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Screening for HIV Infection in Pregnant Women
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Prenatal screening for HIV can inform use of interventions to reduce the risk of mother-to-child transmission. The US Preventive Services Task Force (USPSTF) previously found strong evidence that prenatal HIV screening reduced risk of mother-to-child transmission. The previous evidence review was conducted in 2012.

OBJECTIVE To update the 2012 review on prenatal HIV screening to inform the USPSTF.

DATA SOURCES Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews from 2012 to June 2018, with surveillance through January 2019.

STUDY SELECTION Pregnant persons 13 years and older; randomized clinical trials and cohort studies of screening vs no screening; risk of mother-to-child transmission or maternal or infant harms associated with antiretroviral therapy (ART) during pregnancy; screening yield at different intervals or in different risk groups.

DATA EXTRACTION AND SYNTHESIS One investigator abstracted data; a second checked accuracy. Two investigators independently rated study quality.

MAIN OUTCOMES AND MEASURES Mother-to-child transmission; harms of screening and treatment; screening yield.

RESULTS Sixty-two studies were included in this review, including 29 new studies. There remains no direct evidence on effects of prenatal screening vs no screening on risk of mother-to-child HIV transmission, maternal or infant clinical outcomes, or the yield of repeat or alternative screening strategies. New evidence confirms that combination ART is highly effective at reducing the risk of mother-to-child transmission, with some new cohort studies reporting rates of mother-to-child transmission less than 1% when combination ART was started early in pregnancy (when begun in first trimester, 0%-0.4%; when begun after first trimester, or at any time if timing of ART initiation not reported, 0.4%-2.8%). New evidence on harms of ART was also largely consistent with the previous review. Evidence from primarily observational studies found prenatal combination ART with a boosted protease inhibitor associated with increased risk of preterm delivery (range, 14.4%-26.1%). For other birth outcomes (low birth weight, small for gestational age, stillbirth, birth defects, neonatal death), results were mixed and depended on the specific antiretroviral drug or drug regimen given and timing of prenatal therapy.

CONCLUSIONS AND RELEVANCE Combination ART was highly effective at reducing risk of mother-to-child HIV transmission. Use of certain ART regimens during pregnancy was associated with increased risk of harms that may be mitigated by selection of ART regimen. The 2012 review found that avoidance of breastfeeding and cesarean delivery in women with viremia also reduced risk of transmission and that prenatal screening accurately diagnosed HIV infection.

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Human immunodeficiency virus can be transmitted from mother to child during pregnancy and the postpartum period. Based on a 2006 estimate, approximately 8500 HIV-positive persons give birth each year in the United States,[1] and in 2014 an estimated 12% of HIV-infected women were unaware of their status.[2] From 1985 to 2001, the number of cases of perinatal HIV infections in the United States declined after the widespread adoption of routine prenatal screening, coupled with the use of effective therapies for preventing mother-to-child transmission.[3] In 2016, there were 99 cases of perinatal HIV infections.[4]

In 2013, the US Preventive Services Task Force (USPSTF) reaffirmed its prior recommendation to screen all pregnant persons for HIV infection (A recommendation), based on evidence that screening accurately detects HIV infection during pregnancy, and that interventions—in particular antiretroviral therapy (ART)—are associated with marked reduction in risk of mother-to-child transmission. The purpose of this evidence report was to update the 2012 USPSTF review[5,6] on the benefits and harms of prenatal screening for HIV infection, focusing on previously identified research gaps: direct evidence on benefits and harms of screening vs no screening, optimal frequency of screening, and benefits and long-term harms of currently recommended ART regimens.[7]

