Annals of Internal Medicine | Review

Screening for HIV in Pregnant Women: Systematic Review to Update the 2005 U.S. Preventive Services Task Force Recommendation

Roger Chou, MD; Amy G. Cantor, MD, MHS; Bernadette Zakher, MBBS; and Christina Bougatsos, MPH

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

Purpose: To update the 2005 USPSTF review, focusing on previously identified research gaps and new evidence on treatments.

Data Sources: MEDLINE (2004 to June 2012) and the Cochrane Library (2005 to the second quarter of 2012).

Study Selection: Randomized trials and cohort studies of pregnant women on risk for mother-to-child transmission or harms associated with prenatal HIV screening or antiretroviral therapy during pregnancy.

Data Extraction: 2 reviewers abstracted and confirmed study details and quality by using predefined criteria.

Data Synthesis: No studies directly evaluated effects of prenatal HIV screening on risk for mother-to-child transmission or maternal or infant clinical outcomes. One fair-quality, large cohort study (HIV prevalence, 0.7%) found that rapid testing during labor was associated with a positive predictive value of 90%. New cohort studies of nonbreastfeeding women in the United States and Europe confirm that full-course combination antiretroviral therapy reduces rates of mother-to-child transmission (<1% to 2.4% vs. 9% to 22% with no antiretroviral therapy). New cohort studies found antiretroviral therapy during pregnancy to be associated with increased risk for preterm delivery (<37 weeks' gestation); there were no clear associations with low birthweight, congenital abnormalities, or infant neurodevelopment. Evidence on long-term maternal harms after short-term antiretroviral therapy exposure during pregnancy remains sparse.

Limitations: Only English-language articles were included. Studies conducted in resource-poor settings may be of limited applicability to screening in the United States.

Conclusion: Antiretroviral therapy in combination with avoidance of breastfeeding and elective cesarean section in women with viremia reduces risk for mother-to-child transmission. Use of certain antiretroviral therapy regimens during pregnancy may increase risk for preterm delivery.

Primary Funding Source: Agency for Healthcare Research and Quality.

Ann Intern Med. 2012;157:719-728. www.annals.org

For author affiliations, see end of text.

Between 6000 and 7000 HIV-positive women give birth each year in the United States (1), and approximately 30% of women are unaware of their HIV-positive status before pregnancy (2). Mother-to-child transmission is responsible for more than 90% of pediatric HIV infections in the United States (3, 4). The number of cases of perinatal HIV infections in the United States peaked at about 1650 in 1992 but has since decreased dramatically, with the widespread adoption of routine prenatal screening coupled with the use of more effective therapies for preventing mother-to-child transmission; the number of cases was estimated at 215 to 370 in 2005 (5).

Current U.S. recommendations are for opt-out HIV screening at the initial prenatal visit as part of standard prenatal testing (6, 7). "Opt-out screening" refers to screening that is performed unless the woman specifically declines. The Centers for Disease Control and Prevention recommend that clinicians consider repeated testing in the third trimester in all women who test negative initially, and they recommend repeated testing for women who continue to practice high-risk behaviors or are in a high-incidence setting.

The current standard of care to prevent perinatal transmission of HIV infection in the United States is a 3-drug antiretroviral regimen started at the beginning of the second trimester of pregnancy or earlier (followed by treatment of the infant in the postnatal period) in all HIV-infected women, regardless of viral load or CD4 cell count; elective cesarean delivery before labor or rupture of membranes in women with HIV RNA levels greater than 1000 copies/mL near delivery; and avoidance of breastfeeding in all women (8, 9). Women who are identified as HIV-positive during pregnancy may also benefit from other interventions that would be considered in nonpregnant women with HIV infection, including long-term antiretroviral therapy, prophylaxis against opportunistic infections, immunizations, and counseling to reduce high-risk behaviors for horizontal transmission.

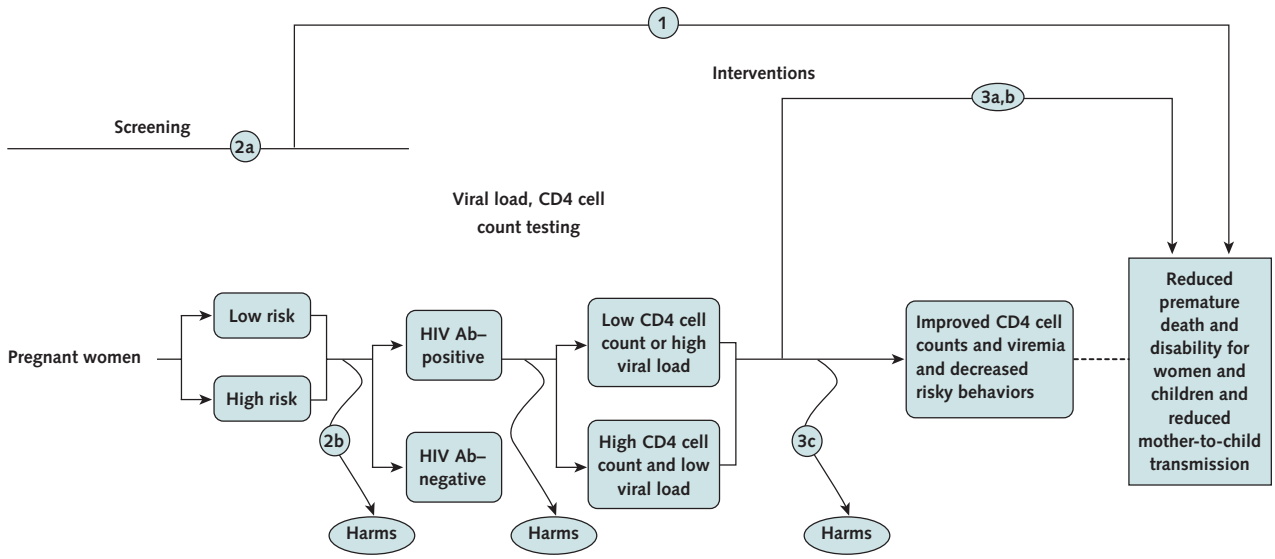
The U.S. Preventive Services Task Force (USPSTF) last reviewed the evidence on prenatal screening for asymptomatic HIV in 2005 (10) and issued a recommendation to screen all pregnant women (grade A recommendation) (7). The USPSTF did not address repeated prenatal screening. This report updates the previous USPSTF review on benefits and harms of prenatal HIV screening, with an emphasis on research gaps identified in that review and new evidence on benefits and harms of antiretroviral medications. Because perinatal practices and interventions related to prevention of HIV infection are substantially af-

See also:

Print

Related article 706

Figure. **Analytic framework and key questions for screening for HIV in pregnant women.**



Key Questions:

1. What are the benefits of HIV screening versus no screening in asymptomatic pregnant women on maternal or child morbidity, mortality, or quality of life or rates of mother-to-child transmission?
2a. What is the yield (number of new diagnoses) of repeat HIV screening in asymptomatic pregnant women?
2b. What are the adverse effects (including false-positive results and anxiety) of rapid versus standard HIV testing in asymptomatic pregnant women?
3a. What is the effectiveness of newer antiretroviral regimens for reducing mother-to-child transmission?
3b. What are the effects of antiretroviral regimens in pregnant, HIV-positive women on long-term maternal morbidity, mortality, or quality of life?
3c. What are the harms (including longer-term harms) to the mother or child associated with antiretroviral therapy during pregnancy?

Ab = antibody.

fected by the availability of resources, the report will emphasize evidence that is more applicable to typical practice in the United States.

METHODS

Scope of the Review

We followed a standardized protocol and developed an analytic framework (**Figure**) that focused on the following key questions:

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

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

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

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

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

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

The full report (11) provides detailed methods and data for the review, including search strategies and multiple tables with quality ratings of individual studies. Laboratory or imaging effects of antiretroviral therapy for children with uncertain clinical implications, such as mitochondrial dysfunction, echocardiographic abnormalities, and hematologic abnormalities, are also reviewed in the full report but are not presented in this article.

