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

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Background: A 2005 U.S. Preventive Services Task Force (USPSTF) review found good evidence that HIV screening is accurate and that antiretroviral therapy (ART) for immunologically advanced disease is associated with substantial clinical benefits, but insufficient evidence to determine the effects on transmission or in less immunologically advanced disease.

Purpose: To update the 2005 USPSTF review on benefits and harms of HIV screening in adolescents and adults, focusing on research gaps identified in the prior review.

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

Study Selection: Randomized trials and observational studies that compared HIV screening strategies and reported clinical outcomes, evaluated the effects of starting ART at different CD4 cell count thresholds and long-term harms, or reported the effects of interventions on transmission risk.

Data Extraction: 2 authors abstracted and checked study details and quality using predefined criteria.

Data Synthesis: No study directly evaluated the effects on clinical outcomes of screening versus no screening for HIV infection. A randomized trial and a subgroup analysis from a randomized trial found that ART initiation at CD4 counts less than 0.250×10^9 cells/L was associated with a higher risk for death or AIDS-defining events than initiation at CD4 counts greater than 0.350×10^9 cells/L (hazard ratios, 1.7 [95% CI, 1.1 to 2.5] and 5.3 [CI, 1.3 to 9.6]). Large, fair-quality cohort studies also consistently found that ART initiation at CD4 counts of 0.350 to 0.500×10^9 cells/L was associated with lower risk for death or AIDS-defining events than delayed initiation. New evidence from good-quality cohorts with longer-term follow-up confirms a previously observed small increased risk for cardiovascular events associated with certain antiretrovirals. Strong evidence from 1 good-quality randomized trial and 7 observational studies found that ART was associated with a 10- to 20-fold reduction in risk for sexual transmission of HIV.

Limitations: Only English-language articles were included. Observational studies were included. Studies done in resource-poor or high-prevalence settings were included but might have limited applicability to general screening in the United States.

Conclusion: Previous studies have shown that HIV screening is accurate, targeted screening misses a substantial proportion of cases, and treatments are effective in patients with advanced immunodeficiency. New evidence indicates that ART reduces risk for AIDS-defining events and death in persons with less advanced immunodeficiency and reduces sexual transmission of HIV.

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In 2008, an estimated 1.2 million persons in the United States were living with HIV, and approximately 1 in 5 were unaware of their status (1–3). Incidence of HIV in the United States is approximately 50 000 cases per year (1, 4), with an estimated 20 000 such cases believed to be due to transmission from persons who are unaware that they are infected (5, 6). Screening for HIV antibodies can detect infection in asymptomatic patients, who might benefit from interventions to reduce risk for AIDS-related clinical events and transmission.

In 2005, the U.S. Preventive Services Task Force (USPSTF) recommended screening all adolescents and adults at increased risk (defined as persons who reported HIV risk factors or were evaluated in settings with an HIV infection prevalence >1%) (7) on the basis of an earlier evidence review (8–10) that found a high yield from screening these patients, good evidence that HIV screening tests are accurate (sensitivity and specificity each >99%), and good evidence that treating HIV infection at immunologically advanced stages of disease (defined as CD4 counts $<0.200 \times 10^9$ cells/L) with antiretroviral therapy (ART) markedly reduces risk for AIDS-related clinical events and death. Although the USPSTF found that ART was associated with short-term adverse events and an increased risk for long-term cardiovascular events, it determined that benefits substantially outweighed harms.

The USPSTF made no recommendation for or against screening for HIV in adolescents and adults who were not at increased risk for HIV infection (7). Because of the lower prevalence of HIV infection in such persons, it determined that the benefits of screening would be smaller than in higher-risk populations. The USPSTF found insufficient evidence to estimate benefits from screening persons at less immunologically advanced stages of disease (CD4

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counts $>0.200 \times 10^9$ cells/L) or on the effects of screening and subsequent interventions on HIV transmission.

In 2006, the Centers for Disease Control and Prevention (CDC) issued its revised guideline (11) recommending routine voluntary HIV screening of all persons aged 13 to 64 years, unless the prevalence of undiagnosed HIV infection was less than 0.1%. A key reason for this recommendation was evidence showing that 20% to 26% of patients with HIV infection report no risk factors (12), suggesting that risk-based screening strategies miss an important proportion of infected persons. Other reasons for the differences between recommendations include that the CDC placed greater weight on studies showing reductions in self-reported risky behaviors after HIV diagnosis, accepted modeling studies to estimate effects of HIV diagnosis on transmission risk, and placed greater weight on modeling studies that showed acceptable incremental cost-effectiveness ratios for screening versus no screening in low-prevalence populations (7).

This report updates the previous USPSTF review on HIV screening in nonpregnant adolescents and adults. It focuses on key research gaps identified in the earlier review with the potential greatest effect on assessment of benefits and harms associated with screening in persons not known to be at higher risk, including effects of screening, counseling, and ART use on HIV transmission risk; effectiveness of ART for HIV-infected persons with CD4 counts greater than 0.200×10^9 cells/L, and long-term harms of ART. The full report (13) provides detailed methods and data for the review, including search strategies and evidence tables with quality ratings of individual studies. Additional key questions about various screening strategies, the effects of knowledge of HIV-positive status and use of ART on risky behaviors, and associations between viremia or risky behaviors and HIV transmission are reviewed in the full report (13) but are not presented here.

Methods

Scope of the Review

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

What are the benefits of universal or targeted HIV screening versus no screening in asymptomatic, nonpregnant adolescents and adults on disease transmission, morbidity, mortality, and quality of life?

What is the yield (number of new diagnoses) of HIV screening at different intervals in nonpregnant adolescents and adults?

How effective is ART for reducing transmission of HIV in nonpregnant adolescents and adults with chronic HIV infection?

How effective is behavioral counseling for reducing transmission of HIV in nonpregnant adolescents and adults with chronic HIV infection?

In asymptomatic, nonpregnant adolescents and adults with chronic HIV infection, what are the effects of initiating ART at different CD4 cell count or viral load thresholds on morbidity, mortality, and quality of life?

What are the longer-term harms associated with ART for nonpregnant adolescents and adults with chronic HIV infection?

We defined "universal" testing to mean routine testing of all persons aged 13 to 64 years, unless the prevalence of HIV infection has been documented to be less than 0.1% (11) and "targeted" screening to mean routine screening of persons who have risk factors or are in high-prevalence (>1%) settings (7).

Data Sources and Searches

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

Study Selection

At least 2 reviewers independently evaluated each study to determine inclusion eligibility. Papers were selected for full review if they were about HIV screening or treatments in nonpregnant adolescents and adults, were relevant to a key question, and met the predefined inclusion criteria (**Appendix Table 1**, available at www.annals.org). For treatment interventions, we focused on ART and counseling to reduce transmission risk. Outcomes were mortality, AIDS-related events, HIV transmission risk, and long-term (defined as ≥2 years after initiation of treatment) cardiovascular harms associated with ART. We included randomized, controlled trials and cohort studies for all key questions. We also included systematic reviews published since 2010 that met all predefined quality criteria (14).

Data Abstraction and Quality Rating

One investigator abstracted details about the study design, patient population, setting, screening method, interventions, analysis, follow-up, and results. A second investigator reviewed data abstraction for accuracy. Two investigators independently applied criteria developed by the USPSTF (15) to rate the quality of each study as good, fair, or poor. Discrepancies were resolved by consensus.

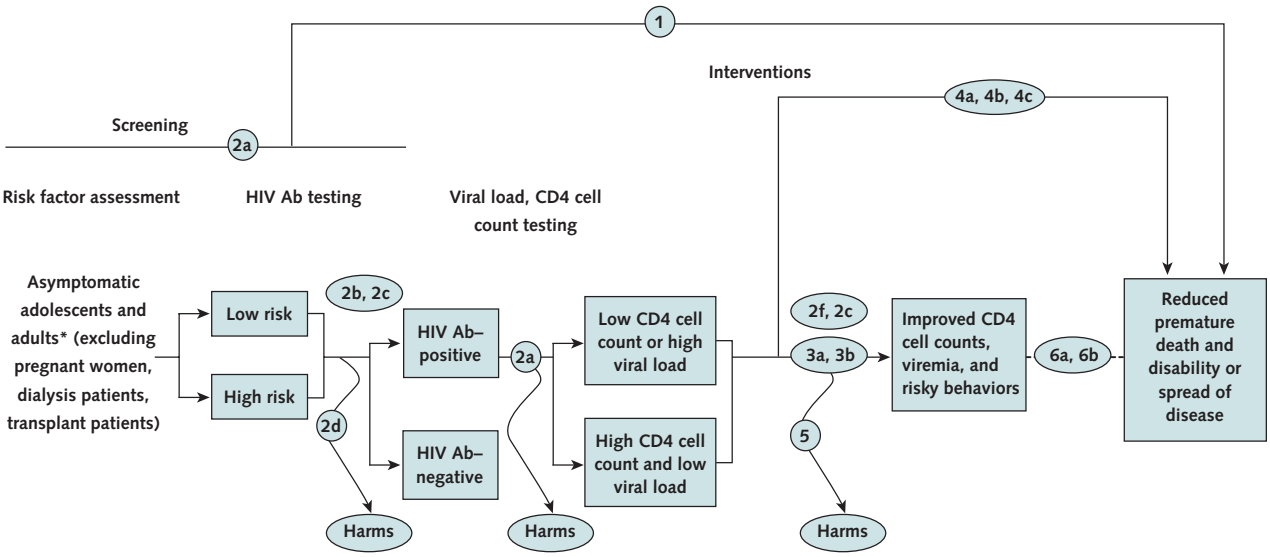
Data Synthesis

We assessed the aggregate internal validity (quality) of the body of evidence for each key question as good, fair, or poor by using methods developed by the USPSTF, on the basis of the number, quality, and size of studies; consistency of results among studies; and directness of evidence (15). Meta-analysis was not attempted, although we reported meta-analyses from published systematic reviews that met our quality criteria.