Methods

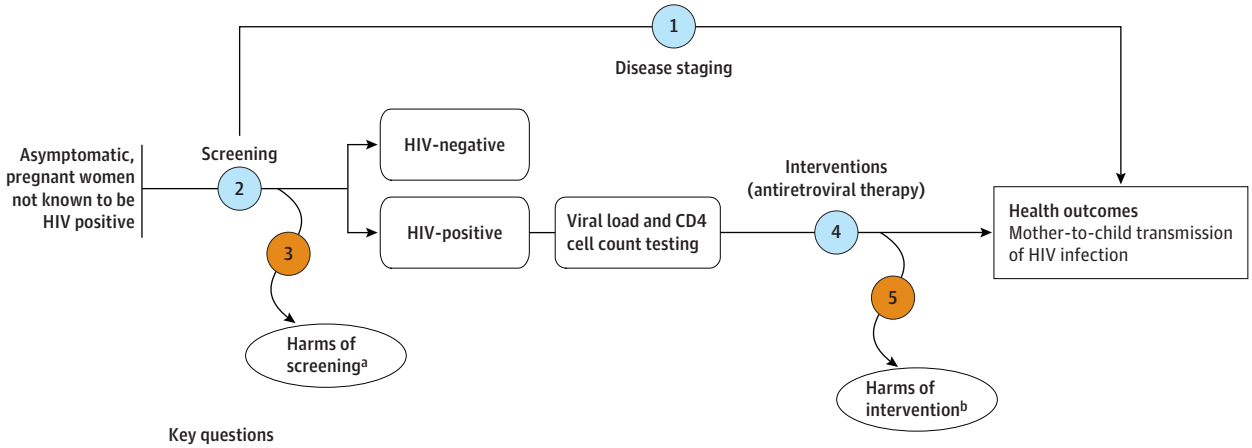
Scope of Review

Detailed methods and additional study details and results on congenital abnormalities are available in the full evidence report at https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/human-immunodeficiency-virus-hiv-infection-screening1. Key studies are highlighted in this manuscript. **Figure 1** shows the analytic framework and key questions (KQs) that guided the review.

Data Sources and Searches

The Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews and Ovid MEDLINE were searched from 2012 through June 2018 (eMethods 1 in the Supplement). Since June 2018, we continued to conduct ongoing surveillance through article alerts and targeted searches of high-impact journals

Figure 1. Analytic Framework: Screening for HIV Infection in Pregnant Women



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?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. Refer to the USPSTF Procedure Manual for further details.[8]

[a] Include false-positive results; anxiety and effects of labeling; and partner discord, abuse, or violence.

[b] Include adverse maternal and infant outcomes associated with use of antiretroviral therapy.

to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and therefore the related USPSTF recommendation. The last surveillance was conducted on January 25, 2019, and identified no relevant new studies. Searches were supplemented with expert suggestions and by reviewing reference lists from relevant systematic reviews and prior USPSTF reports.

Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles using predefined eligibility criteria. Randomized clinical trials (RCTs), cohort studies, and case-control studies of pregnant adolescents (13 to <18 years) and adults were eligible for all KQs. Studies that directly evaluated the associations of prenatal HIV screening vs no screening in asymptomatic persons with clinical outcomes (mortality, AIDS and opportunistic infections, quality of life, function, HIV transmission, and harms [maternal or infant]) were eligible for KQ1 and KQ3. Studies that evaluated the yield (number of new diagnoses per tests performed) of screening for HIV infection at different intervals or in different risk groups were eligible for KQ2. Studies that compared associations with currently recommended[7] full-course (initiated in first or early second trimester) combination ART vs no ART, abbreviated courses of ART, or 1- or 2-drug therapy were eligible for KQ4 and KQ5. Studies could be conducted in any geographic setting, including low- or middle-income countries. For KQ5, cohort studies had to adjust for potential confounders.

Data Abstraction and Quality Rating

For each study, one investigator abstracted information on populations, interventions or screening instruments, comparators, outcomes, study designs, and settings. A second investigator reviewed abstractions for accuracy. Two independent investigators assessed the quality of each study as good, fair, or poor using predefined criteria developed by the USPSTF (eMethods 2 in the Supplement).[8] Quality ratings for individual studies are provided in eTables 1 and 2 in the Supplement.

Data Synthesis

Results were summarized qualitatively. Meta-analysis was not performed because of clinical and methodological heterogeneity among studies. For all KQs, the overall strength of the body of evidence was assessed as high, moderate, low, or insufficient using methods developed by the USPSTF, based on quality of studies, consistency of results between studies, precision of estimates, study limitations, and risk of reporting bias. The applicability of the findings to US primary care populations and settings was also assessed.

Results

Two reviewers independently assessed 1232 unique citations and 162 full-text articles for inclusion (**Figure 2**). Twenty-nine new studies in 36 articles were included (2 trials in 2 articles[9,10] and 27 cohort studies in 34 articles[11-44]), and 33 studies in 35 articles (7 trials in 9 articles,[45-53] 25 cohort studies in 25 articles,[54-78] and 1 systematic review[79]) were carried forward from the prior USPSTF report.[5,6]

Screening for HIV infection

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?

No studies met inclusion criteria for KQ1.

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?

No studies met inclusion criteria for KQ2.

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

No studies met inclusion criteria for KQ3.

