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Prenatal Screening for HIV: A Review of the Evidence for the U.S. Preventive Services Task Force

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Abstract

Background:

Each year in the United States, 6000 to 7000 women with HIV give birth. The management and outcomes of prenatal HIV infection have changed substantially since the U.S. Preventive Services Task Force issued recommendations in 1996.

Purpose:

To synthesize current evidence on risks and benefits of prenatal screening for HIV infection.

Data Sources:

MEDLINE, the Cochrane Library, reference lists, and experts.

Study Selection:

Studies of screening, risk factor assessment, accuracy of testing, follow-up testing, and efficacy of interventions.

Data Extraction:

Data on settings, patients, interventions, and outcomes were abstracted for included studies; quality was graded according to criteria developed by the Task Force.

Data Synthesis:

No published studies directly link prenatal screening for HIV with clinical outcomes. In developed countries, the rate of mother-to-child transmission from untreated HIV-infected women is 14% to 25%. Targeted screening based on risk factors would miss a substantial proportion of infected women. “Opt-out” testing policies appear to increase uptake rates.

Standard HIV testing is highly (>99%) sensitive and specific, and initial studies of rapid HIV tests found that both types of testing had similar accuracy. Rapid testing can facilitate timely interventions in persons testing positive. Recommended interventions (combination antiretroviral regimens, elective cesarean section in selected patients, and avoidance of breastfeeding) are associated with transmission rates of 1% to 2% and appear acceptable to pregnant women.

Limitations:

Long-term safety data for antiretroviral agents are not yet available. Data are insufficient to accurately estimate the benefits of screening on long-term maternal disease progression or other clinical outcomes, such as horizontal transmission.

Conclusions:

Identification and treatment of asymptomatic HIV infection in pregnant women can greatly decrease mother-to-child transmission rates.

Women are the fastest-growing group of persons with new HIV diagnoses, accounting for 30% of new U.S. infections in 2001 (1, 2). An estimated 6000 to 7000 HIV-positive women give birth each year in the United States (3), and 280 to 370 HIV-infected infants were born in the United States annually between 1999 and 2001 (4). In 2000, 40% of HIV-infected infants were born to mothers not known to have HIV infection before delivery (5). As of 2003, about 5000 cumulative deaths from perinatally acquired AIDS had occurred in the United States (6).

Mother-to-child transmission of HIV infection can occur during pregnancy (antepartum), during labor and delivery (intrapartum), and after delivery (postnatal). In the absence of breastfeeding, antepartum transmission is thought to account for 25% to 40% of cases of mother-to-child transmission; the remaining cases occur during labor and delivery (7). Pregnancy and labor management techniques that minimize contact between infected maternal blood and the fetus can decrease the risk for transmission (8). Breastfeeding is thought to be the only important mode for postnatal transmission (4, 9) and accounts for about 44% of infant cases in settings with high breastfeeding rates (10). Higher maternal viral loads and lower CD4 cell counts are associated with an increased risk for transmission (11-15). In the United States, combination antiretroviral regimens, in conjunction with avoidance of breastfeeding and cesarean section before labor and before rupture of membranes (elective cesarean section) in selected women, are the standard of care to reduce mother-to-child transmission of HIV (16, 17).

To update its 1996 recommendations, the U.S. Preventive Services Task Force (USPSTF) commissioned a new systematic review of the risks and benefits of prenatal testing for anti-HIV antibodies in asymptomatic women (18).

Methods

The Figure summarizes the analytic framework and key questions for this review. Key question 1 addresses direct evidence on the effects of screening on clinical outcomes. The other key questions address the chain of evidence necessary to estimate the effects of screening on clinical outcomes if direct evidence is insufficient. Appendix A discusses the scope and the methods used for this review in more detail.

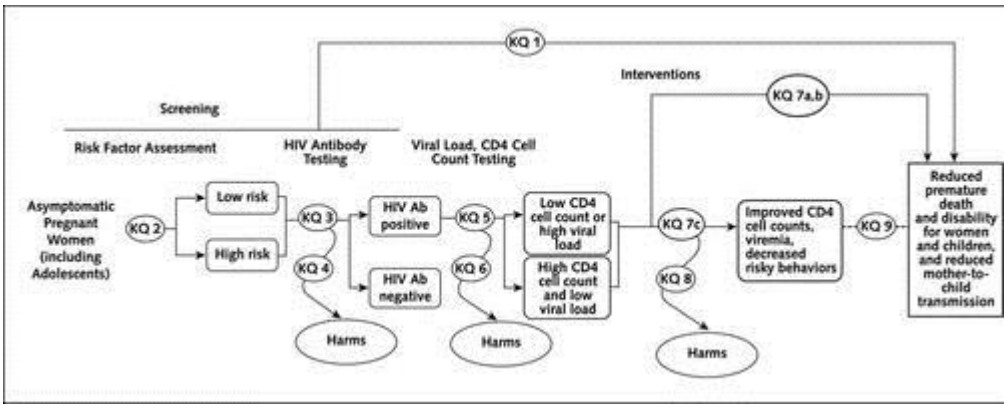

Figure. Screening for HIV—analytic framework for pregnant women.

Key question (*KQ*) 1: Does screening for HIV in pregnant women reduce mother-to-child transmission or premature death and disability? KQ 2: Can clinical or demographic characteristics (including specific settings) identify subgroups of asymptomatic pregnant women at increased risk for HIV infection compared to the general population of pregnant women? KQ 3: What are the test characteristics of HIV antibody (*HIV ab*) test strategies in pregnant women? KQ 4: What are the harms (including labeling and anxiety) associated with screening? Is screening acceptable to pregnant women? KQ 5: How many HIV-infected pregnant women who meet criteria for interventions receive them? KQ 6: What are the harms associated with the work-up for HIV infection in pregnant women? KQ 7: a) How effective are interventions (antiretroviral prophylaxis [to prevent mother-to-child transmission] or treatment [to improve maternal outcomes]; avoidance of breastfeeding, elective cesarean section [in selected patients], or other labor management practices; counseling on risky behaviors; immunizations; routine monitoring and follow-up; or prophylaxis against opportunistic infections) in reducing mother-to-child transmission rates or improving clinical outcomes (mortality, functional status, quality of life, symptoms, or opportunistic infections) in pregnant women with HIV infection? b) Does immediate antiretroviral treatment in HIV-infected pregnant women result in improvements in clinical outcomes compared to delayed treatment until the infected woman becomes symptomatic? c) How well do interventions reduce the rate of viremia, improve CD4 cell counts, or reduce risky behaviors? How does identification of HIV infection in pregnant women affect future reproductive choices? KQ 8: What are the harms (including adverse effects from in utero exposure) associated with antiretroviral drugs and elective cesarean section? KQ 9: Have improvements in intermediate outcomes (CD4 cell counts, viremia, or risky behaviors) in HIV-infected pregnant women been shown to improve clinical outcomes or reduce mother-to-child transmission? A separate report (19) reviews KQs 6, 7b, 9, and parts of 7a (counseling, immunizations, labor management practices other than elective cesarean section, routine monitoring and follow-up, and prophylaxis against opportunistic infections); 7c (effects on viral loads, CD4 counts, and risky behaviors); and 9.

Briefly, we identified relevant studies from MEDLINE (1983 through 30 June 2004) and the Cochrane Clinical Trials Registry (2004, issue 2), reference lists, hand searches of relevant journals, and suggestions from experts (Appendix B). We selected studies that provided evidence on the benefits and harms of screening, risk factor assessment, follow-up testing, interventions, and the acceptability of prenatal HIV testing. For interventions, we focused on studies of the safety and effectiveness of antiretroviral prophylaxis (17). We also reviewed studies on the safety and effectiveness of elective cesarean section (20) and avoidance of breastfeeding. A separate report (19) reviews other recommended interventions, such as vaccinations, prophylaxis against opportunistic infections, and routine monitoring and follow-up (7, 21-23).

We assessed the internal validity and relevance of included studies using predefined criteria developed by the USPSTF (Appendix C) (24). We rated the overall body of evidence for each key question using the system developed by the USPSTF.