This update focuses on research gaps identified in the previous review, such as harms (including false-positive results and anxiety) of rapid versus standard testing and the yield of repeated screening. The diagnostic accuracy of HIV testing and the effectiveness of breastfeeding avoidance and elective cesarean delivery in selected women are well-established (10, 12) and were not rereviewed. Rather, this update focuses on new evidence on the effectiveness of combination antiretroviral regimens on perinatal transmission, as well as evidence on long-term clinical outcomes of prenatal exposure to antiretroviral therapy in the mother and harms to the mother or infant.

Data Sources and Searches

We searched Ovid MEDLINE from 2004 to June 2012 and the Cochrane Library database through the second quarter of 2012 and reviewed reference lists to identify relevant articles published in English.

Study Selection

At least 2 reviewers independently evaluated each study to determine eligibility for inclusion. Articles were selected for full review if they were about HIV infection in pregnancy, were relevant to a key question, and met the predefined inclusion criteria (**Appendix Table 1**, available at www.annals.org). Outcomes were mother-to-child transmission, morbidity, mortality, quality of life, and harms from antiretroviral therapy (such as adverse pregnancy outcomes; adverse congenital, neurodevelopmental, cardiovascular, metabolic, or hematologic outcomes in exposed children; and adverse clinical outcomes in mothers), including long-term outcomes (those occurring ≥1 year after birth for women and ≥2 years after birth for children). We included randomized, controlled trials and cohort studies for all key questions.

For key questions related to harms and other long-term maternal and infant outcomes, we also included case–control studies and intervention series if randomized trials and cohort studies were unavailable or lacking. For some key questions, we included studies from resource-poor settings that evaluated short-course antiretroviral regimens or breastfeeding populations, because these may provide some information about the effectiveness of antiretroviral therapies in U.S. women who present late in pregnancy or about the general effectiveness of combination antiretroviral therapy.

Data Abstraction and Quality Rating

One investigator abstracted details on the study design, patient population, setting, screening method, treatment regimen, analysis, follow-up, and results. A second investigator reviewed data abstraction for accuracy. Two investigators independently applied criteria developed by the USPSTF (13) to rate the quality of each study as good, fair, or poor. Discrepancies were resolved by consensus.

Data Synthesis

We assessed the aggregate internal validity (quality) of the body of evidence for each key question as good, fair, or poor by using methods developed by the USPSTF, based on the number, quality and size of studies, consistency of results between studies, and directness of evidence (13). Meta-analysis was not attempted because the data could not be pooled, owing to differences across studies in design, interventions, populations, and other factors.

Role of the Funding Source

This research was funded by the Agency for Healthcare Research and Quality (AHRQ) under a contract to support the work of the USPSTF. Investigators worked with USPSTF members and AHRQ staff at key points to develop and refine the scope, analytic framework, and key questions; resolve issues arising during the project; and finalize the report. AHRQ staff provided project oversight, reviewed the draft report, and distributed the draft for peer review, including by representatives of professional societies and federal agencies. In addition, AHRQ performed a final review of the manuscript to ensure that the analysis met methodological standards. AHRQ had no role in study selection, quality assessment, synthesis, or development of conclusions. The investigators are solely responsible for the content and the decision to submit the manuscript for publication.

Results

The **Appendix Figure** (available at www.annals.org) shows the results of the search and study selection process.

Key Question 1

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

No randomized trial or observational study compared clinical outcomes (including risk for perinatal transmission) between pregnant women who were screened and not screened for HIV infection.

Key Question 2a

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

No randomized trial or observational study evaluated the yield of repeated prenatal HIV screening compared with 1-time screening or compared the yield of different strategies for repeated screening (such as risk-based repeated screening versus a routinely repeated test).

Key Question 2b

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

The large (7753 participants), prospective, fair-quality MIRIAD (Mother-Infant Rapid Intervention At Delivery) study provides the strongest evidence on the diagnostic accuracy of the rapid OraQuick test (OraSure Technologies, Bethlehem, Pennsylvania) compared with standard enzyme immunoassay HIV testing (14, 15). MIRIAD specifically enrolled women in labor with unknown HIV status (HIV prevalence, 0.7%), for whom immediate test results are needed to help guide treatment decisions.

Initial (2-year) results from MIRIAD (15) were included in the previous USPSTF review (10). Final (40-month) results (14) found that compared with Western blot (the reference standard), sensitivity was 100% for both tests and specificity was 99.9% and 99.8% for the rapid and standard tests, respectively. On the basis of an HIV prevalence of 0.7% (52 of 7753 persons), the positive predictive value was higher for the rapid test (90% [52 of 58 persons]) than for the standard test (74% [52 of 70 persons]). In clinical practice, a positive result from a standard test would not be available in time to inform interventions during labor and delivery and would require Western blot confirmation.

A study (16) of 910 pregnant women, about 90% of whom were Hispanic, at any gestational age (HIV prevalence, 0.5%) found a positive predictive value of 100% (5 of 5) for the OraQuick rapid test and a value of 36% (5 of 14) for standard enzyme immunoassay (before confirmation).

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

Key Question 3a

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

We identified no new randomized trials since the previous review on full-course (started at or before the beginning of the second trimester) combination antiretroviral therapy in non–resource-poor, nonbreastfeeding settings. Consistent with the prior USPSTF review, 3 U.S. and European cohort studies (involving 489 to 7344 participants) published since 2005 found perinatal, full-course, triple antiretroviral therapy to be associated with rates of mother-to-child transmission ranging from less than 1% to 2.4%, compared with 9% to 22% with no antiretroviral therapy (17–19). The largest cohort study (involving 7344 participants), based on U.S. surveillance data from 1999 to 2001, found full-course, single- or multidrug antiretroviral therapy to be associated with a rate of mother-to-child transmission of 2.4%, compared with 22% for no antiretroviral therapy (adjusted odds ratio [OR], 0.09 [95% CI, 0.06 to 0.12]) (18). In women who received antiretroviral therapy, combination regimens with zidovudine plus other drugs were about twice as effective as zidovudine alone for reducing risk for mother-to-child transmission (adjusted ORs, 0.4 to 0.5). Two smaller European cohort studies (17, 19) also reported lower mother-to-child transmission rates with combination antiretroviral therapy (0.6% and 1.0%, respectively) than with no therapy (18% and 9%, respectively).

A fourth study, which analyzed European surveillance data for 7573 participants over 9 years and included 1 of these cohorts, found transmission rates of less than 1% with either zidovudine-sparing or zidovudine-containing regimens of 3 or more drugs (20). **Appendix Table 2** (available at www.annals.org) provides details on these 4 studies.

One good-quality (21) and 5 fair-quality (22–26) randomized trials published since the 2005 USPSTF review evaluated shorter-course prenatal antiretroviral regimens in primarily breastfeeding African women (**Appendix Table 3**, available at www.annals.org). In the United States, these studies are most applicable to HIV-infected women identified later in pregnancy, who cannot receive full-course regimens.

In general, these studies reported lower transmission rates with antiretroviral therapy than expected without treatment. Studies that evaluated longer courses of treatment and regimens that included at least 3 drugs reported the lowest transmission rates; 1 trial (709 participants) of various 3-drug regimens started at 18 to 34 weeks' gestation (median, 26 to 27 weeks) reported an HIV transmission rate of 1.1% at 6 months (24), which was similar to the rates observed in U.S. and European cohort studies (17–20) of full-course, triple-drug regimens.

Transmission rates in studies that evaluated antiretroviral regimens initiated later in pregnancy or with fewer than 3 drugs reported rates of mother-to-child transmission ranging from 4% to 12% (21–23, 25), although rates were still lower than expected without treatment (about 25%) (27). One trial (609 participants) found high rates of mother-to-child transmission with ultrashort-course zidovudine (during labor and given to the infant for 72 hours after birth) plus single-dose maternal and infant nevirapine as well as single-dose nevirapine alone (14% vs. 17%), and a high rate of infant mortality (7% at 6 weeks) (26).

Key Question 3b

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

No study published since the prior USPSTF review evaluated the effects of antiretroviral therapy administered during pregnancy and then discontinued on long-term maternal clinical outcomes. The prior USPSTF review included 1 study of 226 U.S. women that found no difference in risk for AIDS-defining events or death after a mean of 4.1 years between women randomly assigned to receive zidovudine during pregnancy and those assigned to receive placebo (28). A study included in the prior USPSTF review found that women still benefit from subsequent highly active antiretroviral therapy after receiving antiretroviral treatment during pregnancy (29).