Effectiveness of Treatment

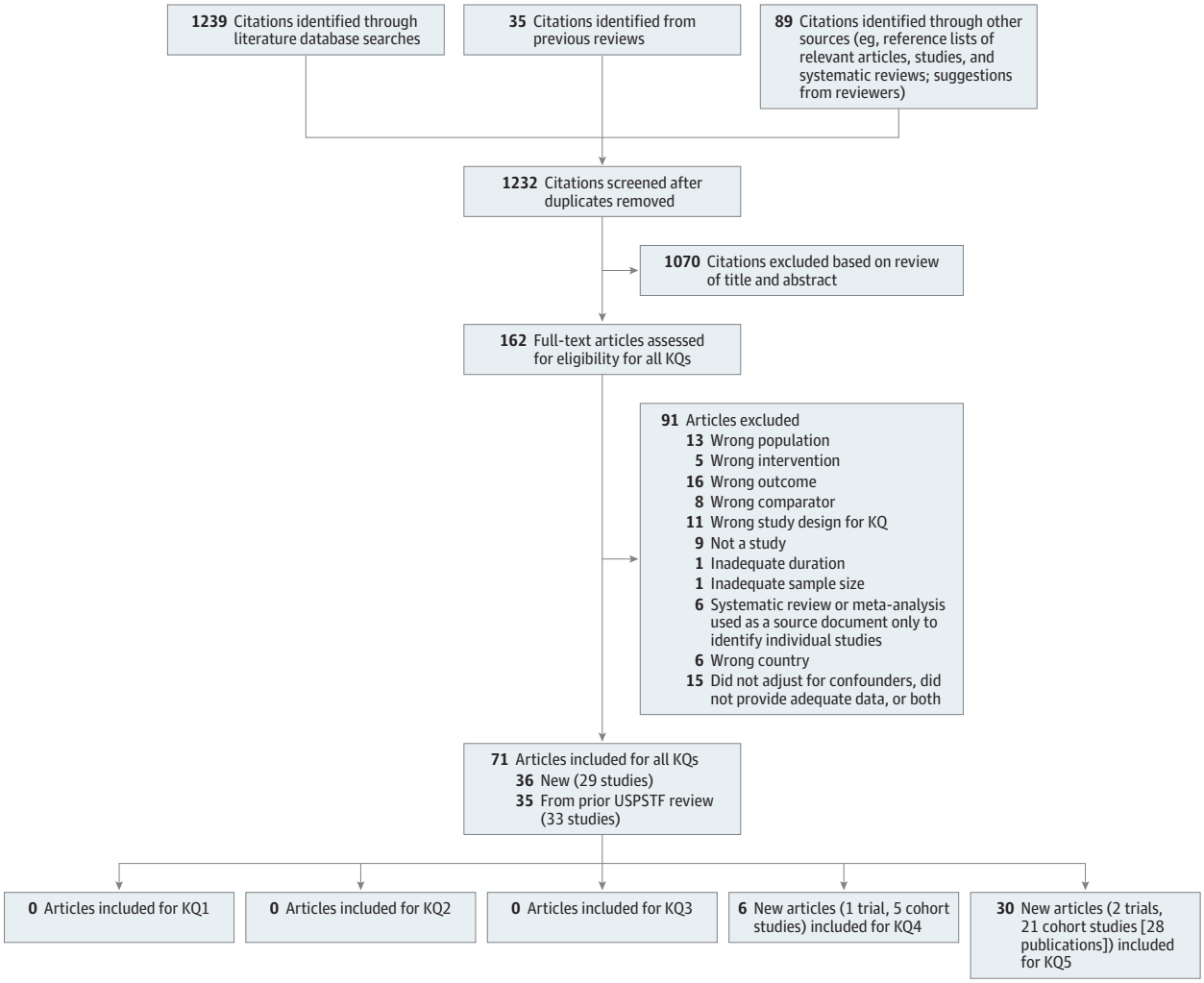
Key Question 4. What is the effectiveness of currently recommended ART regimens for reducing mother-to-child transmission of HIV infection?

The 2012 USPSTF review included 8 US or European cohort studies[70-73,75-78] (N = 27 776) that found full-course combination ART associated with rates of mother-to-child transmission that ranged from less than 1% to 2.4%, compared with 9% to 22% without ART. The prior USPSTF review included 2 RCTs of breastfeeding women in Africa that found 3-drug ART started at 26 to 28 weeks' gestation associated with mother-to-child transmission rates of 1% to 5%[51,52] (eTable 3 in the Supplement) and also included 4 trials that found ART with fewer drugs or more abbreviated courses of therapy also effective (n = 3534).[45-47,53] Five new fair-quality cohort studies[16,25,26,28,39] conducted in high-income settings (**Table 1**) (n = 16 381) and 1 new RCT[9] (n = 3202) conducted in low-income settings (**Table 2**) evaluated associations with combination ART during pregnancy on rates of mother-to-child transmission. Results were consistent with the findings from the prior review, with mother-to-child transmission rates as low as less than 1% with full-course combination ART.

New evidence found that 1 cohort study evaluated infants (n = 4459) born between 1996 and 2010 in 7 European cohorts who were at high risk of acquiring HIV infection (mother with viral load >50 copies/mL in the last 8 weeks of pregnancy, only received intrapartum ART, or received no antenatal or intrapartum ART).[16] Use of 3 or more antiretroviral drugs was associated with decreased risk of mother-to-child transmission compared with no ART (2.8% vs 14.3%; adjusted odds ratio [OR], 0.36 [95% CI, 0.23-0.57]). Results were similar for treating with 1 or 2 antiretroviral drugs (adjusted ORs, 0.33 [95% CI, 0.19-0.55] and 0.12 [95% CI, 0.04-0.40], respectively). The association of the timing of initiation of ART during pregnancy with mother-to-child transmission was not assessed.

