Period 1994-2010</td>
<td>cART</td>
<td>Same as Sibiude 2012</td>
<td>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%</td>
<td>13,124</td>
<td>See above</td>
<td>See above</td>
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<td>French Perinatal Cohort Study (EPF, ANRS C01/C011) and nested PRIMEVA ANRS 135 RCT Sibiude, 2015&lt;sup&gt;43&lt;/sup&gt;</td>
<td>Cohort combining prospectively collected observational data and retrospective analysis of data from an RCT</td>
<td>Same as Sibiude 2014</td>
<td>Up to 24 months Period 1994-2010</td>
<td>A. Zidovudine exposure (n=3,262) B. No zidovudine exposure (n=9,626)</td>
<td>Same as Sibiude 2014</td>
<td>Maternal age: mean NR; 60% age 25 to 34 years Race/ethnicity: NR Maternal geographic origin: 22% France; 61% Africa</td>
<td>12,888</td>
<td>See above</td>
<td>French National Agency for Research on AIDS and Viral Hepatitis</td>
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<td>Fowler, 2017&lt;sup&gt;32&lt;/sup&gt; PROMISE (Promoting Maternal and Infant Survival Everywhere) trial</td>
<td>RCT, open label</td>
<td>14 sites in 7 countries (India, Malawi, South Africa, Tanzania, Uganda, Zambia, Zimbabwe)</td>
<td>Through 6 to 14 days postpartum (antepartum period) Period 2011 to 2014.</td>
<td>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).</td>
<td>Eligibility criteria included a CD4 count of at least 350 cells/mm&lt;sup&gt;3&lt;/sup&gt; (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&lt;sup&gt;3&lt;/sup&gt;, 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, &lt;0.5% other Median CD4 count: 530 cells/mm&lt;sup&gt;3&lt;/sup&gt; Median viral load: 3.9 log10 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</td>
<td>Enrolled 3,529 mother-infant pairs Analyzed: 3,490 mother-infant pairs</td>
<td>Fair</td>
<td>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 companies</td>
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Screening for HIV in Pregnant Women 73 Pacific Northwest EPC
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<tr>
<th>Study Author, year</th>
<th>Study design</th>
<th>No. of centers, Country</th>
<th>Study duration, Mean followup</th>
<th>Intervention</th>
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<th>Patient characteristics</th>
<th>N</th>
<th>Quality rating</th>
<th>Funding source</th>
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<tr>
<td>Kakkar, 2015&lt;sup&gt;th&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>Canada (Montreal)</td>
<td>Period 1988 to 2011</td>
<td>A. Boosted protease inhibitors (PI; n=144) Unboosted PI (n=220) Other treatment (n=166) No treatment (n=59)</td>
<td>Centre Maternel et Infantile sur le SIDA mother-infant 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</td>
<td>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</td>
<td>525 mother-infant pairs</td>
<td>Fair</td>
<td>Fonds de Recherche du Quebec-Sante (FRQ-S)</td>
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<td>Knapp, 2012&lt;sup&gt;th&lt;/sup&gt;</td>
<td>Case-control</td>
<td>Multiple sites International</td>
<td>Through birth Period 2002-2007</td>
<td>Various cART regimens A. Congenital anomaly (n=61) B. No congenital anomaly (n=1,051)</td>
<td>Singleton children born to HIV-infected mothers enrolled in P1025 trial</td>
<td>Maternal age at enrollment, ≤24 years: 33% Maternal age at enrollment, 25 to 34 years: 53% Maternal age at 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 &lt;400 copies/mL: 76%</td>
<td>1,112</td>
<td>Fair</td>
<td>NIH, NIAID</td>
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<td>Author, year, Study design</td>
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<td>Kreitchmann, 2014&lt;sup&gt;40&lt;/sup&gt; Prospective cohort Multi-site Latin America and Caribbean</td>
<td>Through birth Period 2002-2011</td>
<td>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</td>
<td>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</td>
<td>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.</td>
<td>1,563</td>
<td>Fair</td>
<td>NICHD</td>
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<td>Li, 2016&lt;sup&gt;41&lt;/sup&gt; Prospective cohort 10 sites Tanzania</td>
<td>18 months November 2004 to September 2011</td>
<td>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%)</td>
<td>HIV-infected pregnant women who had uninfected HIV-exposed infants at birth</td>
<td>Maternal age: median 30 years Race/ethnicity: NR</td>
<td>3,314</td>
<td>Fair</td>
<td>US President's Emergency Plan for AIDS Relief (PEPFAR)</td>
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<td>Lopez, 2012&lt;sup&gt;42&lt;/sup&gt; Retrospective cohort (case control) 1 site Spain (Barcelona)</td>
<td>January 1986 to June 2010 Through birth</td>
<td>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)</td>
<td>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</td>
<td>HIV infected only: Maternal age: mean 30 years 8% Black; other race/ethnicity NR Low education level: 50% Prior preterm delivery: 8%</td>
<td>519</td>
<td>Fair</td>
<td>Not reported</td>