We used the results of the evidence review to construct an outcomes table estimating the effects of one-time screening for HIV infection in hypothetical cohorts of pregnant women. We calculated numbers needed to screen (NNS) and treat (NNT) to prevent 1 case of mother-to-child transmission or to cause 1 complication from interventions. The point estimates and 95% CIs for NNS and NNT were based on Monte Carlo simulations.

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Data Synthesis

Does Screening for HIV in Pregnant Women Reduce Mother-to-Child Transmission or Premature Death and Disability?

No studies compare clinical outcomes from screening or not screening pregnant women for HIV. Although the number of infants with perinatally acquired HIV transmission has markedly declined in the United States, this reduction is probably due to a combination of increased prenatal screening and increased effectiveness and uptake of therapies (3, 7). No studies estimated the relative impact of these factors.

Can Clinical or Demographic Characteristics Identify Subgroups of Asymptomatic Pregnant Women at Increased Risk for HIV Infection Compared with the General Population of Pregnant Women?

Risk factors for HIV infection appear similar in pregnant and nonpregnant women and include risky sexual behaviors, injection drug use, and transfusion between 1978 and 1985 (22, 25). Heterosexual transmission has become the most common route of HIV infection among U.S. women (26).

The largest (n = 73 472) study of U.S. women at prenatal or obstetrics clinics found that 0.6% were HIV positive (27). Smaller U.S. studies of pregnant women have reported prevalence rates ranging from 0.13% to 5% (28-30). In the United States, HIV prevalence varies by region, and minority women are more likely to be infected (26).

Observational studies in the United States (all published before 1996) found that 8% to 57% of HIV-infected pregnant women had identifiable risk factors (31-35). Differences in the criteria used to define high-risk behaviors and varying stringency of risk factor assessment (31) could explain some of the variation in results. No study evaluated different targeted prenatal screening strategies to determine the proportion of infected women correctly identified.

In 1995, the U.S. Public Health Service (36) and the American Academy of Pediatrics (37) recommended prenatal counseling and voluntary HIV testing. No U.S. studies since 1995 evaluated the yield of targeted compared with universal screening. In a 7-state observational study, however, the proportion of HIV-infected women given a diagnosis before delivery increased from 70% to 80% between 1993 and 1996 (38). In the United Kingdom, 1 observational study found an increased incidence of known HIV seropositivity after the implementation of universal prenatal testing (39), but another found that 50% of seropositive women (identified by anonymous testing) remained undiagnosed (40).

What Are the Test Characteristics of HIV Antibody Test Strategies in Pregnant Women?

The use of enzyme immunoassay followed by confirmatory Western blot or immunofluorescent assay remains the standard method for diagnosing HIV-1 infection. This method is associated with a sensitivity and specificity greater than 99% (41, 42). False-positive diagnoses are rare, even in low-risk settings (43). The diagnostic accuracy of standard HIV testing is thought to be similar for pregnant and nonpregnant persons, although indeterminate results may occur slightly more frequently in pregnancy (44).

Rapid HIV antibody tests provide results in 10 to 30 minutes, compared with 1 to 2 weeks for standard testing (45). Patients should be notified of positive rapid test results before confirmation when doing so might benefit them, such as for women with unknown HIV status presenting in active labor (46). However, this could result in unnecessary exposure to antiretroviral therapy if the rapid test result is a false positive.

Three good-quality (47-49) and 4 fair-quality (50-53) studies evaluated the diagnostic accuracy of rapid HIV testing during pregnancy using standard testing as the reference standard. The only study to evaluate a rapid HIV test currently in use in the United States was a good-quality prospective study of the OraQuick Advance test (OraSure Technologies, Inc., Bethlehem, Pennsylvania) on blood samples from 5744 women (prevalence, 0.59%) who presented in labor (47). The sensitivity was 100% (95% CI, 90% to 100%), the specificity was 99.9% (CI, 99.78% to 99.98%), the positive predictive value was 90% (CI, 75% to 97%), and the negative predictive value was 100%. In studies of nonpregnant persons, the sensitivities of currently available rapid HIV tests ranged from 96% to 100%, and the specificities were all greater than 99% (54-58). No studies have

compared the diagnostic accuracy of prenatal HIV testing using home-based sampling kits or noninvasive (urine or oral) specimens with the accuracy of standard testing as the reference standard. Although 1 Indian study found a lower sensitivity with the OraQuick test on saliva than on plasma (75.0% vs. 86.4%), it did not use standard enzyme immunoassay plus Western blot as the reference standard, and local conditions may have affected saliva specimens (59).

No clinical studies have evaluated the yield of repeated prenatal HIV testing, which would depend in part on the incidence of HIV infections during pregnancy (60).

What Are the Harms Associated with Screening?

In a recent U.S. study of rapid HIV testing during labor, 4 of 4849 women had a false-positive rapid test result and briefly received antiretroviral prophylaxis before negative confirmatory results (47). Other evidence on the frequency and harms from false-positive diagnoses in pregnant women is anecdotal (61) but could include elective pregnancy termination based on incorrect test results, anxiety, discrimination, or altered partner relationships. False-negative and true-negative test results could encourage continued risky behaviors. Data on rates and consequences (such as anxiety) of indeterminate tests in pregnant women are lacking (62).

True-positive tests can also result in anxiety, depression, social stigmatization, changes in relationships with sexual partners, and discrimination (37, 63). Most studies of harms from testing have been performed in nonpregnant populations. One small (n = 40) study of prenatal testing among U.S. women found statistically significantly higher anxiety and depression scores among HIV-positive women compared with matched uninfected controls, as well as a nonsignificant trend toward increased partnership dissolution (64). A recent good-quality cohort study found that receiving a prenatal HIV diagnosis did not increase risk for intimate partner violence (65). Data are insufficient to estimate suicide risk associated with prenatal diagnosis of HIV (66).

Is Screening Acceptable to Pregnant Women?

Because mandatory testing of pregnant women could result in avoidance of prenatal care (67), there remains general consensus that HIV testing should be voluntary and performed after obtaining informed consent (22). A good-quality systematic review found that acceptance rates for HIV testing among more than 174 000 pregnant women in 25 studies published through 1995 ranged from 23% to 100% (68). More recent data from 16 U.S. states and 5 Canadian provinces found a similar range of testing uptake (25% to 98%) (69). A large U.S. survey found that overall prenatal testing rates increased from 41% in 1995 (when recommendations for universal prenatal HIV counseling and testing were issued) to 60% in 1998 (70).

Several factors appear to influence testing rates. One randomized trial found that prenatal testing rates were significantly higher in women offered HIV testing (35%) than in those not receiving a direct offer (6%) (71). Strong provider endorsement of testing also increased uptake (72, 73). Testing rates were generally higher in states and Canadian

provinces that used an "opt-out" policy (in which women are informed that an HIV test is a standard part of prenatal care and that they may decline it) than in those that used an "opt-in" policy (in which women are required to specifically consent to an HIV test)—71% to 98% compared with 25% to 83% (69). Noncomparative studies also reported high (85% to 88%) uptake rates with opt-out testing (71, 74, 75). We identified no studies evaluating the effect of anonymous versus name-based testing on prenatal screening rates, or the effects of streamlined or targeted counseling.

Newer screening methods, such as home sample collection, rapid tests, and noninvasive sampling, could increase rates of prenatal HIV testing (45). A recent U.S. observational study of pregnant women in labor found that 84% accepted rapid testing (47). We identified no studies evaluating the effect of oral sampling or home-based collection on acceptance of prenatal HIV testing.

How Many HIV-Infected Pregnant Women Who Meet Criteria for Interventions Receive Them?

In a large U.S. study, 91% (3690 of 4062) of tested pregnant women received their results (76). One randomized trial from Africa found that rapid testing increased notification rates compared with standard testing (96% vs. 65%) among pregnant HIV-positive women (77).