A French cohort study evaluated 4583 women who received combination ART during pregnancy between 2000 and 2011.[26] Most regimens were protease inhibitor–based triple therapy (82.5%). 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%-7.9%]). There were no instances of HIV transmission among 2651 women who started ART before pregnancy, continued ART throughout pregnancy, and had a viral load less than 50 copies/mL at the time of delivery.

Figure 2. Literature Search Flow Diagram: Screening for HIV Infection in Pregnant Women



Additional articles are indicated for the included studies where relevant. KQ indicates key question; USPSTF, US Preventive Services Task Force.

Two smaller cohort studies, 1 from Canada[25] (n = 645) and 1 from the United Kingdom and Ireland[39] (n = 2406) reported rates of mother-to-child HIV transmission with combination ART of 1% and 0.5%, respectively. In the United Kingdom/Ireland study, ritonavir-boosted lopinavir was associated with a higher transmission rate when ART was initiated during the third trimester (1.9%).[39] An Israeli cohort study[28] (n = 796) found combination ART during pregnancy associated with decreased risk of vertical transmission (adjusted OR, 0.4 [95% CI, 0.1-0.8]); transmission rates were 1.5% with vaginal delivery and 0.6% with cesarean delivery. Results were not stratified by timing of ART administration.

One new, fair-quality RCT, the Promoting Maternal and Infant Survival Everywhere (PROMISE) trial (n = 3490),[9] was conducted in India and Africa among HIV-infected women (92% breastfeeding) with CD4 cell counts of or greater than 350/mm^3 at 14 weeks' or later gestation (Table 2). The rate of mother-to-child transmission was 1.8% with zidovudine alone, 0.5% with ART with zidovudine, lamivudine, and lopinavir/ritonavir, and 0.6% 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%]).

Harms of Treatment

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

Birth Outcomes

The 2012 USPSTF review[5] included 1 RCT[48] (n = 560) and 3 prospective cohort studies[57,59,64] (n = 10 313) 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 inhibitor–based ART (OR, 2.0 [95% CI, 1.3-3.3]),[48] combination ART without a protease inhibitor (adjusted OR, 1.8 [95% CI, 1.1-3.0]),[57] dual therapy (adjusted OR, 1.2 [95% CI, 1.0-1.4]),[64] or monotherapy (adjusted OR, 3.4 [95% CI, 1.1-10])[59] (eTable 4 in the Supplement). A fourth cohort study[65] (n = 4939) found combination therapy associated with increased risk of preterm delivery (adjusted OR, 1.4 [95% CI, 1.1-1.8]) compared with

Table 1. US-Relevant Cohort Studies of Mother-to-Child HIV Transmission While Using Antiretroviral Therapy[a]

Source	Setting or Study	Intervention	Sample	Mother-to-Child Transmission Rates by Treatment Group
Chiappini et al,[16] 2013	European Pregnancy and Paediatric HIV Cohort Collaboration; 7 cohorts from 6 countries (Ukraine excluded because of heterogeneity)	A: ≥3 drugs B: 2 drugs C: 1 drug D: No therapy E: Unknown	4459 High-risk mother-infant pairs: no therapy (28%), intrapartum prophylaxis only (17%), ART received but mother's viral load remained detectable (55%), screen-detected HIV during pregnancy (% NR), no antenatal or only intrapartum ART (45%) None breastfed (Ukraine cohort not included in transmission analysis) Timing of infant HIV testing: NR	A:65/2355 (2.8%) AOR, 0.36 (95% CI, 0.23-0.57); *P* < .001 B: 3/255 (1.2%) AOR, 0.12 (95% CI, 0.04-0.40); *P* < .001 C: 21/681 (3.1%) AOR, 0.33 (95% CI, 0.19-0.55); *P* < .005 D: 158/1107 (14.3%) AOR, 1 [Reference]
Lu et al,[25] 2014	Canada, Canadian Perinatal HIV Surveillance Program	A: Complete ART during pregnancy, zidovudine during labor, infant received zidovudine B: Incomplete ART C: No therapy	645 Mother-child pairs analyzed Rate of cesarean delivery: 43% Breastfeeding rate: NR Follow-up: NR Proportion of mothers born in HIV-endemic country: 65% Analysis of data over 12-y 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: 3/251 (1%) B: 8/336 (2%) C: 39/58 (67%)
Mandelbrot et al,[26] 2015	France, national prospective multicenter French Perinatal Cohort (ANRS-EPF)	First ART: A: Triple NRTI B: PI-based C: NNRTI-based D: 3 classes E: Other	8075 Mother-child pairs analyzed Rate of cesarean delivery: 57% Breastfeeding rate: 0% Follow-up: clinicians encouraged to follow up from birth to 18-24 mo Analysis of data over 11-y 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 [Reference]; first trimester, 0.4%; AOR, 2.9 (95% CI, 0.6-17.7); second trimester, 0.9%; AOR, 6.0 (95% CI, 1.7-29.7); third trimester, 2.2%; AOR, 7.8 (95% CI, 2.1-28.8)
Mor et al,[28] 2017	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 mothers born in Ethiopia; 8 infants were breastfed Timing of infant HIV testing: NR	HAART vs no HAART during pregnancy: AOR, 0.4 (95% CI, 0.1-0.8) Overall transmission: 25/796 (3%) Transmission with HAART and vaginal delivery: 1.5% Transmission with HAART and cesarean delivery: 0.6%
Tookey et al,[39] 2016	United Kingdom and Ireland, National Study of HIV in Pregnancy and Childhood	A: Lopinavir/ritonavir + zidovudine + lamivudine B: Lopinavir/ritonavir + emtricitabine + tenofovir disoproxil fumarate C: Lopinavir/ritonavir + abacavir + lamivudine D: Lopinavir/ritonavir + other or missing NRTIs	4864 Enrolled; 2406 mother-infant pairs (2008-2012); 67% received lopinavir/ritonavir + zidovudine + lamivudine; proportion of mothers born in sub-Saharan Africa: 77% (some mother-infant pairs at high risk for HIV transmission likely also counted in the Chiappini study) Timing of infant HIV testing: NR	By timing of lopinavir/ritonavir initiation: Overall: 12/2406 (0.5% [95% CI, 0.2%-0.8%]); before conception: 2/635 (0.3% [95% CI, 0.1%-1.1%]); first trimester: 0/77 (0%); second trimester: 5/1397 (0.4% [95% CI, 0.2%-0.8%]); third trimester: 5/264 (1.9% [95% CI, 0.8%-4.4%])