Role of the Funding Source

This research was funded by the Agency for Healthcare Research and Quality (AHRQ) under a contract to

Figure. **Analytic framework and key questions for screening for HIV in nonpregnant adolescents and adults.**



Key Questions:

1. What are the benefits of universal or targeted HIV screening versus no screening in asymptomatic, nonpregnant adolescents and adults on disease transmission, morbidity, mortality, and quality of life?

2a. What is the yield (number of new diagnoses) of HIV screening at different intervals in nonpregnant adolescents and adults?

*2b. What are the effects of universal versus targeted HIV screening on testing acceptability and uptake in nonpregnant adolescents and adults?

*2c. What is the effect or opt-out versus opt-in testing or different pre- or posttest HIV counseling methods on screening uptake or rates of follow-up and linkage to care in nonpregnant adolescents and adults?

*2d. What are the adverse effects (including false-positive results and anxiety) of rapid versus standard HIV testing in nonpregnant adolescents and adults not known to be at higher risk?

*2e. What are the effects of universal versus targeted HIV screening on CD4 cell counts at the time of diagnosis?

*2f. What are the effects of universal versus targeted HIV screening on rates of follow-up and linkage to care in nonpregnant adolescents and adults who screen positive?

*3a. To what extent does knowledge of HIV-positive status affect behaviors associated with increased risk for HIV transmission in nonpregnant adolescent and adults?

*3b. To what extent does use of antiretroviral therapy affect behaviors associated with increased risk for HIV transmission in nonpregnant adolescents and adults?

4a. How effective is antiretroviral therapy for reducing transmission of HIV in nonpregnant adolescents and adults with chronic HIV infection?

4b. How effective is behavioral counseling for reducing transmission of HIV in nonpregnant adolescents and adults with chronic HIV infection?

4c. In asymptomatic, nonpregnant adolescents and adults with chronic HIV infection, what are the effects of initiating antiretroviral therapy at different CD4 cell count or viral load thresholds on morbidity, mortality, and quality of life?

5. What are the longer-term harms associated with antiretroviral therapy for nonpregnant adolescents and adults with chronic HIV infection?

*6a. To what extent are improvements in viremia associated with reductions in HIV transmission rates in nonpregnant adolescents and adults?

*6b. To what extent are improvements in risky behaviors associated with reductions in HIV transmission rates in nonpregnant adolescents and adults?

HIV Ab = HIV antibody.

* Selected key questions have been omitted from this article. Details on these key questions are available in the full report (13).

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

RESULTS

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

Clinical Benefits of Universal or Targeted Screening

No randomized trial or observational study compared clinical outcomes between adults and adolescents screened and not screened for HIV infection.

Yield of HIV Screening at Different Intervals

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

Effectiveness of ART for Reducing HIV Transmission

A good-quality systematic review (16) evaluated the association between use of ART and risk for HIV transmission from HIV-positive persons to uninfected sexual partners. It included 1 good-quality randomized, controlled trial (17) and 7 observational studies (18–24) (**Appendix Table 2**, available at www.annals.org).

The randomized, controlled trial (HIV Prevention Trials Network study 052) compared early ART initiation (started at enrollment) with delayed therapy (after CD4 count decreased to $<0.250 \times 10^9$ cells/L or onset of symptoms) in HIV-infected patients with baseline CD4 counts of 0.350 to 0.550×10^9 cells/L and an HIV-negative partner (17). Fifty-four percent of the 1763 couples were from Africa, with the remainder from Brazil, India, Thailand, and the United States. Ninety-seven percent of couples were heterosexual, and 94% were married. All couples received condoms and counseling. The trial was designed to follow patients for 5 years but was terminated early after meeting prespecified criteria for efficacy in interim analyses. At a median follow-up of 1.7 years, risk for seroconversion in HIV-negative partners was much lower in the early-therapy group than in the delayed-therapy group (0.3 vs. 2.2 per 100 person-years; hazard ratio [HR], 0.11 [95% CI, 0.04 to 0.32]). When restricted to cases that were genomically linked to the HIV-infected patient enrolled in the trial, the HR was 0.04 (CI, 0.01 to 0.27).

Results of the 7 observational studies (18–24) included in the systematic review (16) were consistent with the randomized trial (17). Sample sizes ranged from 93 to 3408 couples, with typical follow-up between 1 and 3 years (range, 3 months to 9 years). All were cohort studies of HIV-serodiscordant, heterosexual couples from Africa, Italy, Spain, Brazil, or China. Six studies (18–22, 24) were rated fair-quality and the seventh (23) was a conference abstract. Three studies (19, 21, 24) adjusted for possible confounding variables, such as age, sex, condom use, or frequency of sexual intercourse.

Six (18–23) of the 7 observational studies reported that persons receiving ART had a lower risk for HIV transmission than untreated persons, for a pooled HR of 0.34 (CI, 0.13 to 0.92; $I^2 = 73\%$) (16). Exclusion of 1 study with inadequate person-time data (24) and 1 older study that included persons treated with monotherapy (21) resulted in a pooled HR of 0.16 (CI, 0.07 to 0.35) and eliminated statistical heterogeneity ($I^2 = 0\%$). The treatment effect was also more pronounced when the analysis was restricted to couples in which the HIV-infected person had a CD4 count less than 0.200×10^9 cells/L (pooled HR, 0.06 [CI, 0.01 to 0.54]) (18–20, 22).

Effectiveness of Behavioral Counseling for Reducing Transmission

The previous USPSTF review (8–10) found no randomized trials or controlled observational studies on the effects of counseling HIV-positive persons about risky behaviors on HIV transmission risk.

There remains little direct evidence on the effects of testing and counseling about risky behaviors on HIV transmission. Two studies on effects of counseling regarding sexual behaviors in HIV serodiscordant couples (25, 26) were not designed to assess effects on transmission rates and were severely underpowered (5 new HIV diagnoses were observed in each study). No study estimated the effects of counseling HIV-positive persons about injection drug use behaviors on transmission rates.

Effectiveness of Initiating ART at Different CD4 Cell Count Thresholds on Clinical Outcomes

The previous USPSTF review included good-quality randomized, controlled trials (27–29) and observational studies (30–37) that consistently found a lower risk for AIDS events and death with ART than with placebo or less-intensive regimens in patients with CD4 counts less than 0.200×10^9 cells/L. Evidence showing benefits of starting ART at higher CD4 cell counts was limited. Although a Swiss cohort study (38) found that starting ART at CD4 counts greater than 0.350×10^9 cells/L was associated with a lower risk for death and progression to AIDS than starting at less than 0.350×10^9 cells/L, 3 U.S. cohort studies (35–37) found no difference in risk between starting ART at CD4 counts between 0.350 and 0.500×10^9 cells/L versus delaying until CD4 counts were between 0.200 and 0.350×10^9 cells/L.

Two good-quality randomized trials (17, 39) published since the previous USPSTF review and 1 subgroup analysis (40) from another randomized trial evaluated the effects of initiating ART at different CD4 cell count thresholds (**Table 1**). Five observational studies (reported in 7 publications) (41–45, 48, 49), each of which combined data from 12 to 23 U.S., European, and Australian cohorts (ranging from 9000 to >60 000 participants and 2- to 5-year follow-up, with substantial overlap in the cohorts included in the studies), also evaluated the effects of starting ART at different CD4 cell count thresholds (**Table 1**). All of the observational studies were rated fair-quality. None reported blinding of outcome assessors or persons analyzing data, and attrition rates were often not reported or were unclear. Although all studies adjusted for confounders, most provided insufficient information to determine baseline comparability of patients starting or not starting ART at different CD4 cell count strata.