Several recent U.S. studies found that HIV-infected women used antiretroviral drugs in more than 90% of pregnancies, with a trend toward increased combination regimen use (58% to 80% from 1998 to 1999) (78-82). In 1 U.S. study of rapid testing, all HIV-infected pregnant women (n = 18) who were given a diagnosis during active labor in time to administer intrapartum zidovudine received the drug (47). In recent large U.S. observational studies, scheduled cesarean section rates for HIV-positive women ranged from 37% to 50% (78, 81, 83).

How Effective Are Interventions in Reducing Mother-to-Child Transmission Rates or Improving Clinical Outcomes in Pregnant Women with HIV Infection?

Antiretroviral Agents

In the absence of antiretroviral prophylaxis, the risk for mother-to-child transmission of HIV is 14% to 25% in developed countries and 13% to 42% in countries with high rates of breastfeeding (84). The landmark Pediatric AIDS Clinical Trials Group protocol 076 (PACTG 076) study found that a 3-phase maternal and infant zidovudine regimen in nonbreastfeeding women starting at 14 to 34 weeks' gestation (median, 26 weeks' gestation) through 6 weeks postpartum decreased the risk for transmission from about 25% to 8% compared with placebo (85). A good-quality systematic review of zidovudine monotherapy clinical trials found that any zidovudine regimen (including shorter courses and in breastfeeding women) significantly reduced the risk for mother-to-child transmission compared with placebo (odds ratio, 0.46 [CI, 0.35 to 0.60]) (86). Zidovudine was also associated with decreased risk for infant death within the first year (odds ratio, 0.57 [CI, 0.38 to 0.85]) and stillbirth (relative risk, 0.31 [CI, 0.11 to 0.90]).

In the United States, treatment of seropositive pregnant women has evolved to multidrug regimens, including highly active antiretroviral therapy, or HAART (≥3 drugs, usually from ≥2 classes) (17). The only randomized trial of full-course combination regimens (nelfinavir or nevirapine plus zidovudine) during pregnancy was discontinued early because of a high rate of treatment-limiting or serious side effects in the nevirapine group (87). Four large U.S. or European cohort studies (3 good-quality, 1 fair-quality) evaluated the relative effectiveness of antiviral regimens with 2 or more drugs versus 1-drug regimens or no antiretroviral agents in nonbreastfeeding women (Table 1) (82, 88-90). In all 4 studies, regimens with more antiretroviral drugs were superior to regimens with fewer antiretroviral drugs for preventing mother-to-child transmission (Table 2). The only study that specifically compared the effectiveness of HAART regimens with that of no antiretroviral agents reported an adjusted odds ratio of 0.13 (CI, 0.06 to 0.27) for prevention of mother-to-child transmission (89).

Table 1. Large Observational Cohort Studies of the Effect of Combination Antiretroviral Regimens on Risk for Mother-to Child Transmission of HIV Infection

Table 1. **Large Observational Cohort Studies of the Effect of Combination Antiretroviral Regimens on Risk for Mother-to Child Transmission of HIV Infection***

Study, Year (Reference)	Location	Interventions	Mother–Infant Pairs Enrolled, *n*	Mother-to-Child Transmission Rate, %	Cesarean Section Rate, %	Breastfeeding Rate, %	Internal Validity Rating
Italian Register for HIV Infection in Children, 2002 (88)	Italy	No antiretroviral agents	2440	18.5	97.7 overall, 69.9 elective	2.8 overall	Good
		ZDV alone	743	248			
		≥2 antiretroviral agents	6.1	1.6			
Women and Infants' Transmission Study, 2002 (82)	United States	No antiretroviral agents	396	20.0	20.1	No infant was breastfed	Good
		ZDV alone	710	10.4	24.0		
		2 antiretroviral agents	186	3.8	33.8		
		HAART	250	1.2	44.4†		
European Collaborative Study, 2005 (89)	Europe	No antiretroviral agents	157	11.5	16 emergency; 61 elective overall	2 overall (through 2000)	Good
		HAART	918	1.2			
French Perinatal Study, 2001 (90)	France	ZDV alone (historical control group)	858	6.8	16 elective	0.3	Fair (used historical controls)
		Lamivudine + ZDV from 32nd wk of pregnancy and to the child for 6 wk	437	1.6	22 elective	0.5	

* HAART = highly active antiretroviral therapy; ZDV = zidovudine.
† $P = 0.0001$.

Table 2. Number of Drugs in Full-Course Antiretroviral Regimens and Risk for Mother-to-Child Transmission of HIV Infection

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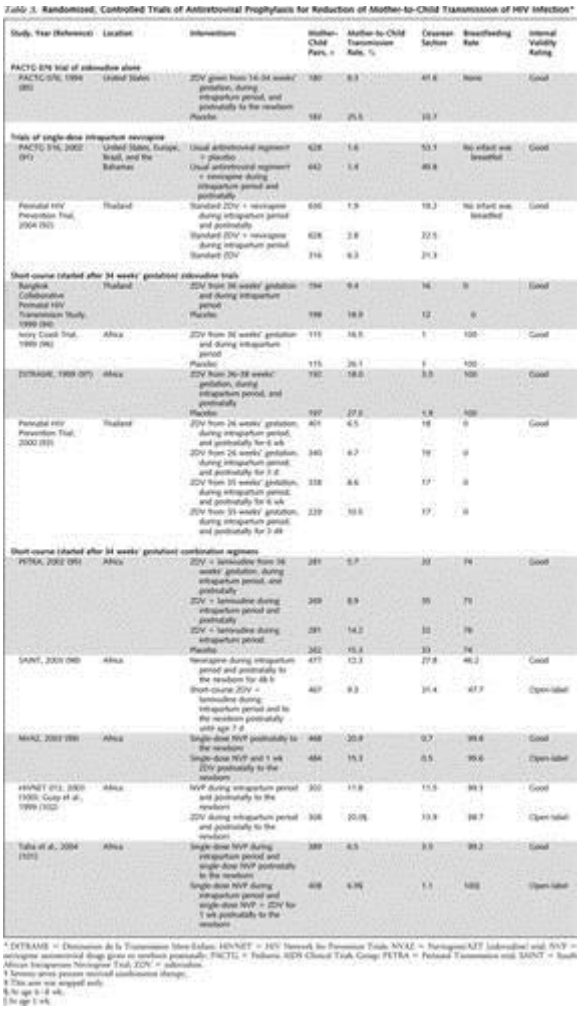
Antiretroviral Regimen Comparison	Risk for Mother-to-Child Transmission	Study, Year (Reference)	Type of Study	Confounders Included in Logistic Models (Observational Studies)
Zidovudine alone (complete PACTG 076) vs. placebo	Relative risk, 0.32 (95% CI, 0.18–0.59)	Connor et al., 1994 (85)	Randomized, controlled trial	Not applicable
Zidovudine alone vs. placebo	Adjusted OR, 0.12 (95% CI, 0.05–0.30)	Italian Register for HIV Infection in Children, 2002 (88)	Prospective cohort study	Mode of delivery, method of feeding, infant sex, gestational age, mother's category of exposure to HIV, whether mother was from an HIV-1–endemic area, maternal clinical condition at delivery, parity, and twinship
1 or 2 antiretroviral agents vs. no antiretroviral agents	Adjusted OR, 0.49 (95% CI, 0.31–0.76)	European Collaborative Study, 2005 (89)	Prospective cohort study	Mode of delivery, prematurity, and maternal CD4 cell count
≥2 antiretroviral agents vs. no antiretroviral agents	Adjusted OR, 0.07 (95% CI, 0.02–0.23)	Italian Register for HIV Infection in Children, 2002 (88)	Prospective cohort study	Listed elsewhere in table
HAART vs. no antiretroviral agents	Adjusted OR, 0.13 (95% CI, 0.06–0.27)	European Collaborative Study, 2005 (89)	Prospective cohort study	Listed elsewhere in table
≥2 antiretroviral agents vs. zidovudine alone	Adjusted OR, 0.22 (95% CI, 0.10–0.59)	Mandelbrot et al., 2001 (90)	Cohort study with historical controls	Mode of delivery, presence of advanced maternal HIV-1 disease, and previous antiretroviral therapy
≥2 antiretroviral agents vs. zidovudine alone	Adjusted OR, 0.30 (95% CI, 0.09–1.02)	Cooper et al., 2002 (82)	Prospective cohort study	Number of pregnancy visits during therapy, maternal CD4 cell count, duration of membrane rupture, mode of delivery, infant birthweight, neonatal antiretroviral therapy, maternal plasma HIV-1 RNA level at delivery, hard drug use during pregnancy, Centers for Disease Control and Prevention class C events, infant gestational age, and antiretroviral use before pregnancy
HAART vs. zidovudine alone	Adjusted OR, 0.27 (95% CI, 0.08–0.94)	Cooper et al., 2002 (82)	Prospective cohort study	Listed elsewhere in table

* HAART = highly active antiretroviral therapy; OR = odds ratio; PACTG = Pediatric AIDS Clinical Trials Group.