Abbreviations: AOR, adjusted odds ratio; ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; NNRTI, nonnucleoside reverse transcriptase inhibitor; NR, not reported; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a] All studies were rated fair quality.

Table 2. African-Based Trial of Mother-to-Child HIV Transmission While Using Antiretroviral Therapy[a]

		Intervention				
Source	Setting	Prenatal	Peripartum	Postpartum	Sample	Mother-to-Child Transmission Rates by Treatment Group
Fowler et al,[9] 2016	India, Malawi, South Africa, Tanzania, Uganda, Zambia, Zimbabwe	Randomized from 14 weeks: A: Zidovudine B: Zidovudine + lamivudine + lopinavir/ritonavir C: Tenofovir disoproxil fumarate + emtricitabine + lopinavir/ritonavir	A: Single-dose nevirapine (zidovudine-only group)	A: Tenofovir disoproxil fumarate + emtricitabine (6-14 d; zidovudine-only group) B: Zidovudine + lamivudine + lopinavir/ritonavir C: Tenofovir disoproxil fumarate + emtricitabine + lopinavir/ritonavir	3202 Live-born infants; mothers primarily black African; 92% breastfed; % screen-detected HIV during pregnancy: NR	A: 25/1386 (1.8%) B: 7/1385 (0.5%) C: 2/325 (0.6%) B + C vs A difference in percentage points, −1.3 (95% CI, −2.1 to −0.4)

Abbreviation: NR, not reported.

[a] Study was rated fair quality.

monotherapy or dual therapy, regardless of whether the antiretroviral regimen included a protease inhibitor.

One new open-label RCT conducted in Africa[9] and 21 new cohort studies (reported in 30 articles)[11-15,17-24,26,27,29-38,40-44] evaluated the

association between maternal exposure to ART and risk of preterm delivery, low birth weight, and other birth outcomes (eTable 4 in the Supplement). Sample sizes ranged from 183 to 13 124 (total n = 71 472). Eight studies were conducted in the United States, 7 in Canada or Europe, and the remainder in Africa or Latin America. One cohort study, the Antiretroviral Pregnancy Registry[12] (n = 22 360), is an international (69 countries) voluntary registry; 74% of data currently are from the United States. 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 or data analysts.

The fair-quality RCT (PROMISE [n = 3490])[9] found ART with zidovudine, lamivudine, and lopinavir/ritonavir associated with increased risk of preterm delivery (20.5% vs 13.1%, $P < .001$) and low birth weight (23.3% vs 12.0%, $P < .001$) vs zidovudine monotherapy. PROMISE also found that ART with tenofovir, emtricitabine, and lopinavir/ritonavir was associated with increased risk of low birth weight (16.9% vs 8.9%, $P = .004$) vs zidovudine monotherapy.[9] Tenofovir-containing ART was associated with increased risk of early infant death vs zidovudine-containing ART (4.4% vs 0.6%, $P < .001$) and increased risk of very preterm (before 34 weeks) delivery (6.0% vs 2.6%, $P = .04$), but there was no significant difference between tenofovir-containing ART vs zidovudine monotherapy in risk of early infant death (4.4% vs 3.2%, $P = .43$) or stillbirth.[9] Methodological limitations of the trial included open-label design and the addition of a third randomization group (tenofovir-containing ART) during the course of the trial (eTable 2 in the Supplement). In addition, there was an unexplained reduction in rate of neonatal death and stillbirth associated with zidovudine-containing ART after the addition of the tenofovir-containing ART group. Five cohort studies found no consistent association between any ART or tenofovir-containing ART and risk of stillbirth, with some studies showing decreased risk of stillbirth.[21,27,30,43,44]