A retrospective subgroup analysis of 477 patients in the SMART (Strategies for Management of Antiretroviral Therapy) randomized trial who were treatment-naive or had stopped therapy for at least 6 months found that ART initiation at CD4 counts less than 0.250×10^9 cells/L was associated with a higher risk for death or AIDS events than initiation at counts greater than 0.350×10^9 cells/L after a mean of 18 months (HR, 5.3 [CI, 1.3 to 9.6]) (40). The SMART trial was done in 33 primarily non–resource-poor

Table 1. **Initiating HAART at Different CD4 Cell Counts or Viral Load Thresholds on Progression to AIDS or Mortality**

Study, Year (Reference)	Study Name	Patients, *n*	Duration of Follow-up	Comparison Groups
RCTs				
Cohen et al, 2011 (17)	HPTN 052	1763	Median, 1.7 y	Delayed treatment (n = 877): Initiation of ART after 2 consecutive CD4 counts $<0.250 \times 10^9$ cells/L or at onset of AIDS-related illness Early treatment (n = 886): Initiation of ART at CD4 count of 0.350 to 0.550 $\times 10^9$ cells/L
Severe et al, 2010 (39)	NA	816	21 mo	Standard treatment (n = 408): Same intervention as early treatment group, started at CD4 count $\leq 0.200 \times 10^9$ cells/L Early treatment (n = 408): CD4 count, 0.201 to 0.350 $\times 10^9$ cells/L; lamivudine, 150 mg, plus zidovudine, 300 mg, twice a day and efavirenz, 600 mg/d
Emery et al, 2008 (40), and El-Sadr et al, 2006 (47)	SMART Study Group	477 (249 ART-naive)	18 mo	Intermittent ART, drug conservation group: CD4 count $<0.250 \times 10^9$ cells/L, CD4 percentage <15%, or symptomatic; 131 ART-naive patients Continuous ART, viral suppression group: CD4 count $>0.350 \times 10^9$ cells/L; 118 ART-naive patients
Cohort studies				
Cain et al, 2011 (42), and Ray et al, 2010 (43)	HIV-CAUSAL Collaboration	20 971 (12 cohorts); restricted to patients with CD4 counts $>0.500 \times 10^9$ cells/L at baseline	Mean, 1 y	By CD4 count*: 0.200×10^9 cells/L (n = 8066) 0.250×10^9 cells/L (n = 8078) 0.300×10^9 cells/L (n = 8101) 0.350×10^9 cells/L (n = 8144) 0.400×10^9 cells/L (n = 8201) 0.450×10^9 cells/L (n = 8281) 0.500×10^9 cells/L (n = 8392)
Ray et al, 2010 (43)	HIV-CAUSAL Collaboration	62 760 (12 cohorts)	Mean, 3 y	By CD4 count: $<0.100 \times 10^9$ cells/L (n = 5319) 0.100 to $<0.200 \times 10^9$ cells/L (n = 6521) 0.200 to $<0.350 \times 10^9$ cells/L (n = 14 886) 0.350 to $<0.500 \times 10^9$ cells/L (n = 15 360) $\leq 0.500 \times 10^9$ cells/L (n = 20 674)
Kitahata et al, 2009 (44)	NA-ACCORD	17 517 (22 cohorts)	Mean, 3 y	CD4 count 0.351 to 0.500×10^9 cells/L: early therapy (n = 2084) and deferred therapy (n = 6278) CD4 count $>0.500 \times 10^9$ cells/L: early therapy (n = 2220) and deferred therapy (n = 6936)

Table 1—**Continued**

Mortality	Progression to AIDS/AIDS-Related Events	Mortality or Progression to AIDS/AIDS-Related Events
Delayed vs. early treatment: 13/877 (1.5%) vs. 10/886 (1.2%); HR, 1.3 (95% CI, 0.6 to 3.0)	Extrapulmonary tuberculosis, delayed vs. early treatment: 17/877 (2%) vs. 3/886 (0.3%); RR, 5.6 (95% CI, 1.7 to 20.0) Pulmonary tuberculosis, delayed vs. early treatment: 15/877 (1.7%) vs. 13/886 (1.5%); RR, 1.2 (95% CI, 0.6 to 2.4)	Delayed vs. early treatment: 65/877 (7.4%) vs. 40/886 (4.5%); HR, 1.7 (95% CI, 1.1 to 2.5)
Standard vs. early treatment: 23/408 (6%) vs. 6/408 (2%); unadjusted HR, 4.0 (95% CI, 1.6 to 9.8)	Tuberculosis, standard vs. early treatment: 36/408 (9%) vs. 18/408 (4%); unadjusted HR, 2.0 (95% CI, 1.2 to 3.6)	Not reported
Not reported	Drug conservation vs. continuous ART (fatal and nonfatal AIDS events): 3/131 (2/100 PYs) vs. 1/118 (0.5/100 PYs); HR, 4.1; $P = 0.22$	Drug conservation vs. continuous ART: 4/131 (2.7/100 PYs) vs. 1/118 (0.5/100 PYs); HR, 5.3 (95% CI, 1.3 to 9.6)
ART initiation at CD4 count 0.500 $\times$ 10^9 cells/L (n = 65/8392) vs. initiation at: 0.200 $\times$ 10^9 cells/L (n = 99/8066): HR, 0.83 (95% CI, 0.68 to 1.03) 0.250 $\times$ 10^9 cells/L (n = 95/8078): HR, 0.92 (95% CI, 0.78 to 1.09) 0.300 $\times$ 10^9 cells/L (n = 97/8101): HR, 0.99 (95% CI, 0.84 to 1.18) 0.350 $\times$ 10^9 cells/L (n = 94/8144): HR, 0.99 (95% CI, 0.82 to 1.19) 0.400 $\times$ 10^9 cells/L (n = 89/8201): HR, 0.95 (95% CI, 0.79 to 1.16) 0.450 $\times$ 10^9 cells/L (n = 81/8281): HR, 0.97 (95% CI, 0.88 to 1.09)	Not reported	ART initiation at CD4 count 0.500 $\times$ 10^9 cells/L (n = 158/8392) vs. initiation at: 0.200 $\times$ 10^9 cells/L (n = 330/8066): HR, 0.53 (95% CI, 0.47 to 0.60) 0.250 $\times$ 10^9 cells/L (n = 329/8078): HR, 0.60 (95% CI, 0.54 to 0.67) 0.300 $\times$ 10^9 cells/L (n = 317/8101): HR, 0.68 (95% CI, 0.61 to 0.75) 0.350 $\times$ 10^9 cells/L (n = 296/8144): HR, 0.72 (95% CI, 0.64 to 0.81) 0.400 $\times$ 10^9 cells/L (n = 256/8201): HR, 0.78 (95% CI, 0.68 to 0.87) 0.450 $\times$ 10^9 cells/L (n = 209/8281): HR, 0.88 (95% CI, 0.82 to 0.93)
ART initiation at CD4 count 0.350 $\times$ 10^9 cells/L (n = 94/8144) vs. initiation at: 0.200 $\times$ 10^9 cells/L (n = 99/8066): HR, 0.85 (95% CI, 0.68 to 1.05) 0.250 $\times$ 10^9 cells/L (n = 95/8078): HR, 0.93 (95% CI, 0.75 to 1.16) 0.300 $\times$ 10^9 cells/L (n = 97/8101): HR, 1.01 (95% CI, 0.79 to 1.28) 0.400 $\times$ 10^9 cells/L (n = 89/8201): HR, 0.97 (95% CI, 0.85 to 1.10) 0.450 $\times$ 10^9 cells/L (n = 81/8281): HR, 0.99 (95% CI, 0.79 to 1.22) 0.500 $\times$ 10^9 cells/L (n = 65/8392): HR, 1.01 (95% CI, 0.74 to 1.41)		ART initiation at CD4 count 0.350 $\times$ 10^9 cells/L (n = 296/8144) vs. initiation at: 0.200 $\times$ 10^9 cells/L (n = 330/8066): HR, 0.73 (95% CI, 0.64 to 0.83) 0.250 $\times$ 10^9 cells/L (n = 329/8078): HR, 0.83 (95% CI, 0.72 to 0.95) 0.300 $\times$ 10^9 cells/L (n = 317/8101): HR, 0.93 (95% CI, 0.81 to 1.09) 0.400 $\times$ 10^9 cells/L (n = 256/8201): HR, 1.06 (95% CI, 0.99 to 1.16) 0.450 $\times$ 10^9 cells/L (n = 209/8281): HR, 1.20 (95% CI, 1.05 to 1.39) 0.500 $\times$ 10^9 cells/L (n = 158/8392): HR, 1.39 (95% CI, 1.14 to 1.69)
Initiation vs. no initiation of ART, by CD4 count: <0.100 $\times$ 10^9 cells/L: HR, 0.29 (95% CI, 0.22 to 0.37) 0.100 to <0.200 $\times$ 10^9 cells/L: HR, 0.33 (95% CI, 0.25 to 0.44) 0.200 to <0.350 $\times$ 10^9 cells/L: HR, 0.38 (95% CI, 0.28 to 0.52) 0.350 to <0.500 $\times$ 10^9 cells/L: HR, 0.55 (95% CI, 0.41 to 0.74) ≤0.500 $\times$ 10^9 cells/L: HR, 0.77 (95% CI, 0.58 to 1.01)	Not reported	Not reported
ART initiation at CD4 count 0.351 to 0.500 vs. ≤0.350 $\times$ 10^9 cells/L: adjusted RR, 0.61 (95% CI, 0.46 to 0.83) ART initiation at CD4 count >0.500 vs. ≤0.500 $\times$ 10^9 cells/L: adjusted RR, 0.54 (95% CI, 0.35 to 0.83)	Not reported	Not reported