Key Question 3c

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

New evidence (27 studies [20, 30–55]) on infant and maternal harms associated with perinatal exposure to antiretroviral therapy was generally consistent with the evidence included in the 2005 USPSTF review (10, 12).

Preterm Birth and Other Birth Outcomes

One randomized trial (40) and 10 cohort studies (30–39) published since the prior USPSTF review reported risk for prematurity, low birthweight, and other birth outcomes after in utero exposure to antiretroviral therapy (**Appendix Table 4**, available at www.annals.org). Sample sizes ranged from 57 to 8793 participants. Eight studies were rated as fair-quality (30, 32, 34, 35, 37–40), and 3 were poor-quality (31, 33, 36). Methodological shortcomings included differences between groups in baseline characteristics and poor reporting of attrition. Six studies reported

risk estimates adjusted for important confounders, such as maternal age, CD4 count, and viral load (30, 32, 34, 36–38).

The randomized trial (530 participants) found that protease inhibitor–based antiretroviral therapy was associated with greater risk for preterm delivery than nonnucleoside reverse transcriptase–based antiretroviral therapy (OR, 2.0 [CI, 1.3 to 3.3]) (40). Three prospective cohort studies (183 to 8793 participants) found maternal exposure to combination antiretroviral therapy with a protease inhibitor to be associated with increased risk for preterm delivery (<37 weeks) compared with combination antiretroviral therapy without a protease inhibitor (adjusted OR, 1.8 [CI, 1.1 to 3.0]) (32), dual therapy (adjusted OR, 1.2 [CI, 1.0 to 1.4]) (37), or monotherapy (adjusted OR, 3.4 [CI, 1.1 to 10]) (34). None found exposure to combination therapy without a protease inhibitor to be associated with increased risk for preterm delivery. However, a large cohort study (4939 participants) found combination therapy to be associated with increased risk for preterm delivery (<37 weeks; adjusted OR, 1.4 [CI, 1.1 to 1.8]; $P = 0.02$) and very preterm delivery (<32 weeks; OR, 2.6 [CI, 1.3 to 5.3]; $P = 0.007$) compared with monotherapy or dual therapy; risk did not differ according to whether the antiretroviral regimen included a protease inhibitor or not (38). Of 4 studies that did not adjust for confounders, 1 found an association between prenatal antiretroviral therapy and preterm delivery (39) and 3 found no clear association (31, 33, 35).

Seven cohort studies (352 to 8192 participants) published since the 2005 USPSTF review found no clear association between maternal use of antiretroviral therapy and low birthweight or intrauterine growth restriction (30–33, 35, 37, 38).

Congenital Abnormalities

Three fair-quality cohort studies (1414, 3740, and 8576 participants) published since the 2005 USPSTF review found no association between perinatal exposure to antiretroviral therapy and congenital abnormalities (41–43). Follow-up ranged from 6 months to 17 years. One large study (7573 participants) of European surveillance data over a 9-year period found no difference in the risk for infant congenital abnormalities with maternal use of zidovudine-sparing versus zidovudine-containing antiretroviral therapy (20).

Neurodevelopmental Outcomes

Two cohort studies published since the 2005 USPSTF review (10, 12) found no clear differences in neurodevelopmental outcomes between children exposed to antiretroviral therapy in utero and postnatally compared with unexposed controls at 18 to 36 months of follow-up (44, 45). Both studies used the Bayley Scales of Infant Development II, which include a mental development index and psychomotor development index.

Maternal Harms

We identified 1 large (2543 participants), fair-quality U.S. cohort study published since the 2005 USPSTF review that found antiretroviral use to be associated with increased risk for maternal anemia compared with nonuse (adjusted OR, 1.6 [CI, 1.1 to 2.4]) (46). It also found late use of antiretroviral therapy (started between 25 and 32 weeks' gestation) to be associated with increased risk for gestational diabetes compared with nonuse (adjusted OR, 3.5 [CI, 1.2 to 10]); however, causality was unclear, because screening for gestational diabetes is typically performed at 24 to 28 weeks' gestation and women may have received a diagnosis before initiation of antiretroviral therapy.

A smaller (167 participants) fair-quality cohort study found exposure to combination therapy to be associated with a trend toward increased risk for gestational diabetes compared with exposure to monotherapy with zidovudine or no antiretroviral therapy, but the difference was not statistically significant (12% vs. 0%; unadjusted relative risk, 0.11 [CI, 0.01 to 1.7]) (47).

Discussion

As in the 2005 USPSTF review (10, 12), we found no direct evidence on effects of prenatal screening for HIV infection versus no screening on risk for mother-to-child transmission or maternal or infant clinical outcomes. Other evidence reviewed in this update is summarized in the **Table**.

The 2005 USPSTF review (10, 12) found that HIV tests are accurate. The strongest evidence on potential harms associated with rapid testing is from the fair-quality MIRIAD study, which found a lower positive predictive value for standard enzyme immunoassay than for a rapid test (74% and 90%, respectively) in a population of women presenting in labor among whom the prevalence of undiagnosed HIV infection was 0.7%. This could result in unnecessary maternal and fetal exposure to antiretroviral therapy (14). The positive predictive value would be expected to be lower in lower-prevalence populations, potentially resulting in more unnecessary antiretroviral exposure.

No study has evaluated the clinical consequences of unnecessary exposure to antiretroviral therapy as a result of an initially positive false-positive rapid HIV test, although any such harms must be weighed against the potential benefits of prenatal identification and treatment of undiagnosed HIV infection. As in the 2005 USPSTF review, no study has evaluated the yield of repeated HIV screening during pregnancy, which depends on the incidence of new HIV infection.

New cohort studies of antiretroviral therapy in nonbreastfeeding women in the United States and Europe con-

Table. **Summary of Evidence**

Main Findings From 2005 USPSTF Review	Number and Type of Studies Identified for the Update	Overall Quality*	Limitations	Consistency	Applicability	Summary of Findings for the 2012 Update
Key question 1: What are the benefits of HIV screening vs. no screening in asymptomatic pregnant women on maternal or child morbidity, mortality, or quality of life or rates of mother-to-child transmission?						
No studies	No studies	Not applicable	No studies	No studies	No studies	No study compared clinical outcomes (including risk for perinatal transmission) between pregnant women screened and not screened for HIV infection.
Key question 2a: What is the yield of repeat HIV screening in asymptomatic pregnant women?						
No studies	No studies	Not applicable	No studies	No studies	No studies	No study evaluated the yield of repeated prenatal HIV screening.
Key question 2b: What are the adverse effects (including false-positive tests and anxiety) of rapid vs. standard HIV testing in asymptomatic pregnant women?						
1 observational study reported a false-alarm rate of 10% with rapid testing during labor (15)	2 observational studies† (14, 16)	Fair	Few studies; small numbers of HIV-infected women	Consistent	No issues	1 large (7753 participants), fair-quality, prospective study of women presenting in labor with unknown HIV status (prevalence, 0.7%) found that the positive predictive value was higher for the rapid test (90% [52/58]) than for the standard test (74% [52/70]) (14). A smaller study reported consistent results, but only 5 cases of HIV were identified. No study evaluated adverse clinical consequences of interventions given because of false-positive results (16).
Key question 3a: What is the effectiveness of newer antiretroviral regimens for reducing mother-to-child transmission?						
4 cohort studies found full-course combination antiretroviral therapy to be associated with substantially lower risk for transmission compared with no antiretrovirals or regimens with fewer drugs (absolute risk, 1%–2%)	4 cohort studies (17–20) and 6 RCTs (21–26)	Fair	No RCTs of full-course combination antiretroviral therapy in non–resource-poor settings	Consistent	RCTs evaluated shorter-course antiretroviral regimens in primarily breastfeeding women in resource-poor countries	3 cohort studies of antiretroviral therapy conducted in nonbreastfeeding women in the United States and Europe confirm the findings from the 2005 USPSTF review that full-course combination antiretroviral therapy reduces risk for mother-to-child transmission (<1% to 2.4% with combination antiretroviral therapy compared with 9% to 22% with no therapy) (17–19). Shorter courses of antiretroviral therapy are not as effective as full-course regimens but reduce risk for mother-to-child transmission.