Consistent with the prior USPSTF review, 1 new RCT[9] and 4 new cohort studies[19,37,40,43] found ART containing a boosted protease inhibitor associated with an increased risk of preterm birth vs treatment without a boosted protease inhibitor (n = 7584). However, 2 new cohort studies (n = 1140) found treatment with a protease inhibitor associated with a decreased risk of preterm delivery[19] or no significant difference in risk[17] when compared with no ART.

The prior review[5] found no consistent evidence of an association between maternal exposure to ART and increased risk of other adverse birth outcomes (eg, low birth weight, small for gestational age). New evidence identified for this update also found mixed evidence on these birth outcomes. Four new cohort studies[21,27,31,34] evaluated the association of ART with risk of low birth weight.

Overall Congenital Abnormalities

The 2012 USPSTF review found no association between perinatal exposure to ART and overall congenital abnormalities, based on 3 cohort studies (n = 13 396).[55,56,63] Five new cohort studies (n = 40 436),[12,18,20,36,41] including the Antiretroviral Pregnancy Registry,[12] evaluated the association between use of combination ART in pregnancy and risk of congenital anomalies (eTable 4 in the Supplement). All of the newer cohort studies included patients who received preferred[7] nucleoside reverse transcriptase inhibitors (abacavir, lamivudine, tenofovir, or emtricitabine) for use in pregnancy. 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.

Cardiovascular Congenital Anomalies

The 2012 USPSTF review included 1 cohort study[60] (n = 382) that found no significant association between in utero exposure to zidovudine and abnormalities in left ventricular structure or function, although another study[61] found an association between in utero ART and echocardiographic findings with unknown clinical significance in children up to age 2 years.

One subsequent RCT and 2 cohort studies (in 3 publications) also reported mixed results for the association between in utero ART exposure and adverse cardiovascular findings.[23,35,41] A US cohort study of HIV-uninfected children (n = 2580) found no statistically significant association between in utero exposure to currently recommended ART drugs and increased risk of cardiovascular defects (adjusted OR, 1.83 [95% CI, 0.96-3.49]).[41] Another study (n = 214 240) found no significant association between ART exposure during the first trimester on cardiovascular anomalies compared with no exposure (adjusted OR, 0.75 [95% CI, 0.31-1.85]).[13]

A French cohort study of 12 888 children 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, 1.5-3.2]).[35,36] A secondary analysis of 400 HIV-uninfected children exposed to ART in utero[23] found that at a median of 4 years of age, exposure to some antiretroviral medications, especially in the first trimester, was associated with echocardiographic abnormalities without significant cardiovascular compromise (left ventricular stress velocity index *z* scores in ART-exposed vs unexposed children, −0.22 [95% CI, −0.42 to −0.01]; $P = .04$; left ventricular posterior wall thickness *z* scores in ART-exposed vs unexposed children, 0.20 [95% CI, 0.03-0.37]; $P = .02$).

A nested RCT within a cohort study of combination ART (zidovudine, lamivudine, and ritonavir-boosted lopinavir) vs protease inhibitor monotherapy (ritonavir-boosted lopinavir alone) performed echocardiographic assessments at ages 1 month (n = 53) and 1 year (n = 42). There was no significant difference in echocardiographic parameters in boys, but in girls combination therapy was associated with higher left ventricular shortening fraction at 1 month (−3.61 [95% CI, −6.57 to −0.65], $P = .02$).[35]

Neurodevelopmental Outcomes in Children

The 2012 USPSTF review included 3 cohort studies (n = 4779) that found no significant association between in utero exposure to ART and long-term adverse effects on child growth and development.[54,58,68] Two new publications of a US cohort of HIV-exposed, uninfected children found no significant association between in utero ART exposure and lower scores on intelligence tests.[29,42] Exposure to tenofovir was associated with higher scores on the Wechsler Preschool and Primary Scale of Intelligence III (WPPSI-III) test than no exposure to tenofovir (WPPSI-III performance IQ scores, 100.8 vs 96.1; $P = .03$). Another publication from this study found in utero exposure to combination ART associated with less neurodevelopmental impairment vs no exposure (adjusted relative risk, 0.47 [95% CI, 0.27-0.83]).[42]