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<td>Study Author, year</td>
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<td>Lu, 2014&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Retrospective cohort, no control</td>
<td>Canada (Ontario)</td>
<td>Through birth Period 1996-2008</td>
<td>A. Complete antiretroviral prophylaxis (n=251) B. Incomplete antiretroviral prophylaxis (n=336)</td>
<td>Data from women delivering 1996 to 2008 in the Ontario group of the Canadian Perinatal HIV Surveillance Program</td>
<td>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)</td>
<td>645 mother-child pairs</td>
<td>Fair</td>
<td>None reported</td>
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<td>Moodley, 2016&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Respective cross sectional analysis</td>
<td>Single center South Africa</td>
<td>July to December 2011 and January to June 2014</td>
<td>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)</td>
<td>Women with viable pregnancies delivering a neonate greater than or equal to 500 g and whose birth outcomes were recorded in the maternity register</td>
<td>Not reported</td>
<td>3,695</td>
<td>Fair</td>
<td>Not reported</td>
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<td>Mor, 2017&lt;sup&gt;64&lt;/sup&gt;</td>
<td>Cohort</td>
<td>Multi-site Israel</td>
<td>Through birth Period 1985-2011</td>
<td>A. Infants born before 1996 (n=80) B. Infant born after 1997 (HAART introduced; n=716)</td>
<td>All HIV-infected women who delivered in Israel and were local citizens between January 1988 and December 2011</td>
<td>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) Cesarean 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%</td>
<td>796 infants born to HIV-infected mothers</td>
<td>Fair</td>
<td>No funding received</td>
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<tr>
<td>Study Author, year</td>
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<td>Pintye, 2017&lt;sup&gt;28&lt;/sup&gt; Partners PrEP Study and Partners Demonstration Project</td>
<td>Cohort</td>
<td>Kenya and Uganda</td>
<td>Partners PrEP: 2008 through 2012 Partners Demonstration Project: 2012-2016</td>
<td>A. TDF-containing 3-drug ART (n=208) B. NonTDF-containing 3-drug ART (n=214)</td>
<td>Women who were HIV-infected at enrollment in Partners PrEP or Partners Demonstration Projects and became pregnant during the study period.</td>
<td>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</td>
<td>422 pregnancies</td>
<td>Fair</td>
<td>National Institutes of Health, University of Washington Center for AIDS Research, University of Washington Global Center for Integrated Health of Women Adolescents and Children</td>
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<td>Ramokolo, 2017&lt;sup&gt;33&lt;/sup&gt; Prevention of Mother to Child Transmission (PWTCT) Program</td>
<td>Cross-sectional cohort</td>
<td>580 sites South Africa</td>
<td>Through 4-8 weeks postpartum Period October 2012 to May 2013</td>
<td>A. Postconception ART (n=780) B. Preconception ART (n=616) C. Zidovudine prophylaxis (n=873) D. No ART (n=330)</td>
<td>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</td>
<td>A vs B vs C vs D Maternal age: 3.1% vs 1.8% vs 7.0% vs 5.2% &lt;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 13.0% age 30-35 years; 14.6% vs 29.8% vs 11.6% vs 14.7% &gt;35 years Education, &lt;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%</td>
<td>2,599 (HIV exposed infants only)</td>
<td>Fair</td>
<td>CDC; South African National Health Scholarship Programme</td>
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<td>Sartorius, 2013&lt;sup&gt;54&lt;/sup&gt; Kesho Bora Trial</td>
<td>RCT</td>
<td>Africa (3 countries)</td>
<td>January 2005 and August 2008 Duration: 28 weeks of pregnancy until 12 to 24 months after delivery</td>
<td>A. Triple ART, CD4 &lt; 200 (n=118) B. Zidovudine plus single-dose nevirapine, CD4 &gt; 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: &gt;70% breastfed</td>
<td>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 ART</td>
<td>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%</td>
<td>1,072</td>
<td>Fair</td>
<td>Not reported</td>
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<td>Short, 2013&lt;sup&gt;67&lt;/sup&gt;</td>
<td>Retrospective analysis</td>
<td>1 site United Kingdom (London)</td>
<td>Period 1996 to 2010</td>
<td>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)</td>
<td>HIV-positive pregnant women managed by a single, multidisciplinary team at St Mary’s Hospital</td>
<td>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</td>
<td>331</td>
<td>Fair</td>
<td>Not reported</td>
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</tbody>
</table>
| Surveillance Monitoring for Antiretroviral Treatment Toxicities (SMARTT) study and Pediatric HIV/AIDS Cohort Study (PHACS) Nozyce, 2014<sup>69</sup> | 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 Communication Disorders, the National Heart Lung and Blood Institute, the National Institute of Dental and Craniofacial...