The addition of single-dose intrapartum (maternal) and postpartum (infant) nevirapine to antiretroviral regimens initiated before 34 weeks' gestation was evaluated in 2 good-quality randomized, controlled trials performed in nonbreastfeeding settings (Table 3) (91, 92). One trial found that the addition of single doses of intrapartum and postpartum nevirapine to a slightly abbreviated (28 weeks' gestation to 1 week postpartum) course of zidovudine alone reduced mother-to-child transmission from 6.3% to 1.9% (92). In contrast, an earlier trial found that the addition of single-dose intrapartum and postpartum nevirapine therapy to primarily (77%) combination antiretroviral regimens did not further decrease already low transmission rates (1.4% to 1.6%) (91).

Table 3. Randomized, Controlled Trials of Antiretroviral Prophylaxis for Reduction of Mother-to-Child Transmission of HIV Infection



Shorter courses of antiretroviral prophylaxis started after 34 weeks' gestation have primarily been evaluated for use in resource-poor countries. Although shorter courses may be associated with an increased risk for antiretroviral drug resistance, they may be considered for use in U.S. women who did not receive a diagnosis early enough to receive a full course. In general, shorter courses were less effective than full courses, although they did reduce transmission rates (Table 3) (93-97). Even very abbreviated regimens administered during labor were associated with some reduction in transmission (98-102). Neonatal prophylaxis alone was less effective than regimens that included maternal prophylaxis (99).

A recent good-quality prospective observational study of HIV-positive women who were given a diagnosis through rapid testing during labor and were treated with zidovudine with or without nevirapine found a transmission rate of 9% (3 of 32) (47).

No studies have evaluated clinical progression, death, quality of life, or horizontal transmission associated with different antiretroviral regimens for HIV-infected women identified during pregnancy.

Avoidance of Breastfeeding

Two meta-analyses of observational studies found that breastfeeding was associated with an overall increased rate of mother-to-child transmission of HIV of 14% to 16% (9, 103). In another recent meta-analysis (104), the rate of late (beyond 4 weeks postnatal) transmission was 9.3% after 36 months.

No randomized, controlled trials have evaluated the rate of mother-to-child transmission associated with breastfeeding in the United States or in women receiving antiretroviral therapy. One large, good-quality prospective Italian cohort study of 3770 children found that breastfeeding significantly increased transmission rates after adjustment for other factors, including antiretroviral use (adjusted odds ratio, 10.20 [CI, 2.73 to 38.11]) (88). An African trial among women not receiving antiretroviral agents found that breastfeeding was associated with a probability of mother-to-child transmission of 36.7% (CI, 29.4% to 44.0%) at 24 months compared with 20.5% (CI, 14.0% to 27.0%) with formula feeding, and a mortality rate of 24.4% (CI, 18.2% to 30.7%) compared with 20.0% (CI, 14.4% to 25.6%), respectively (105).

Elective Cesarean Section

One good-quality European cohort study evaluated the effectiveness of elective cesarean section in the HAART era (89). The rate of mother-to-child transmission was 1.6% in women delivering by elective cesarean compared with 6.5% in those delivering vaginally, with an odds ratio (adjusted for antiretroviral therapy, prematurity, and maternal CD4 cell count and viral load) of 0.33 (CI, 0.11 to 0.94). In the subgroup of women receiving HAART, the odds ratio was 0.64 (CI, 0.08 to 5.37) for elective cesarean compared with vaginal delivery, and in the subgroup with undetectable viremia, the odds ratio was 0.07 (CI, 0.02 to 0.31) for elective cesarean compared with vaginal or emergency cesarean delivery.

Other studies of elective cesarean section were conducted before the widespread use of combination antiretroviral regimens. One good-quality European randomized clinical trial found a mother-to-child transmission rate of 10.5% in women randomly assigned to vaginal delivery compared with 1.8% in those randomly assigned to elective cesarean section (P = 0.009) (106). Among 119 babies delivered to women who received zidovudine and underwent cesarean section, the rate of HIV infection was 0.8%. A good-quality meta-analysis of 15 prospective cohort studies found a 50% reduction in the likelihood of mother-to-child transmission with elective cesarean section compared with other modes of delivery (odds ratio, 0.43 [CI, 0.33 to 0.56]) (107). The benefits of elective cesarean section were additive with zidovudine exposure; the likelihood of transmission was reduced by approximately 87% with both interventions compared with nonelective cesarean section or vaginal delivery and no antiretroviral agents (adjusted odds ratio, 0.13 [CI, 0.09 to 0.19]). A meta-analysis of 7 prospective cohort studies (108) found that cesarean section (elective or nonelective) was associated with a lower risk for transmission in women with viral loads less than 1000 copies/mL; however, the overall transmission rate was low (3.6%) and was reduced by antiretroviral agents alone to about 1%.

How Does Identification of HIV Infection in Pregnant Women Affect Future Reproductive Choices?

Knowledge of HIV status could affect future reproductive choices such as contraceptive use, subsequent pregnancy, sterilization, or abortion. In 2 studies, HIV seropositivity was associated with a lower rate of pregnancy (109), or a trend toward a lower rate (110), than in uninfected women, but another study found an increasing rate of pregnancy among HIV-infected women (111). One U.S. study found that 27% of HIV-infected women chose tubal ligation compared with 15% of uninfected controls, and oral contraceptive use was less likely in seropositive women (110). Two other noncomparative U.S. studies reported rates of tubal ligation among HIV-infected women of 24% and 27% (38, 112). An African study found that single-session postpartum counseling did not appear to influence decisions on condom use or reproductive behavior (113). In 2 U.S. studies, pregnancy termination rates did not differ between HIV-infected and uninfected women (64, 114).

What Are the Harms Associated with Antiretroviral Drugs and Elective Cesarean Section?

Maternal Harms from Antiretroviral Drugs

Antiretroviral exposure during pregnancy is associated with significant short-term nonobstetric adverse events, but these often resolve after therapy with the offending drug or drug combination is discontinued; in addition, effective alternatives are usually available (17). Guidelines reviewing adverse events associated with specific antiretroviral drugs, classes, and combinations in pregnancy are regularly updated, and specific antiretroviral drugs and combinations associated with serious complications are not recommended or should be used only with caution (17, 115).

One good-quality meta-analysis found that zidovudine exposure during pregnancy did not cause any deaths or long-term maternal adverse events (86). The largest (n = 1407) prospective study of combination antiretroviral therapy found that gestational diabetes was the only associated adverse event; it occurred most frequently with regimens that included a protease inhibitor (116). Although continuous nevirapine therapy is associated with serious hepatic and cutaneous adverse events (87, 117-119), no laboratory or clinical evidence of liver toxicity with single-dose intrapartum nevirapine has been reported (92, 98, 100).

Another potential harm of antiretroviral therapy initiated during pregnancy is the development of drug resistance, particularly in women who receive single-dose nevirapine or regimens that do not fully suppress viral replication (120). No studies have evaluated the effects of limited exposure to combination antiretroviral agents during pregnancy on long-term clinical outcomes (121). Studies examining the effect of limited exposure to zidovudine alone did not find a negative impact on disease progression or response to later therapy (122-124). The only study that evaluated the impact of nevirapine resistance mutations (125-127) after single-dose intrapartum exposure found that women who received intrapartum nevirapine were less likely to have complete virologic suppression after 6 months of postpartum treatment with a nevirapine-containing regimen (49% vs. 68%) (128). CD4 cell count response and degree of weight loss, however, did not significantly differ between groups receiving and not receiving intrapartum nevirapine, although longer follow-up is needed.