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Table 1—**Continued**

Study, Year (Reference)	Study Name	Patients, *n*	Duration of Follow-up	Comparison Groups
May et al, 2007 (45); Lanoy et al, 2009 (41); and Moore et al, 2009 (46)	ART Cohort Collaboration	20 379 (12 cohorts)	Mean, 3 y	By CD4 count: <0.025 × 10^9 cells/L (*n* = 2034) 0.025 to 0.049 × 10^9 cells/L (*n* = 1295) 0.050 to 0.099 × 10^9 cells/L (*n* = 2059) 0.100 to 0.199 × 10^9 cells/L (*n* = 3782) 0.200 to 0.349 × 10^9 cells/L (*n* = 5550) ≤0.350 × 10^9 cells/L (*n* = 5659)
Sterne et al, 2009 (49)	When to Start Consortium	45 691 (18 cohorts); 24 444 received HAART	Mean, 3 y	By CD4 count: <0.051 × 10^9 cells/L (*n* = 2594) 0.051 to 0.150 × 10^9 cells/L (*n* = 4638) 0.151 to 0.250 × 10^9 cells/L (*n* = 6406) 0.251 to 0.350 × 10^9 cells/L (*n* = 5753) 0.351 to 0.400 × 10^9 cells/L (*n* = 3260) 0.451 to 0.500 × 10^9 cells/L (*n* = 1793)
Writing Committee for the CASCADE Collaboration, 2011 (48)	NA	9455 (23 cohorts)	Median, 5 y	Unique individuals (numbers overlap): 0 to 0.049 × 10^9 cells/L (*n* = 183) 0.050 to 0.199 × 10^9 cells/L (*n* = 1521) 0.200 to 0.349 × 10^9 cells/L (*n* = 4459) 0.350 to 0.499 × 10^9 cells/L (*n* = 5527) 0.500 to 0.799 × 10^9 cells/L (*n* = 5162)

ART = antiretroviral therapy; CASCADE = Concerted Action on Seroconversion to AIDS and Death in Europe; HAART = highly active antiretroviral therapy; HIV-CAUSAL = HIV Cohorts Analyzed Using Structural Approaches to Longitudinal data; HPTN = HIV Prevention Trials Network; HR = hazard ratio; NA = not applicable; NA-ACCORD = North American AIDS Cohort Collaboration on Research and Design; PY = person-year; RCT = randomized, controlled trial; RD = risk difference; RR = relative risk; SMART = Strategies for Management of Antiretroviral Therapy.
* Patient-level data may cross CD4 cell count thresholds.

countries. The HIV Prevention Trials Network study 052, conducted in 1763 patients from primarily resource-poor countries, also found initiation at CD4 counts less than 0.250 × 10^9 cells/L associated with a higher risk for death or AIDS events than initiation at counts greater than 0.350 × 10^9 cells/L after a median of 1.7 years (HR, 1.7 [CI, 1.1 to 2.5]) (17). Another randomized trial (39) with 816 participants found that ART initiation at CD4 counts less than 0.200 × 10^9 cells/L was associated with higher mortality than initiation at 0.201 to 0.350 × 10^9 cells/L (HR, 4.0 [CI, 1.6 to 9.8]; $P = 0.001$), but this trial was conducted in Haiti and evaluated lower CD4 count cutoffs for treatment than those in the United States.

Four observational studies (42–45, 48) consistently found that ART initiation at CD4 counts between 0.350 and 0.500 × 10^9 cells/L was associated with a lower risk for death than deferred or no ART. One other study (49) found a reduction in risk that was not statistically significant. The HIV-CAUSAL (HIV Cohorts Analyzed Using Structural Approaches to Longitudinal data) collaboration (43), the largest study in our review (62 760 participants from 12 cohorts), found that ART initiation at CD4 counts of 0.350 to 0.500 × 10^9 cells/L was associated with a lower risk for death than noninitiation at these counts after 3.3 years of follow-up (adjusted HR, 0.55 [CI, 0.41 to 0.74]). Similarly, the NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) (44), with 17 517 participants from 22 cohorts, found that ART initiation at CD4 counts of 0.351 to 0.500 × 10^9 cells/L was associated with a lower risk for death than deferred treatment at these CD4 cell counts after 3 years of follow-up (adjusted RR, 0.61 [CI, 0.46 to 0.83]). In 2 studies (45, 49), ART initiation at CD4 counts greater than 0.350 × 10^9 cells/L was also associated with a lower risk for the combined outcome of AIDS-defining events and death than deferred or no ART initiation. One other study (48) found a reduction in risk that was not statistically significant.

Studies on ART initiation at CD4 counts greater than 0.500 × 10^9 cells/L were less consistent. The NA-ACCORD cohort study (44) found that ART initiation at CD4 counts greater than 0.500 × 10^9 cells/L was associated with lower mortality than deferred therapy (adjusted RR, 0.54 [CI, 0.35 to 0.83]) and the HIV-CAUSAL col-

Table 1—Continued

Mortality	Progression to AIDS/AIDS-Related Events	Mortality or Progression to AIDS/AIDS-Related Events
ART initiation at varying CD4 cell counts vs. initiation at $<0.025 \times 10^9$ cells/L: 0.025 to 0.049 $\times 10^9$ cells/L: 111/1295 vs. 222/2034; HR, 0.82 (95% CI, 0.66 to 1.04) 0.050 to 0.099 $\times 10^9$ cells/L: 162/2059 vs. 222/2034; HR, 0.77 (95% CI, 0.63 to 0.95) 0.100 to 0.199 $\times 10^9$ cells/L: 202/3782 vs. 222/2034; HR, 0.67 (95% CI, 0.55 to 0.82) 0.200 to 0.349 $\times 10^9$ cells/L: 178/5550 vs. 222/2034; HR, 0.48 (95% CI, 0.39 to 0.60) $\leq 0.350 \times 10^9$ cells/L: 130/5659 vs. 222/2034; HR, 0.34 (95% CI, 0.27 to 0.44)	Not reported	ART initiation at varying CD4 cell counts vs. initiation at $<0.025 \times 10^9$ cells/L: 0.025 to 0.049 $\times 10^9$ cells/L: 277/1295 vs. 519/2034; HR, 0.85 (95% CI, 0.73 to 0.98) 0.050 to 0.099 $\times 10^9$ cells/L: 408/2059 vs. 519/2034; HR, 0.76 (95% CI, 0.66 to 0.87) 0.100 to 0.199 $\times 10^9$ cells/L: 445/3782 vs. 519/2034; HR, 0.49 (95% CI, 0.43 to 0.56) 0.200 to 0.349 $\times 10^9$ cells/L: 361/5550 vs. 519/2034; HR, 0.29 (95% CI, 0.25 to 0.33) $\leq 0.350 \times 10^9$ cells/L: 298/5659 vs. 519/2034; HR, 0.23 (95% CI, 0.19 to 0.27)
ART initiation at varying CD4 cell counts vs. initiation at 0.351 to 0.400 $\times 10^9$ cells/L: 0.451 to 0.550 $\times 10^9$ cells/L: HR, 0.93 (95% CI, 0.6 to 1.4) 0.251 to 0.350 $\times 10^9$ cells/L: HR, 0.83 (95% CI, 0.59 to 1.25) 0.151 to 0.250 $\times 10^9$ cells/L: HR, 0.67 (95% CI, 0.51 to 0.99) 0.051 to 0.150 $\times 10^9$ cells/L: HR, 0.47 (95% CI, 0.34 to 0.58)	Not reported	ART initiation at varying CD4 cell counts vs. initiation at 0.351 to 0.450 $\times 10^9$ cells/L: 0.251 to 0.350 $\times 10^9$ cells/L: HR, 0.74 (95% CI, 0.59 to 0.95) 0.151 to 0.250 $\times 10^9$ cells/L: HR, 0.45 (95% CI, 0.37 to 0.53) 0.051 to 0.150 $\times 10^9$ cells/L: HR, 0.18 (95% CI, 0.15 to 0.21)
Initiation vs. no initiation of ART during the index month, by CD4 count: 0 to 0.049 $\times 10^9$ cells/L: HR, 0.37 (95% CI, 0.14 to 0.95); RD, −18.2 (95% CI, −32 to −4.4) 0.050 to 0.199 $\times 10^9$ cells/L: HR, 0.55 (95% CI, 0.28 to 1.07); RD, −7.2 (95% CI, −10.1 to −4.4) 0.200 to 0.349 $\times 10^9$ cells/L: HR, 0.71 (95% CI, 0.44 to 1.15); RD, −1.4 (95% CI, −3.0 to 0.3) 0.350 to 0.499 $\times 10^9$ cells/L: HR, 0.51 (95% CI, 0.33 to 0.80); RD, −1.4 (95% CI, −2.2 to −0.6) 0.500 to 0.799 $\times 10^9$ cells/L: HR, 1.02 (95% CI, 0.49 to 2.12); RD, −0.4 (95% CI, −2 to 1.2)	Not reported	Initiation vs. no initiation of ART during index month, by CD4 count: 0 to 0.049 $\times 10^9$ cells/L: HR, 0.32 (95% CI, 0.17 to 0.59); RD, −30 (95% CI, −45.1 to −15) 0.050 to 0.199 $\times 10^9$ cells/L: HR, 0.48 (95% CI, 0.31 to 0.74); RD, −15 (95% CI, −19.7 to −10.3) 0.200 to 0.349 $\times 10^9$ cells/L: HR, 0.59 (95% CI, 0.43 to 0.81); RD, −4.8 (95% CI, −7 to −2.6) 0.350 to 0.499 $\times 10^9$ cells/L: HR, 0.75 (95% CI, 0.49 to 1.14); RD, −2.9 (95% CI, −5 to −0.9) 0.500 to 0.799 $\times 10^9$ cells/L: HR, 1.10 (95% CI, 0.67 to 1.79); RD, 0.3 (95% CI, −3.7 to 4.2)