<table>
<thead>
<tr>
<th>Study Author, year</th>
<th>Study design</th>
<th>No. of centers, Country</th>
<th>Study duration</th>
<th>Mean followup</th>
<th>Intervention</th>
<th>Inclusion criteria</th>
<th>Patient characteristics</th>
<th>N</th>
<th>Quality rating</th>
<th>Funding source</th>
</tr>
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<tbody>
<tr>
<td>Pediatric HIV/AIDS Cohort Study (PHACS) Lipshultz, 2015</td>
<td>Same as Nozyce 2014</td>
<td>Same as Nozyce 2014</td>
<td>Mean 4 years</td>
<td>Period 2007-2012</td>
<td>A. HIV-exposed uninfected (HEU; n=417) B. HIV unexposed controls (n=98)</td>
<td>SMARTT enrolled children with echocardiogram and unexposed controls</td>
<td>A vs. B</td>
<td>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</td>
<td>515</td>
<td>Same as Nozyce 2014</td>
</tr>
<tr>
<td>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</td>
<td>Cohort</td>
<td>2 multisite cohorts USA</td>
<td>Period 2007-2016 for Dynamic cohort of the SMARTT study and 2002-2013 for the P1025 study</td>
<td>All infants with an observed birth outcome in the SMARTT or P1025 study, when the first ART regimen used during pregnancy was one of the following: TDF + FTC + LPV/r, ZDV + 3TC + LPV/r, or TDF + FTC + ATV/r</td>
<td>A vs. B vs. C</td>
<td>Maternal age: 39.1% vs. 37.2% vs. 25.2% &lt;24 years, 52.3% vs. 49.6% vs. 54.4% 25-34 years, 8.6% vs. 13.1% 20.2% &gt;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% &lt;250 cells/mm³, 36.7% vs. 39.9% vs. 38.0% 250-500 cells/mm³, 36.7% vs. 41.7% vs. 38.3% &gt;500 cells/mm³ First viral RNA in pregnancy: 47.7% vs. 29.5% vs. 51.4% &lt;400 copies/ml, 25.8% vs. 37.8% vs. 40.4% 400-10,000 copies/ml, 25.8% vs. 32.0% vs. 22.6% &gt;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</td>
<td>1,621</td>
<td>Fair</td>
<td>Same as Nozyce 2014</td>
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<tr>
<td>Study Author, year, Study design</td>
<td>Study duration, Mean followup</td>
<td>Intervention</td>
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<tr>
<td>Surveillance Monitoring for Antiretroviral Treatment Toxicities (SMARTT) study and Pediatric HIV/AIDS Cohort Study (PHACS) Siberry, 2012</td>
<td>Prospective cohort</td>
<td>Through infant growth at 1 year Period through January 2011</td>
<td>A. TDF-containing ART (n=449) B. nonTDF-containing ART (n=1,580)</td>
<td>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</td>
<td>Race/ethnicity: black 66%, Latino 33% Gestational age: &lt;32 weeks 3%, 32-37 weeks 17%, 37+ weeks 76% Maternal CD4 count &lt;250 cells/mm$^3$ at delivery: 15% HBV+: 2%</td>
<td>2,029</td>
<td>Same as Nozyce 2014</td>
<td>Same as Nozyce 2014</td>
<td></td>
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<tr>
<td>Surveillance Monitoring for Antiretroviral Treatment Toxicities (SMARTT) study and Pediatric HIV/AIDS Cohort Study (PHACS) Watts, 2013</td>
<td>Prospective cohort</td>
<td>Unclear Period 2007-2010</td>
<td>Various maternal cART regimens</td>
<td>HIV-infected mothers and their children enrolled in SMARTT study of the PHACS network. This analysis limited to singleton gestations with maternal enrollment or before October 2010</td>
<td>Mean maternal age at delivery: 27 years Ethnicity: 65% black, 28% white, 7% other [34% Hispanic] Annual household income &lt;$20,000: 63% CD4 count &lt;200: 13% CD4 count 200 to 500: 46% CD4 count &gt;500: 36% Antiretroviral regimen: 3% none, 7% monotherapy or dual therapy, 71% combination with PI (with or without NNRTI), 10% combination with &gt;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%</td>
<td>1,869</td>
<td>Same as Nozyce 2014</td>
<td>Same as Nozyce 2014</td>
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<tr>
<td>Surveillance Monitoring for Antiretroviral Treatment Toxicities (SMARTT) study and Pediatric HIV/AIDS Cohort Study (PHACS)</td>
<td>Combined data from prospective and retrospective cohorts</td>
<td>Period 2007-2012</td>
<td>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</td>
<td>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% &gt;35 years Race/ethnicity: 66% Black; 27% white; 0.5% other; 33% Latino/Hispanic Caregiver not a HS graduate: 5%</td>
<td>2,580</td>
<td>Same as Nozyce 2014</td>
<td>Same as Nozyce 2014</td>
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<td>Study duration Mean followup</td>
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<td>Williams, 2015[1]</td>
<td>Same as Nozyce 2014</td>
<td>Same as Nozyce 2014</td>
<td>Period 2007-2012</td>
<td>2.303 depending on comparison</td>
<td>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 hematologic toxicity, or hearing impairment</td>
<td>No adverse event vs. adverse event Maternal age: mean NR; 33% vs. 33% &lt;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 (&lt;37 weeks gestation) 55% vs. 56% C-section</td>
<td>2,680</td>
<td>Same as Nozyce 2014</td>
<td>Same as Nozyce 2014</td>
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<tr>
<td>Surveillance Monitoring for Antiretroviral Treatment Toxicities (SMARTT) study and Pediatric HIV/AIDS Cohort Study (PHACS) Williams, 2016[2]</td>
<td>Same as Nozyce 2014</td>
<td>Same as Nozyce 2014</td>
<td>Period 2007-2012</td>
<td>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)</td>
<td>No adverse event vs. adverse event Maternal age: mean NR; 33% vs. 33% &lt;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 (&lt;37 weeks gestation) 55% vs. 56% C-section</td>
<td>No adverse event vs. adverse event Maternal age: mean NR; 33% vs. 33% &lt;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 (&lt;37 weeks gestation) 55% vs. 56% C-section</td>