Continued on following page

Table—Continued

Main Findings From 2005 USPSTF Review	Number and Type of Studies Identified for the Update	Overall Quality*	Limitations	Consistency	Applicability	Summary of Findings for the 2012 Update
Key question 3b: What are the effects of antiretroviral regimens in pregnant, HIV-positive women on long-term maternal morbidity, mortality, or quality of life?						
1 study of women originally enrolled in an RCT of zidovudine monotherapy found no adverse maternal outcomes after 4 y (28)	No studies	Not applicable	No studies	No studies	No studies	No new studies evaluated effects of prenatal antiretroviral therapy on long-term maternal clinical outcomes.
Key question 3c: What are the harms (including longer-term harms) to the mother or child associated with antiretroviral therapy during pregnancy?‡						
Pregnancy outcomes 1 meta-analysis and 1 large cohort study found no clear association between combination antiretroviral therapy use and low birthweight, and mixed evidence on premature delivery	1 RCT (40) and 10 cohort studies (30–39)	Fair	No RCTs of full-course combination antiretroviral therapy	Some inconsistency	No issues	One RCT (40) and 4 prospective cohort studies that adjusted for confounders (32, 34, 37, 38) found some antiretroviral regimens to be associated with increased risk for preterm delivery. Four studies that did not adjust for confounders reported inconsistent results (31, 33, 35, 39). Cohort studies found no association between antiretroviral therapy use and low birthweight.
Congenital abnormalities 1 prospective cohort study found no association between in utero antiretroviral exposure and congenital abnormalities	4 cohort studies (20, 41–43)	Fair	No RCTs of full-course combination antiretroviral therapy	Consistent	No issues	Four studies found no association between in utero exposure to antiretroviral drugs and risk for congenital abnormalities (20, 41–43).
Neurodevelopment 1 prospective cohort study found no effect of in utero antiretroviral exposure on neurodevelopment	2 cohort studies (44, 45)	Fair	No RCTs of full-course combination antiretroviral therapy	Consistent	No issues	Two studies found no association between in utero exposure to antiretroviral drugs and neurodevelopment through age 2–3 y (44, 45).
Maternal harms 1 meta-analysis found no association between perinatal zidovudine monotherapy and maternal deaths or long-term harms; 1 study found antiretroviral therapy associated with gestational diabetes; and 1 trial found continuous nevirapine to be associated with serious hepatic or cutaneous toxicity in women with CD4 counts greater than 0.250×10^9 cells/L	2 cohort studies (46, 47)	Fair	No RCTs of full-course combination antiretroviral therapy; not clear whether gestational diabetes was diagnosed before initiation of antiretroviral therapy	Consistent	No issues	Two cohort studies found an association between antiretroviral therapy during pregnancy and gestational diabetes, but causality was unclear or estimates were not statistically significant (46, 47).

RCT = randomized, controlled trial; USPSTF = U.S. Preventive Services Task Force.
* Overall quality is based on new evidence identified for this update plus previously reviewed evidence.
† One of the observational studies reports longer-term follow-up from a study included in the prior review.
‡ Laboratory markers of mitochondrial dysfunction, hematologic abnormalities, and echocardiographic markers of impaired cardiac growth were not described here but are included in the full report.

firm the finding from the 2005 USPSTF review that full-course combination antiretroviral therapy is effective at reducing the rate of mother-to-child transmission (<1% to 2.4% vs. 9% to 22% with no antiretroviral therapy) (17–19). Randomized trials also found low risk for transmission with combination therapy regimens started around the end of the second trimester in breastfeeding African women (21, 24). Shorter courses of antiretroviral therapy evaluated in randomized trials were not as effective as full-course regimens, but they reduced risk for mother-to-child transmission compared with historical transmission rates without antiretroviral therapy and are relevant for women in the United States who might begin therapy late, owing to delayed diagnosis or treatment (22, 23, 25).

Evidence on harms of prenatal antiretroviral therapy was also largely consistent with the 2005 USPSTF review. Current evidence continues to suggest that the long-term harms associated with antiretroviral exposure are relatively small. New cohort studies found that perinatal antiretroviral therapy was associated with increased risk for preterm delivery (31–40), but there was no clear association with low birthweight (30, 32, 33, 35, 37, 38), congenital abnormalities (20, 41–43), or impaired infant neurodevelopment (44, 45). Although other studies (reviewed in the full report [11]) found an association between in utero exposure to antiretroviral therapy and echocardiographic abnormalities (48), hematologic abnormalities (49–51), or markers of mitochondrial dysfunction (52–54), the clinical significance of these findings remains unclear. Evidence on long-term maternal harms associated with short-term exposure to antiretroviral therapy during pregnancy, or antiretroviral therapy started during pregnancy and continued after pregnancy, remains sparse.

Receipt of antiretroviral therapy during pregnancy is associated with the nonobstetric adverse events typically associated with the specific drugs and regimens, but these often resolve after treatment with the offending drug or drug combination is stopped, and effective alternatives are usually available (8). Antiretroviral therapy regimens for use during pregnancy and indications for initiating long-term antiretroviral therapy continue to evolve, and guidelines on selection of antiretroviral therapy for pregnant women are regularly updated (8).

Our study has limitations. We excluded non–English-language articles, which could result in language bias, although we identified no non–English-language studies that would have met our inclusion criteria. We could not formally assess for publication bias with graphical or statistical methods because of small numbers of studies and differences in the study designs, populations, and outcomes assessed. We included observational studies, which are more susceptible to bias and confounding than well-conducted randomized trials, although we focused on results from studies that performed statistical adjustment for potential confounding. We also included studies conducted in resource-poor and high-prevalence settings, which could limit applicability to U.S. practice.

More research is needed on the long-term maternal effects of transient exposure to antiretroviral therapy during pregnancy or use of less intense antiretroviral regimens during pregnancy. Children exposed to antiretroviral therapy in utero should continue to be followed to help identify unexpected or emerging long-term harms from combination regimens. More research is also needed to understand the clinical significance of the hematologic abnormalities, echocardiographic abnormalities, and markers of mitochondrial dysfunction observed in some children exposed to antiretroviral therapy.

In summary, prenatal HIV screening is accurate and antiretroviral therapy in combination with avoidance of breastfeeding and cesarean section in women with HIV RNA levels greater than 1000 copies/mL near the time of delivery is effective at reducing risk for mother-to-child transmission. Use of certain antiretroviral therapy regimens during pregnancy may be associated with increased risk for preterm delivery, but more evidence is needed to fully understand short- and long-term maternal and infant effects.

From the Oregon Evidence-based Practice Center and Oregon Health & Science University, Portland, Oregon.

Acknowledgment: The authors thank Tracy Dana, MLS; Ian Blazina, MPH; Laurie Hoyt Huffman, MS; and Jennifer Croswell, MD, MPH. They also thank U.S. Preventive Services Task Force Leads Susan Curry, PhD; Virginia Moyer, MD, MPH; Wanda Nicholson, MD, MPH, MBA; and Timothy Wilt, MD, MPH.

Grant Support: By contract 290-02-0024 from the Agency for Healthcare Research and Quality.

Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M12-1201.

Requests for Single Reprints: Roger Chou, MD, Oregon Health & Science University, 3181 Southwest Sam Jackson Park Road, Mail Code BICC, Portland, OR 97239; e-mail, chour@ohsu.edu.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Centers for Disease Control and Prevention.** Sexually Transmitted Diseases: STDs & pregnancy—CDC Fact Sheet. Atlanta: Centers for Disease Control and Prevention; 2011. Accessed at www.cdc.gov/std/pregnancy/STDfact-Pregnancy.htm on 11 September 2012.

2. **Centers for Disease Control and Prevention.** HIV Surveillance Supplemental Report: Commentary. Vol. 16, No. 2. Atlanta: Centers for Disease Control and Prevention; 2010. Accessed at www.cdc.gov/hiv/surveillance/resources/reports/2010supp_vol16no2/pdf/commentary.pdf on 12 September 2012.