Maternal Harms from Elective Cesarean Section

Cesarean section is associated with an increased risk for maternal complications compared with vaginal delivery, although elective surgery is safer than an emergency cesarean section (129). Women with HIV infection are at higher risk for cesarean section–related complications than uninfected women (130, 131).

One randomized, controlled trial found that the rate of postpartum fever was 1.1% (2 of 183) in HIV-infected women delivering vaginally and 6.7% (15 of 225) in those having a planned cesarean section, but no serious complications occurred in either group (106). The largest (n = 1186) prospective observational study found that elective cesarean section was associated with increased rates of postpartum fever (14.3%; relative risk, 4.16 [CI, 1.99 to 8.70]), hemorrhage (7.1%; relative risk, 1.58 [CI, 0.58 to 4.26]), endometritis (5.4%; relative risk, 2.57 [CI, 0.78 to 8.51]), urinary tract infection (5.4%; relative risk, 3.64 [CI, 1.06 to 12.54]), and any postpartum morbidity (26.7%; relative risk, 2.62 [CI, 1.61, 4.20]) compared with vaginal delivery (132). A smaller prospective study reported similar findings (133).

Harms Associated with In Utero Exposure to Antiretroviral Drugs

The U.S. Food and Drug Administration classifies the in utero safety of antiretroviral drugs, but for most drugs data are limited or are based on animal studies (134). One good-quality U.S. meta-analysis of 5 prospective cohort studies and 1 good-quality, large European prospective cohort study found no significant differences in the rates of congenital anomalies, neonatal conditions, or low birthweight between infants exposed to any combination of antiretroviral agents and unexposed infants (15, 135). Data on the association between combination antiretroviral regimens and increased rates of premature delivery are mixed. A recent large prospective cohort study found an increased rate of premature birth associated with combination regimens (adjusted odds ratio, 4.14 with a protease inhibitor and 2.66 without a protease inhibitor compared with no treatment) (136), but an earlier meta-analysis found no increased risk (135).

Although molecular and biochemical evidence of mitochondrial dysfunction has been reported in infants exposed in utero to antiretroviral agents (137-139), the clinical impact of such dysfunction is unclear (140, 141). Observational studies have found no clear evidence of clinical symptoms (15, 137, 142) or deaths (143-145) due to mitochondrial dysfunction among uninfected infants exposed to HAART in utero.

Long-term (4 to 6 years) studies of adverse events from in utero antiretroviral exposure are available only for zidovudine. One good-quality meta-analysis and 1 good-quality prospective cohort study found no increase in long-term clinical adverse events or changes in growth or development in exposed infants up to 4 years of age (86, 146), and no tumors or deaths from cancer after 6 years (147).

Estimates of Numbers Needed To Screen

Table 4 estimates the outcomes of one-time prenatal screening before the third trimester in 3 hypothetical cohorts (0.15% prevalence, 0.30% prevalence, and 5% prevalence [high risk]) of 10 000 nonbreastfeeding pregnant women, using the highest-quality and most applicable evidence (see Appendix Table, for base-case assumptions). In settings with a maternal prevalence of 0.15%, the estimated NNS to prevent 1 case of mother-to-child transmission ranged from 3500 to 12 170; in a cohort of high-risk patients, the NNS ranged from 105 to 365. There were insufficient data with which to estimate the long-term benefits of screening on maternal disease progression or other clinical outcomes (such as horizontal transmission).

Table 4. Outcomes of Screening for HIV Infection in 3 Hypothetical Cohorts of 10 000 Asymptomatic Pregnant Women

Table 4. **Outcomes of Screening for HIV Infection in 3 Hypothetical Cohorts of 10 000 Asymptomatic Pregnant Women***

Results	Prevalence, 0.15%	Prevalence, 0.30%	Prevalence, 5% (High Risk)
Women screened, *n*	10 000	10 000	10 000
Women identified as HIV-positive, *n*	15	30	500
Women receiving test results, *n*	13.6	27.3	455
Cases of mother-to-child transmission expected without interventions among women receiving test results, *n*	1.9–3.4	3.8–6.8	64–114
Women receiving combination antiretroviral prophylaxis, *n*	8.2–12.3	16.4–24.6	273–410
Women undergoing elective cesarean section, *n*	5.0–6.8	10.1–13.6	168–228
Cases of mother-to-child transmission prevented with highly active antiretroviral therapy, *n*	1.0–2.9	2.0–5.7	33–95
Cases of mother-to-child transmission prevented with elective cesarean section, *n*	0.8–2.8	1.6–5.7	27–95
NNS_b to prevent 1 case of mother-to-child transmission of HIV	3500–12 170	1750–6090	105–365
NNT_b with antiretroviral prophylaxis to prevent 1 case of mother-to-child transmission of HIV	5.3–18.1	5.3–18.1	5.3–18.1
Postpartum complications caused by elective cesarean section, *n*	0.3–2.3	0.6–4.7	11–78
NNS_H to cause 1 postpartum complication from elective cesarean section	4280–31 640	2140–15 820	130–940
NNT_H to cause 1 postpartum complication from elective cesarean section	6.0 (95% CI, 2.9–15.9)	6.0 (95% CI, 2.9–15.9)	6.0 (95% CI, 2.9–15.9)

* NNS_b = number needed to screen for benefit; NNS_H = number needed to screen for harm; NNT_b = number needed to treat for benefit; NNT_H = number needed to screen for harm.

Discussion

No published studies directly link prenatal screening for HIV with clinical outcomes. Other evidence obtained for the systematic review (summarized in Table 5) indicates that testing is extremely accurate, uptake of recommended interventions is high, and perinatal transmission can be reduced from 14% to 25% without interventions to 1% to 2%.

Table 5. Summary of Findings of Systematic Evidence Review

Appendix Table. Base-Case Assumptions for Outcomes Table (Table 4) of Counseling and One-Time Screening for HIV Infection in Pregnant Women

Appendix Table. **Base-Case Assumptions for Outcomes Table (Table 4) of Counseling and One-Time Screening for HIV Infection in Pregnant Women***

Base-Case Assumptions	Values Used in Outcomes Table	Source, Year (Reference)
Prevalence of HIV infection	Low-risk: 0.15% High-risk: 5%	CDC, 2002 (26) Lindegren et al., 1999 (3) Fehrs et al., 1988 (28) Barbacci et al., 1990 (29)
Accuracy of standard testing	≥99%	CDC, 1990 (42) CDC, 1989 (41)
Proportion of patients receiving test results	91%	Joo et al., 2000 (76)
Proportion of patients receiving antiretroviral prophylaxis	60%–90%	CDC, 2004 (78) CDC, 2002 (79) Wade et al., 2004 (80) Fiscus et al., 2002 (81) Cooper et al., 2002 (82)
Proportion of patients receiving elective cesarean section	37%–50%	Fiscus et al., 2002 (81) Dominguez et al., 2003 (83) CDC, 2004 (78)
Rate of mother-to-child transmission in absence of interventions	14%–25%	Working Group on Mother-to-Child Transmission of HIV, 1995 (84)
Relative risk for mother-to-child-transmission with highly active antiretroviral therapy compared with no antiretroviral therapy	0.13 (95% CI, 0.06–0.27)	European Collaborative Study, 2005 (89)
Rate of postpartum complications in HIV-infected women delivering vaginally	10.3% (95% CI, 8.39%–12.6%)	Read et al., 2001 (132)
Relative risk for postpartum complications from elective cesarean section	2.62% (95% CI, 1.61%–4.20%)	Read et al., 2001 (132)

* CDC = Centers for Disease Control and Prevention.