<td>2,680</td>
<td>Same as Nozyce 2014</td>
<td>Same as Nozyce 2014</td>
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<td>Snijdewind, 2018[1] ATHENA cohort</td>
<td>Retrospective cohort</td>
<td>The Netherlands</td>
<td>Period 1997-2015</td>
<td>A. PI-based (928; 67%) B. NNRTI-based (438; 31%) C. Both or NRTI (12; 1%)</td>
<td>ATHENA cohort database; HIV-positive women &gt;18 years of age who gave birth to HEU infants after a minimum 24 weeks pregnancy; singleton births; includes women who started cART preconception as well as those who began post-conception</td>
<td>Maternal age: median 29 Region of origin: 61.3% sub-Saharan 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/mm³ HIV RNA: 79.1% ≤500 copies/ml Infant birth weight: median 3.090 kg Duration of pregnancy: 85.3% &gt;37 weeks, 11.9% &lt;37 weeks</td>
<td>1,378</td>
<td>Fair</td>
<td>Dutch Health Ministry</td>
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<tr>
<td>Study Author, year</td>
<td>Study design</td>
<td>No. of centers</td>
<td>Country</td>
<td>Study duration</td>
<td>Mean followup</td>
<td>Intervention</td>
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<tr>
<td>Tookey, 2016&lt;sup&gt;68&lt;/sup&gt;</td>
<td>National Study of HIV in Pregnancy and Childhood (NSHPC)</td>
<td>Retrospective cohort, no control</td>
<td>United Kingdom and Ireland</td>
<td>Through birth Period 2003-2012</td>
<td>LPV/r</td>
<td>National Study of HIV in Pregnancy and Childhood participants with pregnancies that were due to deliver</td>
<td>Maternal age: median 30 years Maternal race/ethnicity: 15% white; 77% Black; 8% other Maternal region/country: 14% UK/Ireland; 77% Africa; 10% other</td>
<td>4,118 mothers, 4,864 pregnancies</td>
<td>Fair</td>
<td>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</td>
</tr>
<tr>
<td>Zash, 2016&lt;sup&gt;76&lt;/sup&gt;</td>
<td>Cohort</td>
<td>2 hospitals Botswana</td>
<td>Through birth Period May 2009 to April 2011 and April 2013 to April 2014</td>
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<td>32,583 births, 9,445 HIV infected women</td>
<td>Fair</td>
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<tr>
<td>Study Author, year</td>
<td>Study design</td>
<td>No. of centers</td>
<td>Country</td>
<td>Study duration Mean followup</td>
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<tr>
<td>Zash, 2017²⁵</td>
<td>Surveillance cohort</td>
<td>8 government hospitals</td>
<td>Botswana</td>
<td>Through birth Period August 2014 to August 2016</td>
<td>A. TDF-FTC-EFV (n=2,472)</td>
<td>All women who delivered live-born or still-born infants at 8 government maternity wards in Botswana</td>
<td>Gestational age: 22.0% vs. 59.8% Median CD4 count: 388 vs. 415</td>
<td>47,124</td>
<td>Fair</td>
<td>National Institutes of Health</td>
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<td>B. TDF-FTC-NVP (n=760)</td>
<td>Excluded births that occurred before arrival at hospital and at gestational age &lt;24 weeks, and HIV positive mothers with no ART exposure, unknown ART timing, or unknown ART exposure</td>
<td>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</td>
<td>11,932</td>
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<td>C. TDF-FTC-LPV-R (n=231)</td>
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<td>10,592</td>
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<td>D. ZDV-3TC-NVP (n=1,365)</td>
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<td>Included in analysis</td>
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<td>E. ZDV-3TC-LPV-R (n=167)</td>
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**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-Cal=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

<table>
<thead>
<tr>
<th>Study Author, year</th>
<th>Intervention</th>
<th>HIV transmission</th>
<th>Adverse events</th>
</tr>
</thead>
</table>
| Aaron, 2012<sup>11</sup> | 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<sup>3</sup> | 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<sup>63</sup> Quebec Pregnancy Cohort | A. No ART exposure (n=214,042)  
B. First trimester ART exposure (n=198) | 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 to 3.92 |
| Chagomerana, 2017<sup>24</sup> | A. ART (n=2,909)  
B. No ART (n=165) | Not reported | |

<sup>1</sup> Pacific Northwest EPC

<sup>2</sup> Screening for HIV in Pregnant Women

<sup>3</sup> 85
<table>
<thead>
<tr>
<th>Study Author, year</th>
<th>Intervention</th>
<th>HIV transmission</th>
<th>Adverse events</th>
</tr>
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</table>
| Chen, 2012<sup>56</sup> | 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% (138/2,189) vs 4.1% (283/6,960); qOR 1.5 (95% CI 1.2 to 1.8) |
| Chiappini, 2013<sup>57</sup> 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<sup>80</sup> | 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<sup>57</sup> 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 |
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<tr>
<td>French Perinatal Cohort (ANRS-EPF) study Mandelbrot, 2015&lt;sup&gt;15&lt;/sup&gt;</td>
<td>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%</td>
<td>Overall mother-to-child HIV transmission: 0.7%, 95% CI 0.5 to 0.9 (58/8,075) 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&lt;0.001 Mother-to-child HIV transmission based on viral load (copies/mL) near delivery: &lt;50 0.3 (95% CI 0.1 to 0.4), undetectable &gt;50 0.2 (95% CI &lt;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&lt;0.001, adjusted OR 4.0, 95% CI 1.9 to 8.2</td>