laboration (43) found a lower mortality risk that was not statistically significant (adjusted HR, 0.77 [CI, 0.58 to 1.0]). Another analysis from the HIV-CAUSAL Collaboration (42) that directly compared ART initiation at CD4 counts greater than 0.500×10^9 cells/L with initiation at greater than 0.350×10^9 cells/L found no difference in mortality (HR, 0.99 [CI, 0.89 to 1.2]). Two other large cohort studies found that ART initiation at CD4 counts greater than 0.500×10^9 cells/L was associated with no difference in risk for death when compared with noninitiation (48) or slightly delayed initiation (49). In all 4 studies, absolute mortality rates were low (2% to 5%) in patients with CD4 counts greater than 0.500×10^9 cells/L.

Results were also mixed for the combined outcome of death plus AIDS-defining events (not reported in the NA-ACCORD study [44]). The HIV-CAUSAL collaboration (42) found that ART initiation at CD4 counts greater than 0.500×10^9 cells/L was associated with a lower risk for AIDS-defining events or death than initiation at greater than 0.350×10^9 cells/L (HR, 0.72 [CI, 0.64 to 0.81]). Two other studies (48, 49) found no clear association between starting or not starting ART at CD4 counts greater than 0.500×10^9 cells/L and risk for AIDS-defining events or death.

Longer-Term Harms Associated With ART

The 2005 USPSTF review included results from the large, ongoing DAD (Data Collection on Adverse Events of Anti-HIV Drugs) study (23 468 participants), which found that increased risk for myocardial infarction was associated with longer exposure to ART (adjusted RR, 1.3 per year of exposure [CI, 1.1 to 1.4 per year of exposure]), although absolute event rates were low (3.5 per 1000 person-years) (50).

Subsequent analyses from the DAD study (51–53) and 3 other cohort studies (54–56) reported cardiovascular harms associated with ART through 4 to 6 years of follow-up (**Appendix Table 3**, available at www.annals.org). Sample sizes ranged from 2952 to more than 30 000 persons. All of the studies were rated good-quality except 1, which was rated fair-quality because of lack of detail about baseline patient characteristics and blinding of study personnel (54). All studies adjusted for multiple confounders.

Like the earlier DAD results, the most recent analysis found that longer exposure to indinavir alone (adjusted RR, 1.1 per year of exposure [CI, 1.1 to 1.2 per year of exposure]), ritonavir-boosted indinavir (adjusted RR, 1.2 per year of exposure [CI, 1.1 to 1.3 per year of exposure]), and ritonavir-boosted lopinavir (adjusted RR, 1.1 per year

Table 2. **Summary of Evidence**

Key Question	Main Findings From the 2005 USPSTF Review	Number and Type of Studies Identified for Update	Overall Quality*
What are the benefits of universal or targeted HIV screening versus no screening in asymptomatic, nonpregnant adolescents and adults on disease transmission, morbidity, mortality, and quality of life?	No evidence	No studies	–
What is the yield (number of new diagnoses) of HIV screening at different intervals in nonpregnant adolescents and adults?	No evidence	No studies	–
How effective is ART for reducing transmission of HIV in nonpregnant adolescents and adults with chronic HIV infection?	No studies	1 systematic review (1 RCT and 7 observational studies)	Good
How effective is behavioral counseling for reducing transmission of HIV in nonpregnant adolescents and adults with chronic HIV infection?	No RCTs or controlled observational studies	1 RCT and 1 before–after study	Poor
In asymptomatic, nonpregnant adolescents and adults with chronic HIV infection, what are the effects of initiating ART at different CD4 cell counts or viral load thresholds on morbidity, mortality, and quality of life?	1 cohort study found that initiating ART at CD4 counts $>0.350 \times 10^9$ cells/L was associated with lower risk for AIDS events and mortality than delayed initiation, but 3 others found no difference in risk	3 RCTs and 5 large collaborative cohort studies	Good
What are the longer-term harms associated with ART for nonpregnant adolescents and adults with chronic HIV infection?	1 large cohort study found that longer duration of exposure to some protease inhibitors was associated with increased risk for myocardial infarction (RR, 1.3 per year of exposure [95% CI, 1.1 to 1.4])	4 cohort studies (reported in 6 publications)	Good

ART = antiretroviral therapy; HR = hazard ratio; MI = myocardial infarction; RCT = randomized, controlled trial; RR = relative risk; USPSTF = U.S. Preventive Services Task Force.
* Based on new evidence identified for this update plus previously reviewed evidence.
† Cost-effectiveness modeling studies are not included in this summary table.

of exposure [CI, 1.0 to 1.2 per year of exposure]) were each associated with a slightly higher risk for myocardial infarction than nonuse (53). No other protease inhibitor was associated with increased myocardial risk.

Evidence on the association between the nucleoside reverse transcriptase inhibitor abacavir and risk for myocardial infarction is mixed. Although 2 studies (53, 55) found that abacavir was associated with increased risk (adjusted RRs, 1.7 and 2.0), 2 others (54, 56) found no association (adjusted HRs, 0.6 and 1.2).

The DAD study also found that recent didanosine use was associated with increased myocardial infarction risk (adjusted RR, 1.4 [CI, 1.1 to 1.8]), but found no association when analyses were based on cumulative didanosine exposure (53). No association was found between use of other nucleoside reverse transcriptase inhibitors or the nonnucleoside reverse transcriptase inhibitors nevirapine or efavirenz and increased risk for cardiovascular events (53).

DISCUSSION

As in the 2005 USPSTF review (8–10), we found no direct evidence on the effects of screening for HIV infection versus no screening on clinical outcomes. **Table 2** summarizes the other evidence reviewed in this update.

The 2005 review found good evidence that HIV screening tests are accurate and that identifying undiagnosed HIV infection and treating immunologically advanced disease (CD4 count $<0.200 \times 10^9$ cells/L) are associated with substantial clinical benefits. However, it found insufficient evidence to estimate the effects of diagnosis and subsequent interventions on transmission risks or the clinical benefits of ART in patients with less immunologically advanced disease. New studies included in this update (17, 39, 40, 43–45, 48, 49) provide strong evidence for the effectiveness of initiating ART at CD4 counts between 0.350 and 0.500×10^9 cells/L, although evidence showing benefit is less consistent for ART initiation at greater than 0.500×10^9 cells/L (43, 44, 48, 49). Recent studies indicate that about 54% of patients present for initial HIV care with CD4 counts less than 0.350×10^9 cells/L (57) and about 75% were diagnosed at CD4 counts less than 0.500×10^9 cells/L (58), suggesting that many patients identified by screening would benefit from immediate ART initiation. Additional research (51–

Table 2—**Continued**

Limitations	Consistency	Applicability	Summary of Findings for 2012 Update
No studies	No studies	No studies	No study directly compared clinical outcomes between adults and adolescents screened and not screened for HIV infection.
No studies	No studies	No studies	No study evaluated the yield of repeated HIV screening compared with one-time screening.†
Only 1 RCT	Consistent	Some studies conducted in resource-poor settings	An RCT found that immediate ART in persons with a baseline CD4 count of 0.350 to 0.550 $\times$ 10^9 cells/L was associated with substantially lower risk for transmission than delayed therapy (HR, 0.04 [95% CI, 0.01 to 0.27]). Observational studies were consistent with the RCT (pooled HR, 0.16 [95% CI, 0.07 to 0.35]).
Underpowered to evaluate effects on transmission	Could not determine	No major issues	Studies identified too few cases of new HIV infection to evaluate effects of counseling interventions on transmission risk.
1 RCT reported a subgroup analysis, some overlap in patients evaluated in the cohort studies	Some inconsistency for CD4 cell counts $>0.500 \times 10^9$ cells/L	1 RCT evaluated CD4 cell count thresholds not applicable to U.S. practice in a resource-poor setting	An RCT and a subgroup analysis from another RCT found that initiating ART at CD4 counts $<0.250 \times 10^9$ cells/L was associated with higher risk for death or AIDS events than initiation at CD4 counts $>0.350 \times 10^9$ cells/L. Five large observational studies also found that initiating ART at CD4 counts between 0.350 and 0.500 $\times$ 10^9 cells/L was associated with lower risk for death than deferred or no ART. Four studies on initiation of ART at CD4 counts $>0.500 \times 10^9$ cells/L did not consistently demonstrate clinical benefits.
No major limitations	Consistent	Duration of follow-up about 6 y	Additional follow-up from a large cohort study included in the previous USPSTF review found some protease inhibitors associated with increased risk for MI (RR, 1.1 to 1.2 per year of exposure). Evidence on abacavir from 4 cohort studies was mixed, and no clear association was shown between other antiretrovirals and increased risk for cardiovascular events.