3. **Centers for Disease Control and Prevention.** HIV Surveillance Report, 2009. Vol. 21. Atlanta: Centers for Disease Control and Prevention; 2009. Accessed at www.cdc.gov/hiv/surveillance/resources/reports/2009report/pdf/cover.pdf on 12 September 2012.

4. **Centers for Disease Control and Prevention.** Achievements in public health. Reduction in perinatal transmission of HIV infection—United States, 1985-2005. MMWR Morb Mortal Wkly Rep. 2006;55:592-7. [PMID: 16741495]
5. **Fowler MG, Gable AR, Lampe MA, Etima M, Owor M.** Perinatal HIV and its prevention: progress toward an HIV-free generation. Clin Perinatol. 2010;37:699-719, vii. [PMID: 21078445]
6. **Branson BM, Handsfield HH, Lampe MA, Janssen RS, Taylor AW, Lyss SB, et al; Centers for Disease Control and Prevention (CDC).** Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. MMWR Recomm Rep. 2006;55(RR-14):1-17. [PMID: 16988643]
7. **U.S. Preventive Services Task Force.** Screening for HIV: Recommendation Statement. Rockville, MD: Agency for Healthcare Research and Quality; 2007. Accessed at www.uspreventiveservicestaskforce.org/uspstf/uspshivi.htm on 12 September 2012.
8. **Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission.** Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1–Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. Rockville, MD: U.S. Department of Health and Human Services; 2011. Accessed at http://aidsinfo.nih.gov/contentfiles/lvguidelines/perinatalgl.pdf on 12 September 2012.
9. **American College of Obstetricians and Gynecologists.** Committee Opinion: Scheduled Cesarean Delivery and the Prevention of Vertical Transmission of HIV Infection. Washington, DC: American College of Obstetricians and Gynecologists; 2010. Accessed at www.acog.org/~/media/Committee%20Opinions/Committee%20on%20Obstetric%20Practice/co234.ashx?dmc=1&ts=20120105T1247277577 on 12 September 2012.
10. **Chou R, Smits AK, Huffman LH, Fu R, Korthuis PT; US Preventive Services Task Force.** Prenatal screening for HIV: A review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2005;143:38-54. [PMID: 15998754]
11. **Chou R, Cantor A, Bougatsos C, Zakher B.** Screening for HIV in Pregnant Women: Systematic Review to Update the 2005 U.S. Preventive Services Task Force Recommendation. Rockville, MD: Agency for Healthcare Research and Quality. [Forthcoming].
12. **Chou R, Smits AK, Huffman LH, Korthuis PT.** Screening for Human Immunodeficiency Virus in Pregnant Women: Evidence Synthesis No. 39. Rockville, MD: Agency for Healthcare Research and Quality; 2005. Accessed at www.ahrq.gov/downloads/pub/prevent/pdfser/hivpresyn.pdf on 12 September 2012.
13. **Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al; Methods Work Group, Third US Preventive Services Task Force.** Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20:21-35. [PMID: 11306229]
14. **Jamieson DJ, Cohen MH, Maupin R, Nesheim S, Danner SP, Lampe MA, et al.** Rapid human immunodeficiency virus-1 testing on labor and delivery in 17 US hospitals: the MIRIAD experience. Am J Obstet Gynecol. 2007;197:S72-82. [PMID: 17825653]
15. **Bulterys M, Jamieson DJ, O'Sullivan MJ, Cohen MH, Maupin R, Nesheim S, et al; Mother-Infant Rapid Intervention At Delivery (MIRIAD) Study Group.** Rapid HIV-1 testing during labor: a multicenter study. JAMA. 2004;292:219-23. [PMID: 15249571]
16. **Tung CS, Sangi-Haghpeykar H, Levison J.** Rapid versus standard testing for prenatal HIV screening in a predominantly Hispanic population. J Perinatol. 2010;30:30-2. [PMID: 19741654]
17. **Garcia-Tejedor A, Maiques V, Perales A, Lopez-Aldeguer J.** Influence of highly active antiretroviral treatment (HAART) on risk factors for vertical HIV transmission. Acta Obstet Gynecol Scand. 2009;88:882-7. [PMID: 19557554]
18. **Harris NS, Fowler MG, Sansom SL, Ruffo N, Lampe MA.** Use of enhanced perinatal human immunodeficiency virus surveillance methods to assess antiretroviral use and perinatal human immunodeficiency virus transmission in the United States, 1999-2001. Am J Obstet Gynecol. 2007;197:S33-41. [PMID: 17825649]
19. **Townsend CL, Cortina-Borja M, Peckham CS, de Ruiter A, Lyall H, Tookey PA.** Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. AIDS. 2008;22:973-81. [PMID: 18453857]
20. **Tariq S, Townsend CL, Cortina-Borja M, Duong T, Elford J, Thorne C, et al; European Collaborative Study.** Use of zidovudine-sparing HAART in pregnant HIV-infected women in Europe: 2000-2009. J Acquir Immune Defic Syndr. 2011;57:326-33. [PMID: 21499113]
21. **de Vincenzi I; Kesho Bora Study Group.** Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. Lancet Infect Dis. 2011;11:171-80. [PMID: 21237718]
22. **Chi BH, Chintu N, Cantrell RA, Kankasa C, Kruse G, Mbewe F, et al.** Addition of single-dose tenofovir and emtricitabine to intrapartum nevirapine to reduce perinatal HIV transmission. J Acquir Immune Defic Syndr. 2008;48:220-3. [PMID: 18520682]
23. **Gray G, Violari A, McIntyre J, Jivkov B, Schnittman S, Reynolds L, et al.** Antiviral activity of nucleoside analogues during short-course monotherapy or dual therapy: its role in preventing HIV infection in infants. J Acquir Immune Defic Syndr. 2006;42:169-76. [PMID: 16639342]
24. **Shapiro RL, Hughes MD, Ogwu A, Kitch D, Lockman S, Moffat C, et al.** Antiretroviral regimens in pregnancy and breast-feeding in Botswana. N Engl J Med. 2010;362:2282-94. [PMID: 20554983]
25. **Shapiro RL, Thior I, Gilbert PB, Lockman S, Wester C, Smeaton LM, et al.** Maternal single-dose nevirapine versus placebo as part of an antiretroviral strategy to prevent mother-to-child HIV transmission in Botswana. AIDS. 2006;20:1281-8. [PMID: 16816557]
26. **Thistle P, Spitzer RF, Glazier RH, Pilon R, Arbess G, Simor A, et al.** A randomized, double-blind, placebo-controlled trial of combined nevirapine and zidovudine compared with nevirapine alone in the prevention of perinatal transmission of HIV in Zimbabwe. Clin Infect Dis. 2007;44:111-9. [PMID: 17143826]
27. **Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, et al.** Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med. 1994;331:1173-80. [PMID: 7935654]
28. **Bardeguez AD, Shapiro DE, Mofenson LM, Coombs R, Frenkel LM, Fowler MG, et al; Pediatrics AIDS Clinical Trials Group 288 Protocol Team.** Effect of cessation of zidovudine prophylaxis to reduce vertical transmission on maternal HIV disease progression and survival. J Acquir Immune Defic Syndr. 2003;32:170-81. [PMID: 12571527]
29. **Watts DH, Lambert J, Stiehm ER, Harris DR, Bethel J, Mofenson L, et al; PACTG 185 Study Team.** Progression of HIV disease among women following delivery. J Acquir Immune Defic Syndr. 2003;33:585-93. [PMID: 12902802]
30. **Briand N, Mandelbrot L, Le Chenadec J, Tubiana R, Teglas JP, Faye A, et al; ANRS French Perinatal Cohort.** No relation between in-utero exposure to HAART and intrauterine growth retardation. AIDS. 2009;23:1235-43. [PMID: 19424054]
31. **Carceller A, Ferreira E, Alloul S, Lapointe N.** Lack of effect on prematurity, birth weight, and infant growth from exposure to protease inhibitors in utero and after birth. Pharmacotherapy. 2009;29:1289-96. [PMID: 19857146]
32. **Cotter AM, Garcia AG, Duthely ML, Luke B, O'Sullivan MJ.** Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth? J Infect Dis. 2006;193:1195-201. [PMID: 16586354]
33. **El Beitune P, Duarte G, Machado AA, Quintana SM, Figueiró-Filho EA, Abduch R.** Effect of antiretroviral drugs on maternal CD4 lymphocyte counts, HIV-1 RNA levels, and anthropometric parameters of their neonates. Clinics (Sao Paulo). 2005;60:207-12. [PMID: 15962081]
34. **Grosch-Woerner I, Puch K, Maier RF, Niehues T, Notheis G, Patel D, et al; Multicenter Interdisciplinary Study Group Germany/Austria.** Increased rate of prematurity associated with antenatal antiretroviral therapy in a German/Austrian cohort of HIV-1-infected women. HIV Med. 2008;9:6-13. [PMID: 18199167]
35. **Morris AB, Dobles AR, Cu-Uvin S, Zorrilla C, Anderson J, Harwell JI, et al.** Protease inhibitor use in 233 pregnancies. J Acquir Immune Defic Syndr. 2005;40:30-3. [PMID: 16123678]
36. **Paul ME, Chantry CJ, Read JS, Frederick MM, Lu M, Pitt J, et al.** Morbidity and mortality during the first two years of life among uninfected children born to human immunodeficiency virus type 1-infected women: the women and infants transmission study. Pediatr Infect Dis J. 2005;24:46-56. [PMID: 15665710]
37. **Schulte J, Dominguez K, Sukalac T, Bohannon B, Fowler MG; Pediatric Spectrum of HIV Disease Consortium.** Declines in low birth weight and preterm birth among infants who were born to HIV-infected women during an era