<td>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 (&lt;37 weeks): 20.9% Very preterm delivery (&lt;32 weeks): 2.5% Low birthweight (2,500 grams): 22.1% Very low birthweight (&lt;1,500 grams): 2.5%</td>
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<tr>
<td>French Perinatal Cohort Study (EPF, ANRS C01/C011) Sibiude, 2012&lt;sup&gt;15&lt;/sup&gt;</td>
<td>A. Zidovudine monotherapy (n=2,975) B. NRTI dual therapy (n=1,664) C. cARTV (n=6,738) Substudy: D. Boosted PI (n=1,066) E. Nonboosted PI (n=187)</td>
<td>Not reported</td>
<td>Full cohort, A vs. B vs. C Premature birth: 9.6% vs. 11.3% vs. 14.7%; B vs. A: aOR 1.24 (95% CI 0.96 to 1.60); C vs. A: aOR 1.69 (95% CI 1.38 to 2.07) Substudy, D vs. E 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</td>
</tr>
<tr>
<td>French Perinatal Cohort Study (EPF, ANRS C01/C011) Sibiude, 2014&lt;sup&gt;14&lt;/sup&gt;</td>
<td>cART</td>
<td>Not reported</td>
<td>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 (&lt;37 weeks): 14.5% (1,901/13,124) Low birth weight (&lt;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</td>
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<tr>
<td>Fowler, 2017</td>
<td>A. Zidovudine exposure (n=3,262) B. No zidovudine exposure (n=9,626)</td>
<td>Overall mother-to-child transmission: 1.3% (169/12,888)</td>
<td>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</td>
</tr>
<tr>
<td>French Perinatal Cohort Study (EPF, ANRS C01/C011) and nested PRIMEVA ANRS 135 RCT Sibiude, 2015</td>
<td>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)</td>
<td>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 &lt;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/mm³: 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/mm³: 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, &lt;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: 0.3% (169/12,888)</td>
<td>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% (19/1,510), p&lt;0.001 Any adverse pregnancy outcome: 40.0% (563/1,407) vs. 27.5% (389/1,414), p&lt;0.001 Low birth weight, &lt;2,500g: 23.0% (306/1,332) vs. 12.0% (161/1,347), p&lt;0.001 Preterm delivery, &lt;37 weeks: 20.5% (288/1,406) vs. 13.1% (185/1,411), p&lt;0.001 Any severe adverse pregnancy outcome: 7.1% (99/1,385) vs. 5.9% (83/1,399), p=0.22 Very preterm delivery, &lt;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 ≥2 adverse event: 15.8% (61/385) vs. 15.8% (60/380), p&gt;0.99 Maternal grade ≥2 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, &lt;2,500g: 20.4% (65/319) vs. 16.9% (51/301), p=0.30 Preterm delivery, &lt;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, &lt;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</td>
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<td>Kreitmann, 2014&lt;sup&gt;a&lt;/sup&gt;</td>
<td>At least 28 days 3rd trimester:  A. HAART + PI (888; 59%) B. HAART no PI (410; 27%) C. Non-HAART (134; 9%) D. No ART (80; 5%) Total N=1,512</td>
<td>Not reported</td>
<td>Receiving ART at conception vs. no ART at conception, preterm delivery &lt;37 weeks: 1.53 (1.11 to 2.09)</td>
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<td>Li, 2016&lt;sup&gt;1&lt;/sup&gt;</td>
<td>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%)</td>
<td>Not reported</td>
<td>HAART vs. ZDV started during pregnancy, preterm delivery:  34 to 37 weeks: 0.85 (0.70 to 1.02), p=0.14 &lt;34 weeks: 0.87 (0.60 to 1.25), p=0.45</td>
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<td>Lopez, 2012&lt;sup&gt;2&lt;/sup&gt;</td>
<td>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)</td>
<td>Not reported</td>
<td>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)</td>
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</table>

**Study Author, year**

- Kakkar, 2015<sup>a</sup>
- Knapp, 2012<sup>b</sup>
- Kreitmann, 2014<sup>c</sup>
- Li, 2016<sup>1</sup>
- Lopez, 2012<sup>2</sup>
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<tr>
<td>Lu, 2014&lt;sup&gt;46&lt;/sup&gt;</td>
<td>A. Complete antiretroviral prophylaxis (n=251)</td>
<td>A. 1% (3/251)</td>
<td>C vs. D: aOR 0.44 (95% CI 0.18 to 1.10)</td>
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<tr>
<td>Canadian Perinatal HIV Surveillance Program (CPHSP)</td>
<td>B. Incomplete antiretroviral prophylaxis (n=336)</td>
<td>B. 2% (8/336)</td>
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<td></td>
<td>C. No antiretroviral prophylaxis (n=58)</td>
<td>C. 67% (39/58)</td>
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<tr>
<td>Moodley, 2016&lt;sup&gt;46&lt;/sup&gt;</td>
<td>A. Dual ART (AZT/NVP; n=974)</td>
<td>Not reported</td>
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<td></td>
<td>B. Triple ART (D4T/3TC/NVP; n=907)</td>
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<td>C. Fixed-dose ART (EFV/TDF/FTC; n=1,666)</td>
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<td>D. No ART (n=148)</td>
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<td>Mor, 2017&lt;sup&gt;49&lt;/sup&gt;</td>
<td>A. Infants born before 1996 (n=80)</td>
<td>MTCT</td>
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<td>B. Infant born after 1997 (HAART introduced; n=716)</td>
<td>Overall: 3.1% (25/796)</td>
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<td>A vs. B: 16.3% (13/80) vs. 1.7% (12/716), p&lt;0.01</td>
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<td>Transmission with HAART and vaginal delivery: 1.5%</td>
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<td>Transmission with HAART and C-section: 0.6%</td>
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<td>Variables on MTCT</td>
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<td>HAART vs no HAART during pregnancy: aOR 0.4, 95% CI 0.1 to 0.8</td>