Table 3. Summary of Evidence

No. of Studies; No. of Participants; Study Design	Summary of Findings by Outcome	Consistency and Precision; Reporting Bias	Overall Risk of Bias/Quality	Other Limitations	Strength of Evidence	Applicability
KQ1: Benefits of Screening						
No studies	NA	NA	NA	NA	NA	NA
KQ2: Yield of Repeat HIV Screening at Different Intervals						
No studies	NA	NA	NA	NA	NA	NA
KQ3: Harms of Screening						
No studies	NA	NA	NA	NA	NA	NA
KQ4: Effectiveness of Currently Recommended ART Regimens						
2012 USPSTF review: 6 RCTs (n = 3534) and 8 cohort studies (n = 27 776) New: 1 RCT (n = 3490), 4 cohort studies (n = 14 344), 1 individual patient data analysis of 7 cohorts (n = 4459)	Prior review included 8 cohort studies that found full-course combination ART associated with rates of mother-to-child transmission of <1% to 2.4%, vs 9% to 22% with no ART Five new cohort studies found full-course combination ART associated with a risk of mother-to-child transmission of <1% to 2.8%; 1 African RCT reported a rate of mother-to-child transmission of 0.5%	Consistent; no imprecision No reporting bias detected	Moderate	Most evidence observational, with no RCT conducted in the United States or other high-income setting	High	Cohort studies conducted in high-income settings, but RCT was conducted in Africa Exact ART regimen not specified in most studies Variability in timing of ART initiation
KQ5: Harms of Currently Recommended ART Regimens						
Preterm birth 2012 USPSTF review: 1 RCT (n = 560), 4 cohort studies (n = 15 252) New: 1 RCT (n = 3490) and 17 cohort studies (n = 48 452)	Prior review included 1 RCT and 4 cohort studies that found increased preterm birth associated with ART and 1 RCT and 3 cohort studies that found increased risk of preterm birth associated with ART that included a PI One 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 preterm birth with ART; 1 RCT and 3 cohort studies found ART that included a boosted PI associated with increased risk of preterm birth	Inconsistent; no imprecision No reporting bias detected	Moderate	No US RCTs or trials from non-resource-poor countries	Low	Cohort studies conducted in all settings; RCTs conducted primarily in Africa Exact ART regimen not specified in most studies Variability in timing of ART initiation
Overall birth defects 2012 USPSTF review: 4 cohort studies (n = 21 113) New: 5 cohort studies (n = 27 409)	Prior review found no association between ART and birth defects Five new cohort studies found most currently recommended ART drugs not associated with increased risk of birth defects	Consistent; precise No reporting bias detected	Moderate	No RCTs	Moderate	Cohort studies conducted in high-resource settings Individual ART drugs specified
Low birth weight 2012 USPSTF review: 5 cohort studies (n = 17 976) New: 1 RCT (n = 3490) and 5 cohort studies (n = 11 213)	Prior evidence: no clear association between prenatal ART and low birth weight or intrauterine growth restriction One new RCT and 4 cohort studies found no clear association between ART and low birth weight	Consistent; imprecise No reporting bias detected	Moderate	No US RCTs or trials from non-resource-poor countries	Low	Cohort studies conducted in all settings; RCT was conducted in Africa Exact ART regimen not specified in most studies Variability in timing of ART initiation
Small for gestational age 2012 USPSTF review: 1 cohort study (n = 7635) New: 10 cohort studies (n = 37 670)	Nine new cohort studies found no clear association between ART and small for gestational age	Consistent; imprecise No reporting bias detected	Moderate	No US RCTs or trials from non-resource-poor countries	Low	Cohort studies conducted in all settings; RCT was conducted in Africa Exact ART regimen not specified in most studies Variability in timing of ART initiation

(continued)

Table 3. Summary of Evidence (continued)