53, 55) confirms previous findings of a small but statistically significant increase in risk for long-term cardiovascular harms associated with use of certain protease inhibitors. In the DAD study, the absolute increase in risk per year of exposure with certain older protease inhibitors was about 0.3 myocardial infarctions per 1000 person-years (53), compared with an absolute decrease in mortality of about 3.2 to 20 per 1000 person-years after initiating ART, depending on the CD4 cell count at baseline (43). Whether current first-line protease inhibitors and other antiretrovirals are also associated with increased cardiovascular risk is not yet established. Long-term ART is also associated with other harms, including osteoporotic fractures (59) and lipodystrophy (60), that were not addressed in this review.

Strong evidence from a randomized trial and multiple observational studies (16, 17) indicates that ART use is associated with a 10- to 20-fold reduction in risk for sexual transmission. Recent evidence showing that counseling interventions were relatively ineffective in reducing risky behaviors in HIV-infected persons (61) suggests that the beneficial effects of screening on transmission are probably driven by use of ART.

Our study has limitations. We excluded non–English-language articles, which could have resulted in language bias, although we identified no non–English-language studies that would have met our inclusion criteria. We did not search for studies published only as abstracts and could not formally assess for publication bias by using graphical or statistical methods because of the few studies for each key question and the differences in study design, populations, and outcomes assessed. We included observational studies, which are more susceptible to bias and confounding than well-conducted randomized trials, although we focused on results from studies that performed statistical adjustment for potential confounding. We also included studies conducted in resource-poor and high-prevalence settings, which could limit the applicability of our findings to U.S. practice.

Additional research may further clarify benefits and harms of screening. Continued follow-up of patients receiving ART is needed to further understand the effects of long-term exposure, because many patients receive treatment for far longer than the 6 years evaluated in the longest studies to date. No clinical study has evaluated the yield of repeated HIV screening, which probably depends on the incidence of new infections in a population (61–63). The START (Strategic Timing of Antiretroviral Treatment) randomized trial (64), which compares ART initiation at CD4 counts greater than 0.500 $\times$ 10^9 cells/L with deferred treatment until CD4 counts decrease to less than 0.350 $\times$ 10^9

cells/L, is currently recruiting and should help further clarify the effects of very early ART initiation.

The main area of discrepancy between HIV screening guidelines is whether to routinely screen populations not known to be at increased risk (11, 65). Screening tests for HIV are highly accurate, but targeted screening misses a substantial proportion of infected persons because of undisclosed or unknown risk factors. Evidence published since the 2005 USPSTF review shows highly beneficial effects of ART for reducing sexual transmission of HIV and risk for AIDS-defining events and death in persons with less immunologically advanced stages of disease.

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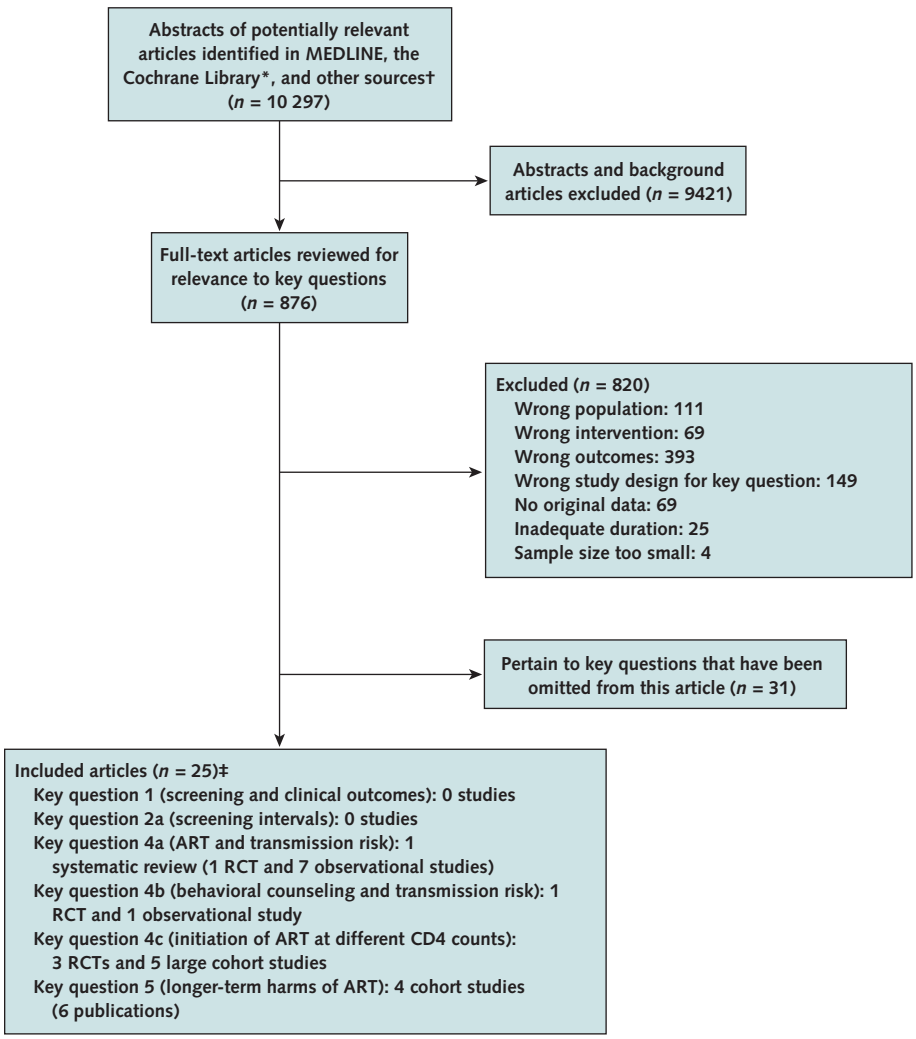
Appendix Table 1. Inclusion and Exclusion Criteria, per Key Question

Key Question	Include	Exclude
All questions		
Settings	Primary care or other settings generalizable to primary care (e.g., family planning clinics or school-based health clinics), other health care settings in which screening is commonly performed (e.g., emergency department or urgent care). Focus on studies conducted in the United States and other developed countries, unless studies are not available in those settings.	Developing countries, unless fair- or good-quality trials and studies in the United States are lacking
What are the benefits of universal or targeted HIV screening versus no screening in asymptomatic, nonpregnant adolescents and adults on disease transmission, morbidity, mortality, and quality of life?		
Populations	Asymptomatic adolescents and adults	Known HIV infection, receiving dialysis, posttransplant, or occupational exposure
Interventions	Rapid or standard HIV testing	
Outcomes	Reduction in transmission rates of HIV and morbidity and mortality related to HIV infection and quality of life	
Comparisons	Universal or targeted HIV screening vs. no screening or each another	
Study designs	Randomized, controlled trials and controlled observational studies	Uncontrolled observational studies
What is the yield (number of new diagnoses) of HIV screening at different intervals in nonpregnant adolescents and adults?		
Populations	Asymptomatic adolescents and adults	Known HIV infection, receiving dialysis, posttransplant, or occupational exposure
Interventions	Rapid or standard HIV testing	
Outcomes	Number of positive test results	
Comparisons	Repeated HIV screening vs. 1-time screening or screening at one interval vs. another interval	
Study designs	Randomized, controlled trials and controlled observational studies	
How effective is ART for reducing transmission of HIV in nonpregnant adolescents and adults with chronic HIV infection?		
Populations	HIV-positive adolescents and adults	Acute HIV infection
Interventions	Use of ART	
Comparisons	Use of ART vs. no ART	
Outcomes	Transmission rates	
Study designs	Randomized, controlled trials or controlled observational studies	
How effective is behavioral counseling for reducing transmission of HIV in nonpregnant adolescents and adults with chronic HIV infection?		
Populations	HIV-positive adolescents and adults	Acute HIV infection
Interventions	Behavioral counseling interventions (pre- and posttest) to reduce risky sexual behaviors or enhance protective sexual behaviors for those who were asymptomatic and identified through screening	
Comparisons	Counseling vs. usual care	
Outcomes	Transmission rates	
Study designs	Randomized, controlled trials or controlled observational studies	
In asymptomatic, nonpregnant adolescents and adults with chronic HIV infection, what are the effects of initiating ART at different CD4 cell count or viral load thresholds on morbidity, mortality, and quality of life?		
Populations	HIV-positive adolescents and adults	Acute HIV infection
Interventions	Antiretroviral regimens	
Comparisons	Initiation of ART earlier vs. later	
Outcomes	Morbidity and mortality related to HIV infection and quality of life	
Study designs	Randomized, controlled trials or controlled observational studies	
What are the longer-term harms associated with ART for nonpregnant adolescents and adults with chronic HIV infection?		
Populations	HIV-positive adolescents and adults	Acute HIV infection or receiving or previously received HAART
Interventions	Antiretroviral regimens	
Outcomes	Cardiovascular effects	
Study designs	Any	
Timing	Long-term follow up, defined as >2 y	

ART = antiretroviral therapy; HAART = highly active antiretroviral therapy.