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<td>Infant ART prophylaxis: aOR 0.2, 95% CI 0.1 to 0.5</td>
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<tr>
<td>Pintye, 2017&lt;sup&gt;78&lt;/sup&gt;</td>
<td>A. TDF-containing 3-drug ART (n=208)</td>
<td>Not reported</td>
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<tr>
<td>Partners PrEP Study and Partners Demonstration Project</td>
<td>B. NonTDF-containing 3-drug ART (n=214)</td>
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Not reported

OR adjusted for study cohort, maternal age, time since HIV diagnosis, and HIV RNA at first pregnancy visit, and year pregnancy occurred
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| Ramokolo, 2017<sup>29</sup> 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<sup>34</sup> 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<sup>67</sup> | 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. 17.9% vs. 0% | |
| Surveillance Monitoring for Antiretroviral Treatment Toxicities (SMARTT) study and Pediatric HIV/AIDS Cohort Study (PHACS) | 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) | 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 |
| Nozyce, 2014<sup>69</sup> | Other intervention: Neonatal prophylaxis defined as antiretroviral drugs used during the first 8 weeks of life | Not reported |  |
| Pediatric HIV/AIDS Cohort Study (PHACS) | A. HIV-exposed uninfected (HEU; n=417)  
B. HIV unexposed controls (n=98) | Not reported |  |
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| **Surveillance Monitoring for Antiretroviral Treatment Toxicities (SMARTT) study and Pediatric HIV/AIDS Cohort Study (PHACS)** | A. TDF + FTC + LPV/r (128; 8%)  
B. ZDV + 3TC + LPV/r (954; 59%)  
C. TDF + FTC + ATV/r (539; 33%) | Not reported | 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)  
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)** | A. TDF-containing ART (n=449)  
B. nonTDF-containing ART (n=1,580) | Not reported | 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  
|  

Rough, 2018<sup>12</sup>  
Siberry, 2012<sup>13</sup>
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| Surveillance Monitoring for Antiretroviral Treatment Toxicities (SMARTT) study and Pediatric HIV/AIDS Cohort Study (PHACS) Watts, 2013<sup>33</sup> | 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<sup>31</sup> | A. Any ART (n=1,219)  
B. Any HAART (n=1,025)  
C. NNRTI (n=214)  
D. NRTI (n=1,211)  
E. No ART exposure of any kind (n=1,298 to 2,303 depending on comparison)  
D. Pro tease 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 0.87 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 sulf: 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. NNRTI exposed (n=395)  
C. NRTI (n=1,907)  
D. Protease inhibitor (n not reported)  
E. 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)  
Pro tease inhibitors, metabolic cases: aRR 0.69 (95% CI 0.52 to 0.92)  
Zidovudine exposure, metabolic cases: aRR 1.61 (95% CI 1.01 to 2.58) |
<table>
<thead>
<tr>
<th>Study Author, year</th>
<th>Intervention</th>
<th>HIV transmission</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams, 2016</td>
<td></td>
<td></td>
<td>Lopinavir exposure, metabolic cases: aRR 0.46 (95% CI 0.31 to 0.69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lopinavir (1st trimester), metabolic cases: aRR 0.39 (95% CI 0.20 to 0.78)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ritonavir (as booster), metabolic cases: aRR 0.59 (95% CI 0.43 to 0.81)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ritonavir (1st trimester), metabolic cases: aRR 0.61 (95% CI 0.40 to 0.95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NRTIs, impaired growth: aRR 0.48 (95% CI 0.24 to 0.96)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neurodevelopmental impairment:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HAART: aRR 0.47 (95% CI 0.27 to 0.83)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NNRTIs: aRR 0.38 (95% CI 0.14 to 1.04)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Lamivudine: aRR 0.36 (95% CI 0.36 to 1.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ZVD + 3TC: aRR 0.71 (95% CI 0.41 to 1.17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lamivudine (1st trimester): aRR 0.64 (95% CI 0.35 to 1.18)</td>
</tr>
<tr>
<td>Snijdewind, 2018</td>
<td>A. PI-based  (928; 67%)</td>
<td>Not reported</td>
<td>Preterm delivery</td>
</tr>
<tr>
<td>ATHENA cohort</td>
<td>B. NNRTI-based (438; 31%)</td>
<td></td>
<td>Unadjusted OR:</td>
</tr>
<tr>
<td></td>
<td>C. Both or NRTI (12; 1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A. 1 (reference)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B. 1.30 (0.95 to 1.77), p=0.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C. 1.15 (0.41 to 3.19), p=0.78</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low birthweight</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unadjusted OR:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A. 1 (reference)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B. 1.19 (0.88 to 3.97), p=0.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C. 1.47 (0.54 to 3.97), p=0.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Small for gestational age</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>Unadjusted OR:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A. 1 (reference)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B. 1.04 (0.80 to 1.16), p=0.76</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C. 2.51 (1.16 to 5.53), p=0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adjusted OR:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A. 1 (reference)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B. 0.95 (0.71 to 1.27), p=0.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C. 2.11 (0.98 to 4.57), p=0.06</td>