of increased use of maternal antiretroviral drugs: Pediatric Spectrum of HIV Disease, 1989-2004. Pediatrics. 2007;119:e900-6. [PMID: 17353299]
38. **Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA.** Antiretroviral therapy and premature delivery in diagnosed HIV-infected women in the United Kingdom and Ireland. AIDS. 2007;21:1019-26. [PMID: 17457096]
39. **Rudin C, Spaenhauer A, Keiser O, Rickenbach M, Kind C, Aebi-Popp K, et al; Swiss HIV Cohort Study (SHCS).** Antiretroviral therapy during pregnancy and premature birth: analysis of Swiss data. HIV Med. 2011;12:228-35. [PMID: 20726902]
40. **Powis KM, Kitch D, Ogwu A, Hughes MD, Lockman S, Leidner J, et al.** Increased risk of preterm delivery among HIV-infected women randomized to protease versus nucleoside reverse transcriptase inhibitor-based HAART during pregnancy. J Infect Dis. 2011;204:506-14. [PMID: 21791651]
41. **Watts DH, Huang S, Culnane M, Kaiser KA, Scheuerle A, Mofenson L, et al.** Birth defects among a cohort of infants born to HIV-infected women on antiretroviral medication. J Perinat Med. 2011;39:163-70. [PMID: 21142844]
42. **Townsend CL, Willey BA, Cortina-Borja M, Peckham CS, Tookey PA.** Antiretroviral therapy and congenital abnormalities in infants born to HIV-infected women in the UK and Ireland, 1990-2007. AIDS. 2009;23:519-24. [PMID: 19165088]
43. **Patel D, Thorne C, Fiore S, Newell ML; European Collaborative Study.** Does highly active antiretroviral therapy increase the risk of congenital abnormalities in HIV-infected women? [Letter]. J Acquir Immune Defic Syndr. 2005;40:116-8. [PMID: 16123696]
44. **Alimenti A, Forbes JC, Oberlander TF, Money DM, Grunau RE, Papsdorf MP, et al.** A prospective controlled study of neurodevelopment in HIV-uninfected children exposed to combination antiretroviral drugs in pregnancy. Pediatrics. 2006;118:e1139-45. [PMID: 16940166]
45. **Williams PL, Marino M, Malee K, Brogly S, Hughes MD, Mofenson LM; PACTG 219C Team.** Neurodevelopment and in utero antiretroviral exposure of HIV-exposed uninfected infants. Pediatrics. 2010;125:e250-60. [PMID: 20083530]
46. **Tuomala RE, Watts DH, Li D, Vajaranant M, Pitt J, Hammill H, et al; Women and Infants Transmission Study.** Improved obstetric outcomes and few maternal toxicities are associated with antiretroviral therapy, including highly active antiretroviral therapy during pregnancy. J Acquir Immune Defic Syndr. 2005;38:449-73. [PMID: 15764963]
47. **Martí C, Peña JM, Bates I, Madero R, de José I, Pallardo LF, et al.** Obstetric and perinatal complications in HIV-infected women. Analysis of a cohort of 167 pregnancies between 1997 and 2003. Acta Obstet Gynecol Scand. 2007;86:409-15. [PMID: 17486461]
48. **Lipshultz SE, Shearer WT, Thompson B, Rich KC, Cheng I, Orav EJ, et al.** Cardiac effects of antiretroviral therapy in HIV-negative infants born to HIV-positive mothers: NHLBI CHAART-1 (National Heart, Lung, and Blood Institute Cardiovascular Status of HAART Therapy in HIV-Exposed Infants and Children cohort study). J Am Coll Cardiol. 2011;57:76-85. [PMID: 21185505]
49. **Bunders MJ, Bekker V, Scherpbier HJ, Boer K, Godfried M, Kuijpers TW.** Haematological parameters of HIV-1-uninfected infants born to HIV-1-infected mothers. Acta Paediatr. 2005;94:1571-7. [PMID: 16303696]
50. **Mussi-Pinhata MM, Rego MA, Freimanis L, Kakehasi FM, Machado DM, Cardoso EM, et al; NISDI Perinatal Protocol Study Group.** Maternal antiretrovirals and hepatic enzyme, hematologic abnormalities among human immunodeficiency virus type 1-uninfected infants: the NISDI perinatal study. Pediatr Infect Dis J. 2007;26:1032-7. [PMID: 17984811]
51. **Pacheco SE, McIntosh K, Lu M, Mofenson LM, Diaz C, Foca M, et al; Women and Infants Transmission Study.** Effect of perinatal antiretroviral drug exposure on hematologic values in HIV-uninfected children: An analysis of the women and infants transmission study. J Infect Dis. 2006;194:1089-97. [PMID: 16991083]
52. **Aldrovandi GM, Chu C, Shearer WT, Li D, Walter J, Thompson B, et al.** Antiretroviral exposure and lymphocyte mtDNA content among uninfected infants of HIV-1-infected women. Pediatrics. 2009;124:e1189-97. [PMID: 19933732]
53. **Brogly SB, Ylitalo N, Mofenson LM, Oleske J, Van Dyke R, Crain MJ, et al.** In utero nucleoside reverse transcriptase inhibitor exposure and signs of possible mitochondrial dysfunction in HIV-uninfected children. AIDS. 2007;21:929-38. [PMID: 17457086]
54. **Côté HC, Raboud J, Bitnun A, Alimenti A, Money DM, Maan E, et al.** Perinatal exposure to antiretroviral therapy is associated with increased blood mitochondrial DNA levels and decreased mitochondrial gene expression in infants. J Infect Dis. 2008;198:851-9. [PMID: 18684095]
55. **Benhammou V, Warszawski J, Bellec S, et al.** Incidence of cancer in children perinatally exposed to nucleoside reverse transcriptase inhibitors. AIDS. 2008;22:2165-77. [PMID: 18832880]

Current Author Addresses: Drs. Chou, Cantor, and Zahker and Ms. Bougatsos: Oregon Health & Science University, 3181 Southwest Sam Jackson Park Road, Mail Code BICC, Portland, OR 97239.