Targeted prenatal screening for HIV according to risk factor assessment would miss a substantial proportion of infected women who report no risk factors. Although universal screening in low-prevalence settings could lead to thousands of women being tested for each case of perinatal HIV prevented, a high priority is placed on prevention of perinatal HIV infection in the United States. Several U.S. expert panels recommend universal prenatal HIV screening (7, 148, 149).

Despite the tremendous efficacy of interventions for preventing mother-to-child transmission of HIV infection, uptake of HIV screening and use of antiretroviral therapy remain incomplete in the United States. Data indicate that use of "opt-out" testing policies could improve uptake rates, and use of rapid tests could facilitate timely interventions for persons testing positive.

The case for universal prenatal screening would be further strengthened by data showing improvements in long-term maternal or other outcomes, such as horizontal transmission, future reproductive choices, or risky behaviors. Other important areas requiring additional study include clinical trials to identify optimal combination antiretroviral regimens, methods to improve uptake of screening and recommended interventions, and methods to improve access to screening. In addition, further studies to determine the risk for potential harms from prenatal screening, such as intimate partner violence and methods to minimize those risks, are needed. Additional studies assessing long-term maternal outcomes and effects of brief, interrupted, or less intensive antiretroviral regimens on future response to HAART and long-term maternal and infant risks from antiretroviral exposure will also help further clarify risks and benefits of interventions.

Perinatal HIV infection is a largely preventable disease. Despite major reductions in the incidence of perinatal HIV infection in the United States since the early 1990s, more thorough uptake of prenatal testing and use of recommended interventions could reduce the incidence further.

Appendix A. Methods

Scope of Evidence Synthesis

The analytic framework in the Figure shows the target populations, interventions, and intermediate and health outcome measures we examined. The analytic framework was developed in consultation with the USPSTF and was refined after review by 7 content experts. We included all pregnant women regardless of age. Our review considered the standard screening strategy for HIV-1 infection to be an office-based venipuncture with a repeatedly reactive serum anti-HIV enzyme-linked immunosorbent assay, followed by confirmatory Western blot or immunofluorescent assay for positive test results. The other major screening method that we considered was the use of rapid testing in women with unknown HIV status who presented to labor and delivery units. We also considered data on the use of home-based collection methods and tests using noninvasive samples such as saliva or urine in pregnant women. Testing of viral load and CD4 cell counts was considered the standard work-up to determine the stage of infection in seropositive patients.

For treatment of HIV infection in pregnant women, we evaluated recommended antiretroviral prophylaxis (to prevent mother-to-child transmission) and treatment (to improve maternal outcomes), avoidance of breastfeeding, elective cesarean section in women with viral loads greater than 1000 copies/mL, immunizations, prophylaxis against opportunistic infections, counseling to reduce risky behaviors, and routine monitoring and follow-up. A separate review (19) reports results for the latter 4 interventions. We did not include interventions not shown to be effective or not recommended in current guidelines for antiretroviral-naive pregnant women in the United States, such as hydroxyurea, HIV immune globulin, vitamin supplementation, routine resistance testing, and specific antiretroviral agents (such as efavirenz in the first trimester or the oral liquid formulation of amprenavir) or combinations (such as stavudine plus didanosine) (17, 20) that are no longer recommended. The major clinical outcome of interest in this review was mother-to-child transmission of HIV. We also reviewed data on the risk for clinical progression and death in HIV-positive women whose infection is diagnosed during pregnancy. Adverse outcomes of interventions in both mothers and infants were reviewed, with emphasis on severe or intolerable events. We were particularly interested in evidence on long-term maternal and child risks from antiretroviral exposure during pregnancy. Although antiretroviral exposure is associated with significant short-term side effects, many patients can be switched to effective alternative regimens, and intolerable or serious side effects are incorporated into intention-to-treat analyses of clinical outcomes (150). Intermediate outcomes were loss of detectable viremia, improvement in CD4 cell counts, and changes in risky behaviors. We also reviewed harms from screening, work-up, and treatment. Although the potential for the development of antiretroviral resistance is an important consideration in deciding which antiretroviral regimen to use during pregnancy, we primarily focused on reviewing the effects of resistance on long-term clinical outcomes (125, 126, 151, 152).

Methods

Literature Search and Strategy

We searched the topic of HIV in the MEDLINE and Cochrane Library databases. Most searches were done from 1983 (the year that HIV was characterized) through 30 June 2004. For antiretroviral regimens, electronic searches were performed from 1998, the year that HAART was first recommended in U.S. guidelines (153); these searches were supplemented by an electronic search for systematic reviews of antiretroviral regimens from 1983. We performed a total of 13 searches covering the areas of risk factor assessment, screening tests, work-up, and interventions. Because a preliminary search found that search strategies limited by terms for pregnancy excluded relevant studies, we performed general searches on topics of interest and performed supplemental searches specifically related to pregnancy. Appendix B presents detailed electronic search strategies and results. Periodic hand searching of relevant medical journals, reviews of reference lists, and peer review suggestions supplemented the electronic searches. Abstracts were not included in systematic searches, but major abstracts cited in reference lists or presented at recent conferences were included. We also obtained reviews, policy statements, and other papers with contextual value.

Inclusion and Exclusion Criteria

We selected papers for full review if they were about HIV infection in pregnant women, were relevant to key questions, and met inclusion criteria. For all key questions, articles were limited to those that evaluated the general population of pregnant women with HIV infection. Although the population of interest was pregnant women with unsuspected HIV infection who would be identified by screening, we included studies of pregnant women with a broad spectrum of chronic HIV disease to get a picture of the benefits and adverse effects of screening and treatment in patients with different degrees of immune deficiency. We included studies performed in the United States, Australia, Canada, and western Europe (areas in which the epidemiology and management of chronic HIV infection are similar). When important studies for a specific key question had been performed only in other countries, we also included these studies. We excluded studies of nonhuman subjects and those without original data. We considered non–English-language papers if they reported on clinical trials and if an abstract was available in English. We searched for relevant systematic reviews for all key questions. A separate report lists additional key question–specific inclusion criteria (19).

Data Extraction and Synthesis

We used predefined criteria from the USPSTF to assess the internal validity of included systematic reviews, trials, and observational studies, which we rated as "good," fair," or "poor." We also rated the applicability of each study to the population that would be identified by screening. The rating system was developed by the USPSTF and is described in detail elsewhere (24) and summarized in Appendix C. For included trials and systematic reviews, we abstracted information about setting, patients, interventions, and outcomes. We rated the overall body of evidence for each key question using the system developed by the USPSTF.

Methods for Outcomes Table

Table 4 estimates the outcomes from screening before the third trimester in 3 hypothetical cohorts (0.15% prevalence, 0.30% prevalence, and 5% prevalence [high risk]) of 10 000 pregnant women. We did not include areas in this table in which no reliable data were available to estimate the clinical magnitude of benefit or harm, such as harms from screening (anxiety, labeling, violence, suicide, partnership dissolution) or decreased horizontal transmission from counseling. We focused on the benefits of combination antiretroviral regimens for reducing mother-to-child transmission because this intervention has the greatest impact on transmission rates and because there were insufficient or limited data on other clinical outcomes (such as long-term maternal outcomes or horizontal transmission rates) or benefits associated with other interventions (such as prophylaxis against opportunistic infections, counseling on risky behaviors, immunizations, routine monitoring and follow-up, or additional benefits from elective cesarean section in women receiving HAART). For harms of interventions, we focused on the rate of postpartum complications from elective cesarean section because studies have not shown clear evidence of long-term infant adverse events from antiretroviral exposure and because there are insufficient data on the risks for antiretroviral agents on long-term maternal outcomes. We calculated NNS and NNT to prevent 1 case of mother-to-child transmission and to

cause 1 postpartum complication (postpartum fever, endometritis, hemorrhage, or urinary tract infection) from elective cesarean section.

To estimate the benefits of counseling and screening for HIV infection in pregnant women, we made several assumptions. We used recent estimates of rates of combination antiretroviral therapy (60% to 90%) (78-82) and elective cesarean section (37% to 50%) by HIV-infected pregnant women in the United States (78, 81, 83). Our estimates of the effectiveness of interventions were conservative and did not include potential benefits from elective cesarean section or avoidance of breastfeeding in women receiving combination therapy (15, 88). We also did not include potential benefits from screening on long-term maternal outcomes.