</tr>
<tr>
<td>Tookey, 2016</td>
<td>LPV/r</td>
<td>2003 to 2007</td>
<td>Infant mortality: 0.5% (24/4,762)</td>
</tr>
<tr>
<td>National Study of HIV in Pregnancy and Childhood (NSHPC)</td>
<td>Overall: 18/1,633 (1.1%, 95% CI 0.6 to 1.6)</td>
<td>Gestational age -</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LPV/r initiation -</td>
<td>- Before conception: 2/6,333 (0.6%, 95% CI 0.2% to 2.2%)</td>
<td>&lt;32 weeks: 2.5% (112/4,762)</td>
</tr>
<tr>
<td></td>
<td>- First trimester: 0/33 (0%)</td>
<td>- Second trimester: 8/858 (0.9%, 95% CI 0.5% to 4.1%)</td>
<td>32 to 36 weeks: 10.4% (473/4,762)</td>
</tr>
<tr>
<td></td>
<td>- Third trimester: 8/376 (2.1%, 1.1% to 4.1%)</td>
<td></td>
<td>≥37 weeks: 87% (3971/4,762)</td>
</tr>
<tr>
<td></td>
<td>2008 to 2012</td>
<td>Overall: 12/2,406 (0.5%, 95% CI 0.2% to 0.8%)</td>
<td>Birth weight -</td>
</tr>
<tr>
<td></td>
<td>LPV/r initiation -</td>
<td>- Before conception: 2/635 (0.3%, 95% CI 0.1% to 1.1%)</td>
<td>&lt;1500 g: 2.3% (101/4,762)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1500 to 2499 g: 12.4% (545/4,762)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥2500 g: 85.3% (3749/4,762)</td>
</tr>
<tr>
<td>Study Author, year</td>
<td>Intervention</td>
<td>HIV transmission</td>
<td>Adverse events</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------</td>
<td>------------------</td>
<td>----------------</td>
</tr>
</tbody>
</table>
| **Zash, 2016**<sup>76</sup> | 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 |
| **Zash, 2017**<sup>75</sup> | 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 | 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 |

Screening for HIV in Pregnant Women  
95  
Pacific Northwest EPC
<table>
<thead>
<tr>
<th>Study Author, year</th>
<th>Intervention</th>
<th>HIV transmission</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1.68</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
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<tr>
<td></td>
<td></td>
<td>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</td>
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<tr>
<td></td>
<td></td>
<td>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</td>
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<tr>
<td></td>
<td></td>
<td>Very SGA (&lt;3rd percentile)</td>
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<tr>
<td></td>
<td></td>
<td>A. 7.1% (176/2472), reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
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<tr>
<td></td>
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<td>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</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
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<tr>
<td></td>
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<td>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</td>
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<tr>
<td></td>
<td></td>
<td>Stillbirth</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A. 2.4% (59/2472), reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
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<tr>
<td></td>
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<td>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</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
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<tr>
<td></td>
<td></td>
<td>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</td>
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<tr>
<td></td>
<td></td>
<td>Neonatal death</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>A. 1.2% (29/2472), reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
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<tr>
<td></td>
<td></td>
<td>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</td>
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<tr>
<td></td>
<td></td>
<td>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</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

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 V IQ=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

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?</th>
<th>Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?</th>
<th>Did the study maintain groups through the study period?</th>
<th>Did the study use accurate methods for ascertaining exposures and potential confounders?</th>
<th>Were outcome assessors and/or data analysts blinded to the exposure being studied?</th>
<th>Did the article report attrition?</th>
<th>Is there high attrition?</th>
<th>Were outcomes prespecified and defined, and ascertained using accurate methods?</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aaron, 2012&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Yes</td>
<td>Not relevant</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Anteretroviral Pregnancy Registry Interim Report&lt;sup&gt;43&lt;/sup&gt;</td>
<td>Not relevant (volunteer database); encourages participating MDs to enter all cases</td>
<td>Not relevant</td>
<td>Yes but no adjustment for confounding</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Berard, 2017&lt;sup&gt;77&lt;/sup&gt;</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Chagomerana, 2017&lt;sup&gt;74&lt;/sup&gt;</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Chen, 2012&lt;sup&gt;56&lt;/sup&gt;</td>