Appendix Figure. **Summary of evidence search and selection.**



ART = antiretroviral therapy; RCT = randomized, controlled trial.
* Includes the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
† Includes reference lists and sources suggested by peer reviewers.
‡ Some articles are included for more than 1 key question.

Appendix Table 2. Evidence Table of Studies of Counseling or ART Use on HIV Transmission

Study, Year (Reference)	Study Design Details	Location	Duration of Follow-up	Treatment and Comparison Groups	Demographic Characteristics/Baseline Disease	Participants	Virologic Response	CD4 Cell Count Response	Outcomes	Quality Rating
RCT										
Cohen et al, 2011 (17)	RCT	Botswana, Kenya, Malawi, South Africa, Zimbabwe, India, Brazil, Thailand, and United States	Median, 42 mo	Treatment: Immediate ART Comparison: Delayed ART initiated after CD4 count decreased to $\leq 0.250 \times 10^9$ cells/L or onset of AIDS-related illness	61% of participants between ages 26 and 40 y; median CD4 count, 0.442×10^9 cells/L for early-therapy group and 0.428×10^9 cells/L for delayed-therapy group	10 838 screened, 1763 couples enrolled	Virologic failure, immediate vs. delayed treatment: 5% (45/886) vs. 3% (5/184); $P = 0.23$	Treatment: 0.442×10^9 cells/L at enrollment to 0.603×10^9 cells/L at 12 mo Comparison: 0.428×10^9 cells/L at enrollment to 0.399×10^9 cells/L at 12 mo	Immediate vs. delayed treatment: Transmission events: 4 events (IR, 0.3/100 PYs [95% CI, 0.1 to 0.6/100 PYs]) vs. 35 events (IR, 2.2/100 PYs [95% CI, 1.6 to 3.1/100 PYs]; HR, 0.11 [95% CI, 0.04 to 0.32]); $P < 0.001$) Total clinical events: HR, 0.59 (95% CI, 0.40 to 0.88) Linked transmission: HR, 0.04 (95% CI, 0.01 to 0.28)	Good
Observational studies										
Del Romero et al, 2010 (18)	Prospective cohort	Spain	1355 couple-years	ART vs. no ART	Men, 83% (index cases); median age, 29 y (women) and 32 y (men); median CD4 count, 0.500×10^9 cells/L (IQR, 0.295 to 0.700×10^9 cells/L); median plasma HIV RNA, 200 copies/mL (IQR, ND to 8876 copies/mL); 54% detectable viral load	648 eligible couples; 602 were serodiscordant at first visit and 424 were serodiscordant at follow-up	Detectable viral load in 93% (111/120) not receiving ART vs. 21% (30/145) receiving ART; $P < 0.001$	Not reported	No ART vs. ART: Proportion engaging in unprotected sexual intercourse: 57% (73/476) vs. 46% (69/149); $P = 0.019$ Transmission: 5 instances (0.4/100 couple-years [95% CI, 0.2 to 1.4/100 couple-years]) vs. 0 instances (0/100 couple-years [95% CI, 0 to 1.1/100 couple-years])	Fair
Donnell et al, 2010 (19)	Pre–post analysis of prospective cohort data	14 sites in 7 African countries (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia)	Median at ART initiation, 13 mo	Pre-ART vs. post-ART transmission	HIV-infected partner vs. HIV-susceptible partner: mean age, 32 vs. 33 y; women, 68% vs. 32%; HSV-2–positive, 100% vs. 68%	3408 enrolled, 3381 analyzed Note: 27 couples' baseline serology did not confirm HIV-1 and HSV-2	Not reported	Not reported	Pre- vs. post-ART transmission: Overall: 102/4558 PYs (IR, 2.24 [95% CI, 1.84 to 2.72]) vs. 1/273 PYs (IR, 0.37 [95% CI, 0.09 to 2.04]) Overall adjusted incidence rate ratio: 0.08 (95% CI, 0.00 to 0.57)	Good
Melo et al, 2008 (20)	Retrospective cohort	Brazil	Median, 25.5 mo (transmitters) vs. 22.3 mo (nontransmitters)	Transmitters vs. nontransmitters	Women, 72% (index cases); IDUs, 57.7%; unprotected sex, 91%; STD diagnosis, 23.6%	4500 screened retrospectively, 93 enrolled (56 enrolled retrospectively plus 37 enrolled prospectively)	Not reported	Not reported	Transmissions, ART vs. no ART: 0/41 vs. 6/52 Median viral load, transmitters vs. nontransmitters: 24 082 (range, 1479 to 100 539) vs. 4583 (range, 78 to 47 974); $P = 0.042$	Fair
Musicco et al, 1994 (21)	Prospective cohort	Italy	Mean, 2 y (740 PYs)	Zidovudine vs. no zidovudine	Mean age, 26 y; women, 100%; median duration of relationship with HIV-positive partner, 3 y; consistent condom use, 56%; regular sexual intercourse, 53%; anal sex, 15%; oral sex, 48%	Number screened not reported, 525 eligible, 436 enrolled, number withdrew and percentage analyzed unclear; data from 103 PYs excluded	Not reported	Not reported	Seroconversions, zidovudine vs. no zidovudine: 3.8/100 PYs vs. 4.4/100 PYs; adjusted RR, 0.5 (95% CI, 0.1 to 0.9)	Fair

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Appendix Table 2—**Continued**

Study, Year (Reference)	Study Design Details	Location	Duration of Follow-up	Treatment and Comparison Groups	Demographic Characteristics/Baseline Disease	Participants	Virologic Response	CD4 Cell Count Response	Outcomes	Quality Rating
Reynolds et al, 2011 (22)	Retrospective cohort	Uganda	Median, 1.57 y before ART initiation and 1.54 y after ART initiation	Pre-ART vs. post-ART transmission	Male index partner, 58% (142/250); consistent condom use, 4%; polygamous husbands, 20%	15 000 screened, 250 eligible, 250 enrolled	6 months: 71.4% (20/28) below detectable limit and remaining 28.6% (8/28) below 2000 copies/mL 12 months: 85.2% (23/27) below 400 copies/mL, 14.8% (4/27) ranging from 2293 to 672 513 copies/mL 24 months: 100% (28/28) below 400 copies/mL	Not reported	Transmission: Pre-ART: 9.2/100 PYs (95% CI, 6.59 to 12.36/100 PYs) Post-ART: 0/53.6 PYs (95% CI −11.91 to 16.38/53.6 PYs); $P = 0.010$	Fair
Sullivan et al, 2009 (23)	Retrospective cohort (abstract only)	Rwanda and Zambia	Median, 512 d (1.4 y)	ART vs. no ART	Not reported	2993 enrolled	Not reported	Not reported	Transmission, ART vs. no ART: 4/175 (0.7/100 PYs) vs. 171/175 (3.4/100 PYs); RR, 0.21 (95% CI, 0.08 to 0.59); HR, 0.21 (95% CI, 0.09 to 0.52)	Could not assess for quality
Lu et al, 2010 (24)	Retrospective cohort	China	Median, 2.8 y	ART vs. no ART	Mean age, 44 y; women, 43%; regular sexual intercourse, 84%; condom use, 78%; monogamous, 99%	4348 screened, 4301 eligible, 1927 enrolled, no withdrawals, 100% analyzed	Not reported	Not reported	Seroconversions, ART vs. no ART: 66/1369 (4.8%) vs. 18/558 (3.2%); univariate RR, 0.76 (95% CI, 0.45 to 1.28)	Fair

ART = antiretroviral therapy; HR = hazard rate; HSV = herpes simplex virus; IDU = injection drug user; IQR = interquartile range; IR = incidence rate; ND = not detectable; PY = person-year; RCT = randomized, controlled trial; RR = relative risk; STD = sexually transmitted disease.