No. of Studies; No. of Participants; Study Design	Summary of Findings by Outcome	Consistency and Precision; Reporting Bias	Overall Risk of Bias/Quality	Other Limitations	Strength of Evidence	Applicability
Stillbirth 2012 USPSTF review: 0 New: 6 cohort studies (n = 30 417)	Three new cohort studies found no clear association between ART and stillbirth Three new cohort studies found mixed results for treatment with tenofovir disoproxil fumarate/emtricitabine vs zidovudine/lamivudine	Consistent; imprecise No reporting bias detected	Moderate	No US RCTs or trials from non-resource-poor countries	Low	Cohort studies conducted in all settings; RCT was conducted in Africa Exact ART regimen not specified in most studies Variability in timing of ART initiation
Neonatal death 2012 USPSTF review: 0 New: 1 RCT (n = 3490) and 3 cohort studies (n = 7038)	One new RCT and 3 cohort studies found mixed results for neonatal death	Consistent; imprecise No reporting bias detected	Moderate	No US RCTs or trials from non-resource-poor countries	Low	Cohort studies conducted in all settings; RCT was conducted in Africa Exact ART regimen not specified in most studies Variability in timing of ART initiation
Infant cardiac harms 2012 USPSTF review: 2 cohort studies (n = 734) New: 3 cohort studies (n = 15 888)	Prior review included 1 cohort study that reported reduced left ventricular mass and increased left ventricular contractility at age 2 y with in utero ART exposure and 1 that found no association; no echocardiographic differences in children aged 2-5 y Three new cohort studies found mixed evidence for zidovudine in first trimester for increased congenital heart defects; mixed evidence for several ART drugs and echocardiographic changes but not clinical changes	Consistent; imprecise No reporting bias detected	Moderate	No RCTs; no studies of in utero-exposed, HIV-uninfected children beyond age 7 y	Low	Cohort studies conducted in high-resource settings Variability in timing of ART initiation
Infant neurodevelopmental harms 2012 USPSTF review: 3 cohort studies (n = 2590) New: SMARTT cohort (n = 3542)	Prior review found no association between in utero ART exposure and worse neurodevelopmental outcomes New evidence from SMARTT cohort found no association between in utero exposure to ART and long-term effects on child growth and development or on intelligence test scores; there was an association between in utero ART exposure and less neurodevelopmental impairment, compared with no exposure	Consistent; precise No reporting bias detected	Moderate	No RCT; drug regimens often not provided	Low	Cohort studies conducted in high-income settings Variability in timing of ART initiation
Maternal harms 2012 USPSTF review: 1 meta-analysis (n = 1391) and 3 cohort studies (n = 4117) New: 2 RCTs (n = 12 338)	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 because of adverse events	Inconsistent; precise No reporting bias detected	Moderate	No US RCTs or trials from non-resource-poor countries	Low	Cohort studies conducted in all settings; RCTs conducted in Africa Exact ART regimen not specified in most studies Variability in timing of ART initiation

Abbreviations: ART, antiretroviral therapy; KQ, key question; NA, not applicable; PI, protease inhibitor; RCT, randomized clinical trial; SMARTT, Surveillance Monitoring for ART Toxicities; USPSTF, US Preventive Services Task Force.

Maternal Harms

The 2012 USPSTF review included 3 studies (n = 4117) that found receipt of ART during pregnancy associated with increased risk of gestational diabetes (adjusted OR, 3.5 [95% CI, 1.2-10]) and anemia (adjusted OR, 1.6 [95% CI, 1.1-2.4]), compared with no ART.[62,66,67]

In the PROMISE trial (n = 3490; see KQ4 for study details),[9] 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* = .008). There was no increased risk in all-cause mortality, anemia, or diabetes among ART regimens.[80] There were few study withdrawals attributable to adverse events.

Discussion

As in previous USPSTF reviews,[6,81] there remains no direct evidence on effects of prenatal screening vs no screening on risk of mother-to-child HIV transmission or maternal or infant clinical outcomes, or the yield of repeat or alternative screening strategies. **Table 3** summarizes the other evidence reviewed in this update.

New evidence[16,25,26,39] confirms findings from the 2012 USPSTF review that 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% when started early in pregnancy.[26,39] New evidence on harms of ART was also largely consistent with the 2012 USPSTF review. Evidence from primarily observational studies found prenatal combination ART with a boosted protease inhibitor associated with increased risk of preterm delivery.[9,19,37,43] For other birth outcomes (low birth weight, small for gestational age, stillbirth, birth defects, neonatal death), results were mixed and depended on the specific antiretroviral drug or drug regimen given and timing of prenatal therapy. Preferred drug regimens in pregnancy are frequently revised as drugs are developed and safety data become available.

Limitations

This review had several limitations. First, inclusion was restricted to English-language articles, although no non–English language articles that would have met inclusion criteria were identified. Second, meta-analysis was not possible because of differences in study designs, populations, study setting, antiretroviral regimens evaluated, and outcomes. Because pooling was not performed, it was also not possible to formally assess for publication bias with graphical or statistical methods. Third, observational studies, which are more susceptible to bias and confounding than well-conducted RCTs, were included, although inclusion was restricted to observational studies that performed statistical adjustment for potential confounding. Fourth, RCTs of combination ART have only been conducted in Africa, which could reduce their applicability to US practice because of differences in the antiretroviral drugs evaluated, delayed initiation of ART, inclusion of women who breastfeed, and other factors. Fifth, most studies reported results for individual ART agents and classes rather than for ART regimens as a whole, making it difficult to apply findings to currently recommended regimens.

Conclusions

Combination ART was highly effective at reducing risk of mother-to-child HIV transmission. Use of certain ART regimens during pregnancy was associated with increased risk of harms that may be mitigated by selection of ART regimen. The 2012 review found that avoidance of breastfeeding and cesarean delivery in women with viremia also reduced risk of transmission and that prenatal screening accurately diagnosed HIV infection.

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Disclaimer: This evidence report is presented as a document in support of the accompanying USPSTF Recommendation Statement. It did not undergo additional peer review after submission to *JAMA*.

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