<td>Yes</td>
<td>Differences in age, past adverse pregnancy outcome, receipt of antenatal care, CD4 count, parity</td>
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<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Chiappini, 2013&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Yes</td>
<td>Not relevant</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Duryea, 2015&lt;sup&gt;80&lt;/sup&gt;</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Floridia, 2013&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Yes</td>
<td>Not relevant</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>French Perinatal Cohort (ANRS-EPF) study Mandelbrot, 2015&lt;sup&gt;48&lt;/sup&gt; Sibiude, 2012&lt;sup&gt;65&lt;/sup&gt; Sibiude, 2014&lt;sup&gt;67&lt;/sup&gt; Sibiude, 2015&lt;sup&gt;63&lt;/sup&gt;</td>
<td>Yes</td>
<td>Not relevant</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Kakkar, 2015&lt;sup&gt;58&lt;/sup&gt;</td>
<td>Yes</td>
<td>Differences in study time period, parity, ethnicity</td>
<td>Unclear</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Knapp, 2012&lt;sup&gt;79&lt;/sup&gt;</td>
<td>Yes</td>
<td>Not relevant</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Kreitchmann, 2014&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Yes</td>
<td>Not relevant</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Li, 2016&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Yes</td>
<td>Differences in delivering prior to year 2007, CD4 count, nutritional status, and other diseases and symptoms</td>
<td>Unclear</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Lopez, 2012&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Yes</td>
<td>Differences in nulliparity and prior preterm birth for case control analysis</td>
<td>Unclear</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Lu, 2014&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Yes</td>
<td>Not relevant</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Mor, 2017&lt;sup&gt;79&lt;/sup&gt;</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Moodley, 2016&lt;sup&gt;76&lt;/sup&gt;</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Pintye, 2017&lt;sup&gt;74&lt;/sup&gt;</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
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<td>Ramokolo, 2017&lt;sup&gt;79&lt;/sup&gt;</td>
<td>Yes</td>
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<td>Unclear</td>
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<td>Fair</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?</td>
<td>Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?</td>
<td>Did the study maintain groups through the study period?</td>
<td>Did the study use accurate methods for ascertaining exposures and potential confounders?</td>
<td>Were outcome assessors and/or data analysts blinded to the exposure being studied?</td>
<td>Did the article report attrition?</td>
<td>Is there high attrition?</td>
<td>Were outcomes prespecified and defined, and ascertained using accurate methods?</td>
<td>Quality rating</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------</td>
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<td>---------------------------------------------------------------------------------</td>
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<td>Rough, 2018 PHACS and IMPAACT P1025</td>
<td>Yes</td>
<td>Differences in age, timing of regimen initiation, viral load, and timing of HIV diagnosis</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
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<td>Yes</td>
<td>Fair</td>
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<td>Snijdewind, 2018</td>
<td>Yes</td>
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<td>Not relevant</td>
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<td>Yes</td>
<td>Fair</td>
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<td>Tookey, 2016</td>
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<td>Not relevant</td>
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<td>Yes</td>
<td>Fair</td>
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<tr>
<td>Zash, 2016</td>
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<td>Yes</td>
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<td>Unclear</td>
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<tr>
<td>Zash, 2017</td>
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<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
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**Abbreviations:** PHACS=Pediatric HIV/AIDS Cohort Study; SMARTT=Surveillance Monitoring for Antiretroviral Treatment Toxicities study.
### Appendix B4. Quality Assessment of Randomized Trials

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Randomization adequate?</th>
<th>Allocation concealment adequate?</th>
<th>Groups similar at baseline?</th>
<th>Eligibility criteria specified?</th>
<th>Outcome assessors masked?</th>
<th>Care provider masked?</th>
<th>Patient masked?</th>
<th>Attrition and withdrawals reported?</th>
<th>Loss to followup: differential (&gt;10%)/ high (&gt;20%)?</th>
<th>Analyze people in the groups in which they were randomized?</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fowler, 2016(^{13})</td>
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<td>Fair</td>
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<td>Sartorius, 2013(^{14})</td>
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<td>Unclear</td>
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<td>No, No</td>
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