Calculations of NNS and NNT were based on estimates from different sources in the literature (Appendix Table). The indicated range of estimates and variation associated with estimates were incorporated in the calculations and are reflected by the ranges in the calculated NNS and NNT. We used Monte Carlo simulations to incorporate variation associated with the estimates. The sampling distributions of the estimates used in the simulations were either the underlying distribution on which the calculation of 95% CI was based or one that best approximated the point estimate and CI. For example, if the estimate was a rate or proportion, the logit of the rate or proportion was sampled assuming an approximately normal distribution and was then transformed back to its original scale. For relative risk, we assumed that the log of relative risk was approximately normally distributed. The log of the relative risk was sampled from the normal distribution and then transformed back to relative risk. In each iteration of the Monte Carlo simulation, 1 sample of each proportion, relative risk, or other estimate was drawn to calculate the NNS_B and NNT_B. The point estimates and 95% CIs of NNS and NNT were based on 1 000 000 samples. A simple program using R statistical language was written to perform simulations and calculate summary statistics (154).

Appendix B. Search Strategies

Immunization—Database: MEDLINE (1996 to Present)

1. exp hiv infections/ or exp hiv/

2. exp Viral Hepatitis Vaccines/

3. exp Influenza Vaccine/

4. exp Bacterial Vaccines/

5. 2 or 3 or 4

6. 1 and 5

7. exp IMMUNIZATION/

8. exp Immunization Programs/

9. 7 or 8

10. exp HEPATITIS/

11. exp INFLUENZA/

12. exp PNEUMONIA/

13. 10 or 11 or 12

14. 1 and 9 and 13

15. 6 or 14

16. exp Evaluation Studies/

17. exp Epidemiologic Studies/

18. Comparative Study/

19. 16 or 17 or 18

20. 15 and 19

21. limit 15 to (clinical trial or guideline or meta-analysis or multicenter study or practice guideline)

22. 20 or 21

23. limit 22 to (human and english language)

24. from 23 keep 1-206

Prophylaxis—Database: MEDLINE (1996 to Present)

1. exp AIDS-Related Opportunistic Infections/pc [Prevention & Control]

2. prophyla$.mp.

3. exp HIV Infections/co [Complications]

4. exp AIDS-Related Opportunistic Infections/

5. 2 and (3 or 4)

6. 1 or 5

7. limit 6 to (human and english language and (clinical trial or guideline or meta-analysis or multicenter study or practice guideline))

8. from 7 keep 1-396

Counseling—Database: MEDLINE (1996 to Present)

1. exp HIV Infections/ or exp HIV/

2. exp COUNSELING/

3. 1 and 2

4. exp impulsive behavior/ or risk reduction behavior/ or risk-taking/

5. 1 and 4

6. 3 or 5

7. exp Evaluation Studies/

8. Comparative Study/

9. exp Epidemiologic Studies/

10. 7 or 8 or 9

11. 6 and 10

12. limit 6 to (clinical trial or guideline or meta-analysis or multicenter study or practice guideline)

13. 11 or 12

14. limit 13 to (human and english language)

15. from 14 keep 1-1272

Risk Factors—Database: MEDLINE (1996 to Present)

1. exp RISK/

2. exp HIV Infections/mo, ep, eh, et, tm, pc [Mortality, Epidemiology, Ethnology, Etiology, Transmission, Prevention & Control]

3. 1 and 2

4. limit 3 to (human and english language and (clinical trial or guideline or meta-analysis or multicenter study or practice guideline))

5. exp HIV/

6. 1 and 5

7. limit 6 to (human and english language and (clinical trial or guideline or meta-analysis or multicenter study or practice guideline))

8. 4 or 7

9. exp Evaluation Studies/

10. Comparative Study/

11. exp Epidemiologic Studies/

12. 9 or 10 or 11

13. (3 or 6) and 12

14. limit 13 to (human and english language)

15. from 8 keep 1-573

Screening—Database: MEDLINE (1996 to Present)

1. exp AIDS Serodiagnosis/

2. exp HIV SERONEGATIVITY/ or exp HIV ANTIGENS/ or exp HIV/ or exp HIV SEROPREVALENCE/ or exp HIV SEROPOSITIVITY/ or exp HIV ANTIBODIES/

3. exp Mass Screening/

4. 2 and 3

5. 1 or 4

6. exp “Sensitivity and Specificity”/

7. 5 and 6

8. ae.fs.

9. exp stress, psychological/

10. Life Change Events/

11. exp prejudice/ or prejudic$.mp.

12. 8 or 9 or 10 or 11

13. 5 and 12

14. exp diagnostic errors/

15. 5 and 14

16. 7 or 13 or 15

17. exp Evaluation Studies/

18. Comparative Study/

19. exp longitudinal studies/

20. 17 or 18 or 19

21. 16 and 20

22. limit 16 to (clinical trial or guideline or meta-analysis or multicenter study or practice guideline or review)

23. 22 or 21

24. limit 23 to (human and english language)

25. limit 23 to (human and abstracts)

26. 24 or 25

27. from 26 keep 1-247

Antiviral Drug—Database: MEDLINE (1998 to Present)

1. exp HIV Infections/dt [Drug Therapy]

2. exp HIV/de [Drug Effects]

3. 1 or 2

4. exp Reverse Transcriptase Inhibitors/ad, tu

5. exp HIV Protease Inhibitors/ad, tu

6. exp antihiv agents/ad, tu

7. 4 or 5 or 6

8. 3 and 7

9. limit 8 to (human and english language and (clinical trial or guideline or meta-analysis or multicenter study or practice guideline))

10. exp Reverse Transcriptase Inhibitors/ae, ct, to, po

11. exp HIV Protease Inhibitors/ae, ct, to, po

12. exp antihiv agents/ae, ct, to, to

13. 10 or 11 or 12

14. 3 and 13

15. limit 14 to (human and english language and (clinical trial or guideline or meta-analysis or multicenter study or practice guideline))

16. 14 and exp epidemiologic studies/

17. 14 and (exp evaluation studies/ or exp comparative study/)

18. 16 or 17

19. limit 18 to (human and english language)

20. 15 or 19

21. limit 9 to yr = 1998-2003

22. from 21 keep 1-1157

Adverse Effects—Database: MEDLINE (1998 to Present)

1. exp HIV Infections/dt [Drug Therapy]

2. exp HIV/de [Drug Effects]

3. 1 or 2

4. exp Reverse Transcriptase Inhibitors/ad, tu

5. exp HIV Protease Inhibitors/ad, tu

6. exp antihiv agents/ad, tu

7. 4 or 5 or 6

8. 3 and 7

9. limit 8 to (human and english language and (clinical trial or guideline or meta-analysis or multicenter study or practice guideline))

10. exp Reverse Transcriptase Inhibitors/ae, ct, to, po

11. exp HIV Protease Inhibitors/ae, ct, to, po

12. exp antihiv agents/ae, ct, to, to

13. 10 or 11 or 12

14. 3 and 13

15. limit 14 to (human and english language and (clinical trial or guideline or meta-analysis or multicenter study or practice guideline))

16. 14 and exp epidemiologic studies/

17. 14 and (exp evaluation studies/ or exp comparative study/)

18. 16 or 17

19. limit 18 to (human and english language)

20. 15 or 19

21. limit 9 to yr = 1998-2003

22. from 21 keep 1-1157

23. limit 20 to yr = 1998-2003

24. from 23 keep 1-732

25. from 24 keep 1-732

Work-up—Database: MEDLINE (1998 to Present)