Appendix Table 1. Inclusion and Exclusion Criteria

Key Question Detail*	Included	Excluded
All key questions		
Settings	Primary care or other settings generalizable to primary care (e.g., family planning clinics, school-based health clinics); other health care settings in which screening is commonly performed (e.g. emergency department or urgent care). Focus on studies conducted in the United States and other developed countries, except for randomized trials of antiretroviral therapies (Africa)	Developing countries, unless fair- or good-quality trials and studies in the United States are lacking
Key question 1		
Populations	Asymptomatic pregnant women; neonates, infants, and children who were exposed to HAART in utero	Known HIV infection, on dialysis, posttransplant, occupational exposure
Interventions	Rapid or standard HIV testing	
Comparisons	HIV screening vs. no screening	
Outcomes	Mother-to-child transmission rates of HIV, mortality related to HIV infection, and quality of life for mothers and their newborns	Pharmacokinetics
Study designs	RCTs and controlled observational studies	Modeling studies
Key question 2a		
Populations	Asymptomatic pregnant women	Known HIV infection, receiving dialysis, posttransplant, occupational exposure
Interventions	Rapid or standard HIV testing	
Comparisons	Repeated HIV screening during pregnancy vs. one-time screening, or screening at one interval vs. another interval	
Outcomes	Number of positive tests	
Study designs	RCTs and controlled observational studies	Modeling studies
Key question 2b		
Populations	Asymptomatic pregnant women	Known HIV infection, receiving dialysis, posttransplant, occupational exposure
Interventions	Rapid or standard HIV testing	
Comparisons	Rapid vs. standard HIV testing	
Outcomes	False-positive result, anxiety and effects of labeling, partner discord, abuse or violence, and other effects	
Study designs	RCTs and comparative observational studies	Modeling studies
Key question 3a		
Populations	Pregnant women with HIV; neonates, infants that were exposed to antiretroviral regimens in utero	Women already or previously receiving HAART before pregnancy; acute HIV or HIV subtypes
Interventions	Newer antiretroviral regimens	Discontinuing HAART during pregnancy; treatment interruption
Comparisons	Newer antiretroviral regimens vs. placebo, older antiretroviral regimens, or one another	
Outcomes	Mother-to-child transmission rates of HIV	
Study designs	RCTs and controlled observational studies	Modeling studies
Key question 3b		
Populations	Women who were on antiretroviral regimens while pregnant	Women already or previously on antiretroviral therapy before pregnancy; acute HIV or HIV subtypes
Interventions	Newer antiretroviral regimens	Discontinuing antiretroviral therapy during pregnancy; treatment interruption
Comparisons	Newer antiretroviral regimens vs. placebo, older antiretroviral regimens, or one another	
Outcomes	Long-term maternal morbidity, mortality, or quality of life	Pharmacokinetics
Study designs	Any	
Timing	≥1 y after giving birth	Less than 1 y after giving birth
Key question 3c		
Populations	Women who were receiving antiretroviral regimens while pregnant; neonates, infants, and children who were exposed to antiretroviral therapy in utero	Women already or previously on antiretroviral therapy before pregnancy; acute HIV or HIV subtypes
Interventions	Newer antiretroviral regimens	Discontinuing antiretroviral therapy during pregnancy; treatment interruption
Comparisons	Newer antiretroviral regimens vs. placebo, older antiretroviral regimens, or one another	
Outcomes	Harmful effects on pregnancy outcomes, neonatal outcomes, or effects on exposed children; long-term cardiovascular and metabolic maternal outcomes	Pharmacokinetics
Study designs	Any	
Timing	Any	

HAART = highly active antiretroviral therapy; RCT = randomized, controlled trial.

* Key questions were as follows:

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

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

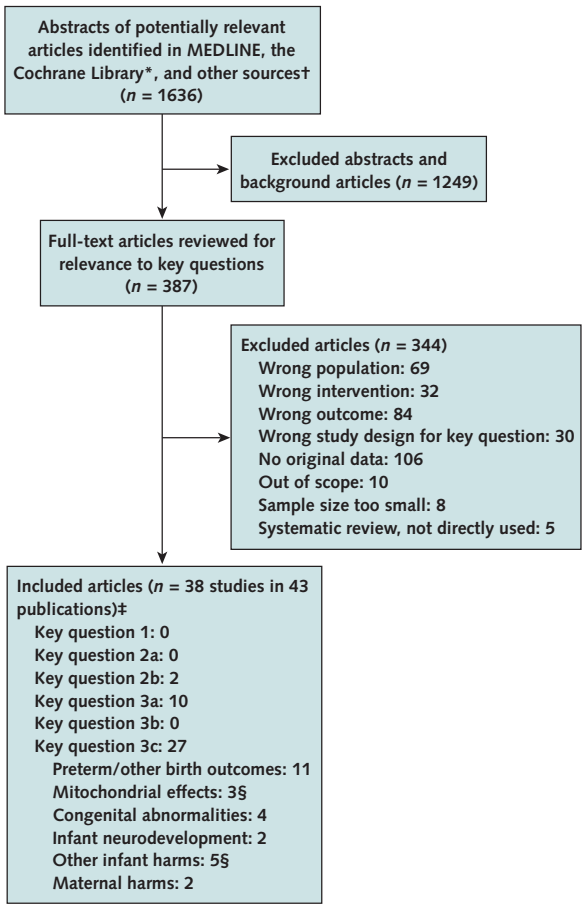
2b. What are the adverse effects (including false-positive tests and anxiety) of rapid vs. standard HIV testing in asymptomatic pregnant women?

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

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

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

Appendix Figure. **Evidence search and selection.**



* Includes the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
† Include reference lists suggested by peer reviewers.
‡ Some articles are included for more than 1 key question.
§ These studies were included in the full report but omitted from the manuscript.

Author Contributions: Conception and design: R. Chou, C. Bougatsos.
Analysis and interpretation of the data: R. Chou, A.G. Cantor, B. Zakher, C. Bougatsos.
Drafting of the article: R. Chou, A.G. Cantor, B. Zakher, C. Bougatsos.
Critical revision of the article for important intellectual content: R. Chou, A.G. Cantor, B. Zakher.
Final approval of the article: R. Chou, A.G. Cantor, B. Zakher.
Statistical expertise: R. Chou.
Obtaining of funding: R. Chou.
Administrative, technical, or logistic support: R. Chou, A.G. Cantor, C. Bougatsos.
Collection and assembly of data: R. Chou, B. Zakher, C. Bougatsos.

Appendix Table 2. Cohort Studies of Mother-to-Child HIV Transmission Rates While Using ART

Study, Year (Reference)	Setting	Intervention	Sample	Mother-to-Child Transmission Rate and ORs, by Treatment Group	Quality Rating
Garcia-Tejedor et al, 2009 (17)	Spain; maternity hospitals	ART during pregnancy A: No treatment B: Mono/dual therapy C: HAART	489 mother–infant pairs were analyzed; rate of cesarean delivery, 51%; no infants were breastfed; follow-up not reported	A: 18% (39/214) B: 8.6% (10/116) C: 0.6% (1/159) $P < 0.001$	Fair
Harris et al, 2007 (18)	United States; population surveillance data from areas reporting >60 HIV-positive women giving birth per year	Arms of ART A: No treatment B: Prenatal, intrapartum, and neonatal ART*	7344 HIV-exposed infants with ART data; rate of cesarean delivery, 53%; breastfeeding rate not reported; follow-up by health department every 6 mo until HIV status determined; analyses of data over 3-y study period	A: 22% (59/265); reference B: 2.4% (139/5757); AOR, 0.09 (95% CI, 0.06–0.12)* Prenatal ART regimen and infant infection status among patients in 3 treatment groups (5602 participants, owing to exclusions): ZDV: reference ZDV and other drugs with PI: AOR, 0.4 (CI, 0.3–0.7) ZDV and other drugs, no PI: AOR, 0.5 (CI, 0.3–0.8) Other drugs with PI, no ZDV: AOR, 0.6 (CI, 0.2–1.4) Other drugs, no PI, no ZDV: AOR, 0.3 (CI, 0.1–1.5)	Fair
Tariq et al, 2011 (20)	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	Antenatal ART regimen A: ZDV-containing B: ZDV-sparing	7573 mother–child pairs analyzed; rate of cesarean delivery, 74%; breastfeeding rate not reported; follow-up not reported; analyses of data over 9-y study period	56/6130 (0.9% [CI, 0.7%–1.0%]) of infants were infected; infection status available for 80% (6130/7645) of infants at analysis A: 0.9% (5214 infants); reference B: 0.8% (897 infants); AOR, 1.8 (CI, 0.8–4.3); $P = 0.18$	Fair
Townsend et al, 2008 (19)	Ireland, United Kingdom; population surveillance data from National Study of HIV in Pregnancy and Childhood	Antepartum treatment A: HAART B: Dual therapy C: Monotherapy D: No therapy	5027 mother–infant pairs with ART data; rate of cesarean delivery, 78%. 0.6% of infants breastfed; follow-up not reported; analyses of data over 6-y study period	A: 1.0% (40/4120) B: 0.8% (1/126) C: 0.5% (3/638) D: 9.1% (13/143) AORs (4084 participants, owing to exclusions): A: 1.0 B: 1.7 (CI, 0.2–13); $P = 0.61$ C: 0.6 (CI, 0.2–1.9); $P = 0.37$ D: 3.2 (CI, 1.2–8.6); $P = 0.02$	Fair

AOR = adjusted odds ratio; ART = antiretroviral therapy; HAART = highly active antiretroviral therapy; OR = odds ratio; PI = protease inhibitor; ZDV = zidovudine.
* Not all study interventions are shown.