Appendix Table 3. Cardiovascular Events and ART Use

Study, Year (Reference)	Study Name	Duration of Follow-up	Population Characteristics	Interventions	Adjusted Variables for Statistical Analysis	MI	Other Cardiovascular Events/Composite Outcomes
Bedimo et al, 2011 (54)	NA	Median, 4 y	Participants: 19 424 Median age: 46 y Men: 98% Smokers: 29% Diabetes: 13% Hypertension: 38% Hypercholesterolemia: 26% Chronic kidney disease: 8% HCV infection: 32%	Any ART (n = 14 063)	Age, diabetes, hypertension, hypercholesterolemia, and smoking	Adjusted HR for cumulative MI exposure (95% CI): Abacavir: 1.18 (0.92 to 1.5) Other NRTIs: 0.99 (0.87 to 1.11) Mono- or dual-ART: 1.29 (1.10 to 1.52)	Not reported
Worm et al, 2010 (53)	DAD Study	Median, 6 y	Participants: 33 308 Median age: 44 y Women: 26% Race: not reported Framingham risk, total population: Low: 53% Moderate: 15% High: 4% Framingham risk, patients with MI: Low: 26% Moderate: 30% High: 18% Framingham risk, patients without MI: Low: 54% Moderate: 15% High: 4%	PIs: nelfinavir (n = 10 370), indinavir (n = 11 985), lopinavir–ritonavir (n = 9995), and saquinavir (n = 8070) NRTIs: zidovudine (n= 25 754), didanosine (n = 13 851), zalcitabine (n = 4951), stavudine (n = 16 840), lamivudine (n = 28 835), abacavir (n = 12 511), and tenofovir (n = 13 100) NNRTIs: nevirapine (n = 12 194) and efavirenz (n = 13 522)	Age, sex, HIV transmission group, race, calendar year, cohort, smoking, family history of CVD, previous CV event, BMI, and exposure to other ART	Adjusted relative rate (95% CI): Cumulative PI use: Nelfinavir: 1.04 (0.98 to 1.11) Indinavir: 1.12 (1.07 to 1.18) Lopinavir–ritonavir: 1.13 (1.05 to 1.21) Saquinavir: 1.04 (0.98 to 1.11) Per year of PI exposure: Indinavir: 1.11 (1.05 to 1.18) Indinavir plus ritonavir: 1.18 (1.07 to 1.30) Saquinavir: 1.07 (0.97 to 1.20) Saquinavir plus ritonavir: 1.06 (0.97 to 1.14) Adjusted relative rate for cumulative NRTI use (95% CI): Zidovudine: not significant (data not reported) Didanosine: 1.41 (1.09 to 1.82) Zalcitabine: not significant (data not reported) Stavudine: not significant (data not reported) Lamivudine: not significant (data not reported) Abacavir: 1.07 (1.00 to 1.14) Tenofovir: 1.04 (0.91 to 1.18) Recent NRTI use: Abacavir: 1.7 (1.17 to 2.47) Tenofovir: 1.14 (0.85 to 1.53) Cumulative NNRTI use: Nevirapine: 0.97 (0.92 to 1.03) Efavirenz: 1.02 (0.96 to 1.08)	Not reported
Sabin et al, 2008 (52)	DAD Study	Median, 5 y	Participants: 33 347 Mean age: 43 y Women: 26% Framingham risk, patients with MI: Low: 22% (113/517) Moderate: 26% (134/517) High: 23% (120/517) Unknown: 29% (150/517)	NRTIs (numbers not reported): zidovudine, didanosine, stavudine, lamivudine, abacavir	Age, sex, risk group, race, cohort, BMI, family history of CVD, smoking, previous CV event, year, and cumulative exposure to other ART	Adjusted relative rate (95% CI): Cumulative exposure: Zidovudine: 1.04 (0.99 to 1.09) Didanosine: 1.00 (0.93 to 1.07) Stavudine: 1.02 (0.95 to 1.09) Lamivudine: 0.99 (0.93 to 1.06) Abacavir: 1.00 (0.92 to 1.08) Recent exposure: Zidovudine: 1.22 (0.82 to 1.81) Didanosine: 1.53 (1.10 to 2.13) Stavudine: 1.22 (0.84 to 1.77) Lamivudine: 1.69 (1.02 to 2.8) Abacavir: 1.94 (1.48 to 2.55) Past exposure: Zidovudine: 1.29 (0.89 to 1.85) Didanosine: 1.08 (0.84 to 1.39) Stavudine: 1.24 (0.93 to 1.66) Lamivudine: 1.45 (0.88 to 2.4) Abacavir: 1.29 (0.94 to 1.77)	Adjusted relative rates for MI, CV death, or invasive CV procedure (95% CI): Cumulative exposure: Zidovudine: 1.04 (1.00 to 1.08) Didanosine: 0.99 (0.94 to 1.05) Stavudine: 1.04 (0.99 to 1.10) Lamivudine: 1.01 (0.96 to 1.06) Abacavir: 1.03 (0.96 to 1.10) Any recent exposure: Zidovudine: 0.98 (0.79 to 1.21) Didanosine: 1.40 (1.11 to 1.77) Stavudine: 0.99 (0.78 to 1.25) Lamivudine: 1.15 (0.91 to 1.44) Abacavir: 1.63 (1.3 to 2.04)

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Appendix Table 3—Continued

Study, Year (Reference)	Study Name	Duration of Follow-up	Population Characteristics	Interventions	Adjusted Variables for Statistical Analysis	MI	Other Cardiovascular Events/Composite Outcomes
Friis-Møller et al, 2007 (51) and 2003 (50)	DAD Study	Median, 5 y	Participants: 23 437 Median age: 39 y Women: 24% Current/former smokers: 61% Hypertension: 14% Dyslipidemia: 42%	Any ART (n = 21 921), PIs (n = 18 919), and NNRTIs (n = 15 142)	Model 1: Age, sex, cohort, HIV transmission group, race, age, BMI, family history of CVD, smoking, previous CV event, and calendar year Model 2: All from model 1 plus total cholesterol level, HDL cholesterol level, hypertension, and diabetes	ART use: Incidence: 97 events/16 805 PYs (5.77/1000 PYs) Adjusted relative rate, model 1 (95% CI): 1.16 (1.09 to 1.23) Adjusted relative rate for PI use (95% CI): Model 1: 1.16 (1.10 to 1.23) Model 2: 1.10 (1.04 to 1.18) Excluding patients exposed to NRTIs: 1.15 (1.06 to 1.25) Adjusted relative rate for NRTI use (95% CI): Model 1: 1.05 (0.98 to 1.13) Model 2: 1.00 (0.93 to 1.09) Excluding patients exposed to PIs: 0.94 (0.74 to 1.19)	Not reported
Obel et al, 2010 (55)	Danish HIV cohort study	Mean, 6 y	Participants: 2952 Median age: 39 y Men: 76% CV risk factors: not reported	Triple NRTI regimen, including abacavir, and NNRTI or PI regimen, including abacavir Specific drugs: abacavir (n = 1761), zidovudine (n = 2711), lamivudine (n = 2867), stavudine (n = 1031), didanosine (n = 813)	Age, sex, year of diagnosis, year of ART initiation, CD4 cell count, viral load, race, injection drug use, use of other antiretrovirals, and comorbid conditions	Abacavir use vs. nonuse: Any abacavir exposure: Incidence, 2.4/1000 PYs (95% CI, 1.7 to 3.4/1000 PYs) vs. 5.7/1000 PYs (95% CI, 4.1 to 7.9/1000 PYs); adjusted RR, 2.0 (95% CI, 1.1 to 3.6) RR (95% CI): Actual abacavir use: 1.95 (1.05 to 3.6) Early abacavir use: 2.37 (0.88 to 6.36) Abacavir as part of triple NRTI: 1.91 (0.88 to 4.17) Abacavir with NNRTI or PI: 2.06 (1.06 to 4.01) Abacavir initiated ≤2 y of ART: 1.77 (0.82 to 3.82) Abacavir initiated >2 y of ART: 2.66 (1.31 to 5.39)	Not reported
Ribaudo et al, 2011 (56)	NA	Median, 3 y	Participants: 5056 (1122 with 6-y data) Median age: 37 y Female: 18% White: 40% Black: 36% Hispanic: 21% Previous injection drug use: 10% ≥2 CVD risk factors: 15% CVD 10-y risk score ≤10: 5%	Abacavir (n = 1704) and no abacavir (n = 3352)	Age, sex, race, CVD risk factors, smoking, and family history of CVD	Adjusted HR, abacavir use vs. nonuse (95% CI): 1 y: 0.7 (0.2 to 2.6) 6 y: 0.6 (0.3 to 1.4)	Adjusted HR for serious CVD events, abacavir use vs. nonuse (95% CI): 1 y: 1.1 (0.5 to 2.1) 6 y: 0.9 (0.5 to 1.3)

ART = antiretroviral therapy; BMI = body mass index; CV = cardiovascular; CVD = cardiovascular disease; DAD = Data Collection on Adverse Events of Anti-HIV Drugs; HCV= hepatitis C virus; HDL = high-density lipoprotein; HR = hazard ratio; MI = myocardial infarction; NA = not applicable; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor, PY = person-year; RR = relative risk.