1. exp HIV/

2. viral load.mp. or Viral Load/

3. VIREMIA/

4. exp HIV Infections/

5. 1 or 4

6. 2 or 3

7. 5 and 6

8. (exp leukocyte count/ and cd4.mp.) or exp cd4 lymphocyte count/

9. exp "pathologic conditions, signs and symptoms"/ or disease progression/

10. 7 and 8 and 9

11. exp "sensitivity and specificity"/

12. 10 and 11

13. exp epidemiologic studies/

14. 10 and 13

15. limit 10 to (human and english language and (clinical trial or guideline or meta-analysis or multicenter study or practice guideline))

16. limit 14 to (human and english language)

17. 15 or 16

18. from 17 keep 1-232

Maternal—Database: MEDLINE (1996 to Present)

1. exp HIV/ or exp HIV INFECTIONS/

2. exp Anti-HIV Agents/ad, ae, po, ct, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Contraindications, Therapeutic Use, Toxicity]

3. exp Reverse Transcriptase Inhibitors/ad, ae, po, ct, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Contraindications, Therapeutic Use, Toxicity]

4. exp HIV Protease Inhibitors/ad, ae, po, tu, ct, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Contraindications, Toxicity]

5. 1 and (2 or 3 or 4)

6. exp Disease Transmission, Vertical/

7. exp HIV Infections/tm

8. pregnancy complications/ or exp pregnancy complications, infectious/

9. exp Pregnancy/

10. 6 or 7

11. 8 or 9

12. 10 and 11

13. 5 and 12

14. limit 13 to (human and english language and (clinical trial or guideline or meta-analysis or multicenter study or practice guideline))

15. exp Evaluation Studies/

16. Comparative Study/

17. exp Epidemiologic Studies/

18. 15 or 16 or 17

19. 13 and 18

20. limit 19 to (human and english language)

21. 14 or 20

22. from 21 keep 1-373

Cesarean—Database: MEDLINE (1996 to Present)

1. exp HIV/ or exp HIV INFECTIONS/

2. exp Anti-HIV Agents/ad, ae, po, ct, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Contraindications, Therapeutic Use, Toxicity]

3. exp Reverse Transcriptase Inhibitors/ad, ae, po, ct, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Contraindications, Therapeutic Use, Toxicity]

4. exp HIV Protease Inhibitors/ad, ae, po, tu, ct, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Contraindications, Toxicity]

5. exp cesarean section/

6. 1 and (2 or 3 or 4 or 5)

7. exp Disease Transmission, Vertical/

8. exp HIV Infections/tm

9. pregnancy complications/ or exp pregnancy complications, infectious/

10. exp Pregnancy/

11. 7 or 8

12. 9 or 10

13. 11 and 12

14. 6 and 13

15. limit 14 to (human and english language and (clinical trial or guideline or meta-analysis or multicenter study or practice guideline))

16. exp Evaluation Studies/

17. Comparative Study/

18. exp Epidemiologic Studies/

19. 16 or 17 or 18

20. 14 and 19

21. limit 20 to (human and english language)

22. 15 or 21

Cost of Screening—Database: MEDLINE (1996 to Present)

1. exp HIV Infections/

2. exp HIV/

3. 1 or 2

4. exp "Costs and Cost Analysis"/

5. 3 and 4

6. Comparative Study/

7. exp Evaluation Studies/

8. exp epidemiologic study characteristics/

9. 5 and (6 or 7 or 8)

10. limit 9 to (human and english language)

11. exp Mass Screening/

12. 9 and 11

13. 5 and 11

14. limit 13 to (human and english language)

15. ec.fs.

16. 3 and 15

17. 16 and 11

18. limit 17 to (human and english language)

19. 14 or 18

20. from 19 keep 1-179

Systematic Reviews—Database: PubMed

1. hiv/de [mh] OR hiv infections/dt [mh]

2. anti hiv agents[pa] OR reverse transcriptase inhibitors[pa] OR hiv protease inhibitors [pa]

3. #1 OR #2

4. evaluation studies[mh] OR epidemiologic studies[mh] OR comparative study [mh]

5. #3 AND #4

6. tu[sh] OR ad[sh] OR ae[sh] OR to[sh] OR po[sh] OR ct[sh]

7. #5 AND #6

8. #7 AND systematic [sb]

9. #8 AND Limits: Publication Date from 1989 to 1997, English, Human

Note: Systematic [sb] represents the following strategy as taken from the Clinical Queries search help page within PubMed.

((systematic review$ OR systematic literature review$ OR meta-analysis.pt. OR meta-analysis.ti. OR meta-analysis.ti. OR meta-analyses.ti. OR evidence-based medicine OR (evidence-based AND (guideline.tw. OR guidelines.tw. OR recommendations)) OR (evidenced-based AND (guideline.tw. OR guidelines.tw. OR recommendation$)) OR consensus development conference.pt. OR health planning guidelines OR guideline.pt. OR cochrane database syst rev OR acp journal club OR health technol assess OR evid rep technol assess summ OR evid based nurs OR evid based ment health OR clin evid) OR ((systematic.tw. OR systematically OR critical.tw. OR (study.tw. AND selection.tw.) OR (predetermined OR inclusion AND criteri$.tw.) OR exclusion criteri$ OR main outcome measures OR standard of care) AND (survey.tw. OR surveys.tw. OR overview$ OR review.tw. OR reviews OR search$ OR handsearch OR analysis.tw. OR critique.tw. OR appraisal OR (reduction AND risk AND (death OR recurrence))) AND (literature.tw. OR articles OR publications.tw. OR publication.tw. OR bibliography.tw. OR bibliographies OR published OR unpublished OR citation OR citations OR database OR internet.tw. OR textbooks.tw. OR references OR trials OR meta-analysis.mh. OR (clinical.tw. AND studies) OR treatment outcome)) NOT (case report.ti. OR case report.mh. OR editorial.ti. OR editorial.pt. OR letter.pt. OR newspaper article.pt.))

Appendix C. USPSTF Quality Rating Criteria

Diagnostic Accuracy Studies

Criteria

1. Screening test relevant, available for primary care, adequately described.

2. Credible reference standard, performed regardless of test results.

3. Reference standard interpreted independently of screening test.

4. Indeterminate results handled in a reasonable manner.

5. Spectrum of patients included in study.

6. Sample size.

7. Administration of reliable screening test.

Definition of Ratings Based on Above Criteria

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; assesses reliability of test; has few or handles indeterminate results in a reasonable manner; includes large number (>100) broad-spectrum patients with and without disease.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independently of screening test; has moderate sample size (50 to 100 participants), and includes a "medium" spectrum of patients.

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

Randomized, Controlled Trials and Cohort Studies

Criteria

1. Initial assembly of comparable groups: randomized, controlled trials—adequate randomization, including concealment and statement of whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts.

2. Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination).

3. Important differential loss to follow-up or overall high loss to follow-up.

4. Measurements: equal, reliable, and valid (includes masking of outcome assessment).

5. Clear definition of interventions.

6. Important outcomes considered.

7. Analysis: adjustment for potential confounders for cohort studies, or intention-to-treat analysis for randomized, controlled trials.

Definition of Ratings Based on Above Criteria

Good: Meets all criteria—comparable groups are assembled initially and maintained throughout the study (follow-up ≥80%), reliable and valid measurement instruments are used and applied equally to the groups, interventions are spelled out clearly, important outcomes are considered, and appropriate attention to confounders in analysis.

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

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

Case–Control Studies

Criteria

1. Accurate ascertainment of cases.

2. Nonbiased selection of case-patients and controls, with exclusion criteria applied equally to both.

3. Response rate.

4. Diagnostic testing procedures applied equally to each group.

5. Measurement of exposure accurate and applied equally to each group.

6. Appropriate attention to potential confounding variable.

Definition of Ratings Based on Above Criteria

Good: Appropriate ascertainment of cases and nonbiased selection of case-patients and controls, exclusion criteria applied equally to case-patients and controls, response rate of 80% or greater, diagnostic procedures and measurements accurate and applied equally to case-patients and controls, and appropriate attention to confounding variables.

Fair: Recent, relevant, without major apparent selection or diagnostic work-up bias but with response rate less than 80% or attention to some but not all important confounding variables.

Poor: Major selection or diagnostic work-up biases, response rates less than 50%, or inattention to confounding variables.