Appendix Table 3. African-Based Trials of Mother-to-Child HIV Transmission Rates While Using ART

Study, Year (Reference)	Setting	Prenatal Intervention	Peripartum Intervention	Postpartum Intervention	Sample	Mother-to-Child Transmission Rate, by Treatment Group	Quality Rating
Chi et al, 2008 (22)	Zambia	From 32 wk: ZDV to all groups	A: TDF/FTC + NVP B: NVP	All neonates: NVP dose in hospital + ZDV for 1 wk	355 mother–infant pairs analyzed; 92% of infants breastfed in both groups	At 6 wk postpartum: A: 6% B: 8% $P = 0.4$	Fair
de Vincenzi et al, 2011 (21)	Burkina Faso, Kenya, South Africa	From 28 wk: A: ZDV + 3TC + ABT-378 + RTV B: ZDV	A: ZDV + 3TC + ABT-378 + and RTV B: ZDV + sdNVP	A: Maternal ZDV + 3TC + ABT-378 + RTV until cessation of breastfeeding (maximum, 6.5 mo postpartum) B: Maternal 3TC + ZDV for 1 wk postpartum* All neonates: ZDV for 1 wk*, NVP dose within 72 h of birth, cotrimoxazole from age 6 wk to 12 mo unless not HIV-infected after cessation of breastfeeding	805 live-born infants; 77% of infants in group A and 78% in group B were ever breastfed	At age 12 mo: A: 5.4% (95% CI, 3.6% to 8.1%); 21/333 infants B: 9.5% (CI, 7.0% to 13%); 37/305 infants RR reduction, 43% $P = 0.03$	Good
Gray et al, 2006 (23)	South Africa	From 34 wk: A: d4T B: ddI C: d4T + ddI D: ZDV	A: d4T B: ddI C: d4T + ddI D: ZDV	Infants received same ART regimen as mother until age 6 wk	362 mother–infant pairs analyzed; no infants breastfed	At 24 wk postpartum: A: 12% (CI, 6.2 to 21); 11/91 infants B: 11% (CI, 5.2 to 19); 10/94 infants C: 4.6% (CI, 1.3 to 11); 4/88 infants D: 5.6% (CI, 1.9 to 13); 5/89 infants All groups: 8.3% (CI, 5.7 to 12); 30/362 infants	Fair
Shapiro et al, 2010 (24)	Botswana	Randomization groups† From 26 wk: A: ABC + ZDV + 3TC B: ABT-378 + RTV + ZDV + 3TC Observational group‡ From 18 wk: C: NVP + ZDV + 3TC	A: ABC + ZDV + 3TC B: ABT-378 + RTV + ZDV + 3TC C: NVP + ZDV + 3TC	A: ABC + ZDV + 3TC B: ABT-378 + RTV + ZDV + 3TC; above to continue until weaning or 6 mo postpartum, whichever came first C: NVP + ZDV + 3TC to continue indefinitely All neonates: sdNVP at birth + ZDV from birth to age 4 wk	709 live-born infants (including 156 in the observational group); 97% of live-born infants breastfed, 71% continued for >5 mo	At age 6 mo: A: 2.1% (6/283 infants) B: 0.4% (1/270 infants) Difference, 1.7 percentage points (CI, 2.0 to 7.1 percentage points)§ All groups: 1.1% (CI, 0.5–2.2); 8/709 infants	Fair
Shapiro et al, 2006 (25)	Botswana	From 34 wk: ZDV to all groups‖	A: sdNVP B: placebo	All neonates: NVP at birth and ZDV from birth to age 1 mo¶	694 live first-born infants; 50% of infants in both groups were breastfed; infant follow-up until age 1 mo	At age 1 mo: A: 4.3% (2 SDs, 2.3); 15/345 infants B: 3.7% (1 SDs, 2.2); 13/346 infants 95% CI for difference, –2.4% to 3.8% (met equivalence)	Fair
Thistle et al, 2007 (26)	Zimbabwe	Not applicable	A: ZDV + sdNVP B: sdNVP	A: Infant ZDV for 72 h after delivery and NVP dose within 72 h of delivery B: Infant NVP dose within 72 h of delivery	Study terminated owing to futility; 609 infants with data. 89% of infants in group A and 91% of infants in group B were breastfed at 6 wk (1 infant in group A was breastfed and formula-fed)	At age 6 wk: A: 14% (45/312 infants) HIV-positive; 7.4% (23/312 infants) dead; 22% (68/312) met primary outcome (death or HIV infection) B: 17% (49/297 infants) HIV-positive; 7.1% (21/297 infants) dead; 24% (70/297 infants) met primary outcome	Fair

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

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

† Women with CD4 count $>0.200 \times 10^9$ cells/L.

‡ Women with CD4 count $<0.200 \times 10^9$ cells/L or with an AIDS-defining illness.

§ Study not powered for between-group comparisons of transmission rates.

‖ HAART was offered to women with CD4 counts $<0.200 \times 10^9$ cells/L or AIDS-defining illness at any point during study participation. If women started HAART before delivery, they did not receive peripartum NVP or placebo.

¶ Infants confirmed to be HIV-infected were also given HAART.

Appendix Table 4. **Preterm Birth Outcomes***

Study, Year (Reference)	ART Regimen	Preterm Definition, *wk*	Gestational Age Distribution	Magnitude of Risk: Adjusted OR (95% CI)
Cotter et al, 2006 (32)	Any combination therapy; combination + PI	<37 (<32 = very preterm)	Median gestational age at delivery: 39 wk	Combination with vs without PI: <37 wk: 1.8 (1.1–3.0); $P = 0.03$ Combination + PI: rate ($n = 134$) <37 wk: 36.6% of women ($P < 0.05$) <32 wk: 2.2% of women (P = NS)
Schulte et al, 2007 (37)	HAART + PI	<37	Mean gestational age: 37.3 wk (range, 26–42 wk)	1.21 (1.04–1.48); *P* value not reported
Townsend et al, 2007 (38)	HAART ± PI	<37	<37 wk: 14.1%† <35 wk: 7.8% <32 wk: 1.4%	<37 wk: 1.39 (1.05–1.83); $P = 0.020$ <35 wk: 2.02 (1.35–3.04); $P = 0.001$ <32 wk: 2.63 (1.3–5.33); $P = 0.007$
Grosch-Woerner et al, 2008 (34)	HAART ± PI	<36	<36 wk: 34%† (crude rate)	HAART, no PI: 0.89 (0.38–2.12); $P = 0.8$ HAART + PI: 3.40 (1.13–10.2); $P = 0.030$
Powis et al, 2011 (40)	PI-based HAART	<37	<37 wk: 11.8%† receiving triple NRTI therapy, 21.4% receiving PI-based therapy	HAART, no PI (NRTI-based): 1.0
	NRTI based HAART		<32 wk: 2.6% ($n = 12$); 8/12 associated with HAART + PI, 4/12 with triple NRTI therapy	HAART + PI: 2.02 (1.25–3.27); unadjusted $P = 0.004$

ART = antiretroviral therapy; HAART = highly active antiretroviral therapy; NRTI = nucleoside reverse transcriptase inhibitor; NS = not significant; OR = odds ratio; PI = protease inhibitor.

* This table shows only randomized trials and cohort studies that adjusted for potential confounders. Reference 40 was a randomized trial; all other studies were cohort studies.

† Percentage of study population.