Screening for HIV Infection in Asymptomatic, Nonpregnant Adolescents and Adults
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Untreated HIV infection can result in significant morbidity, mortality, and HIV transmission. A 2012 review for the US Preventive Services Task Force (USPSTF) found antiretroviral therapy (ART) associated with improved clinical outcomes and decreased transmission risk in persons with CD4 cell counts less than 500/mm³.

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

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

STUDY SELECTION Nonpregnant individuals 12 years and older; randomized clinical trials (RCTs) and controlled observational studies of screening vs no screening, alternative screening strategies, earlier vs later initiation of ART, and long-term harms of ART.

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

MAIN OUTCOMES AND MEASURES Mortality, AIDS events, quality of life, function, and HIV transmission; harms of screening and long-term (≥2 years) harms of ART; screening yield.

RESULTS Eighteen new studies (5 RCTs, 11 cohort studies, and 2 systematic reviews; N = 266,563) were included, and 11 studies (2 RCTs and 9 cohort studies; N = 218,542) were carried forward from the prior USPSTF report. No study directly evaluated effects of HIV screening vs no screening on clinical outcomes or harms, or the yield of alternative screening strategies. Two newly identified RCTs conducted completely or partially in low-resource settings found ART initiation at CD4 cell counts greater than 500/mm³ associated with lower risk of a composite outcome of mortality, AIDS-defining events, or serious non-AIDS events (relative risk [RR], 0.44 [95% CI, 0.31-0.63] and RR, 0.57 [95% CI, 0.35-0.95]); results were consistent with those from a large observational study. Early ART was not associated with increased risk of cardiovascular events. Early ART initiation was associated with sustained reduction in risk of HIV transmission at 5.5 years (RR, 0.07 [95% CI, 0.02-0.22] for linked transmission). New evidence regarding the association between abacavir use and risk of cardiovascular events was inconsistent. Certain antiretroviral regimens were associated with increased risk of long-term neuropsychiatric, renal, hepatic, and bone adverse events.

CONCLUSIONS AND RELEVANCE In nonpregnant adolescents and adults there was no direct evidence on the clinical benefits and harms of screening for HIV infections vs no screening, or the yield of repeat or alternative screening strategies. New evidence extends effectiveness of ART to asymptomatic individuals with CD4 cell counts greater than 500/mm³ and shows sustained reduction in risk of HIV transmission at longer-term follow-up, although certain ART regimens may be associated with increased risk of long-term harms.

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Approximately 990,000 people in the United States were living with HIV infection in 2016. Among infected individuals, it was estimated that approximately 15% were unaware of their status. The incidence of HIV infection in the United States decreased from about 42,000 in 2011 to 40,000 each year from 2013 to 2016. Screening could identify HIV infection in asymptomatic patients, who could benefit from interventions to reduce risk of AIDS-related clinical events and transmission.

In 2013, the US Preventive Services Task Force (USPSTF) recommended that clinicians screen all adolescents and adults aged 15 to 65 years for HIV infection, as well as younger adolescents and older adults at increased risk (A recommendation). This recommendation, which expanded on a previous USPSTF recommendation for risk-based HIV screening, was based on new evidence supporting the effectiveness of earlier vs delayed antiretroviral therapy (ART) for HIV infection and the effectiveness of ART for decreasing transmission risk.

This evidence report updates the previous USPSTF HIV screening review in nonpregnant adolescents and adults to inform an updated USPSTF recommendation. It targets gaps identified in the prior review, including direct evidence on the benefits and harms of screening, the yield of screening at different intervals, and long-term harms of currently recommended ART regimens. This review also addresses effects of earlier vs later initiation of ART, focusing on patients with baseline CD4 cell counts greater than 350/mm³, given expanded treatment indications for ART. Prenatal HIV screening is addressed in a separate report.

**Methods**

**Scope of the Review**

Detailed methods and additional study details are available in the full evidence report at https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/human-immunodeficiency-virus-hiv-infection-screening. Figure 1 shows the analytic framework and key questions (KQs) that guided the review.

**Data Sources and Searches**

Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews were searched.
for English-language articles published from 2012 through June 2018 (eMethods 1 in the Supplement). Searches were supplemented by review of reference lists from relevant systematic reviews and prior USPSTF reports. Since June 2018, ongoing surveillance was conducted through article alerts and targeted searches of journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on January 25, 2019, and identified no eligible studies.

Study Selection
Two investigators independently reviewed titles, abstracts, and full-text articles using predefined eligibility criteria. Randomized clinical trials (RCTs), cohort studies, and case-control studies of adolescents (13 to <18 years) and adults were eligible for all KQs. Studies that directly evaluated the effects of HIV screening vs no screening in asymptomatic individuals on clinical outcomes (mortality, AIDS and opportunistic infections, quality of life, function, HIV transmission, and harms) were eligible for KQ1 and KQ3. Studies that evaluated the yield (number of new diagnoses per tests performed) of screening for HIV infection at different intervals or in different risk groups were eligible for KQ2. Studies that compared effects of initiating ART at higher vs lower CD4 cell count on clinical outcomes were eligible for KQ4; observational studies had to enroll at least 1000 patients. Studies that evaluated longer-term (≥2 years) harms associated with currently recommended ART regimens were eligible for KQ5. This update focused on studies conducted in the United States and other settings with similar prevalence and management of HIV infection, unless such studies were not available.

Data Abstraction and Quality Rating
For each study, one investigator abstracted information on populations, interventions or screening instruments, comparators, adherence, outcomes, study designs, and settings. A second investigator reviewed abstracted information for accuracy. Randomized trials of early vs delayed ART primarily reported outcomes using hazard
Table 1. Randomized Clinical Trials of Immediate vs Delayed Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Source</th>
<th>Primary Composite Outcome</th>
<th>Mortality</th>
<th>AIDS-Related Events</th>
<th>Tuberculosis or Bacterial Infection</th>
<th>HIV Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSIGHT START</td>
<td>All-cause mortality, serious AIDS-related events, and serious non-AIDS-related events: RR, 0.44 (95% CI, 0.31-0.63)</td>
<td>All-cause mortality: RR, 0.58 (95% CI, 0.29-1.18)</td>
<td>Serious AIDS-related event: RR, 0.28 (95% CI, 0.16-0.31)</td>
<td>Tuberculosis: RR, 0.20 (95% CI, 0.12-0.76)</td>
<td>Grade 4 bacterial infection: RR, 0.39 (95% CI, 0.21-0.73)</td>
</tr>
<tr>
<td>TEMPRANO ANRS</td>
<td>All-cause mortality, progression to AIDS, AIDS-defining cancer, or non-AIDS-defining invasive bacterial disease: RR, 0.57 (95% CI, 0.35-0.95)</td>
<td>All-cause mortality: RR, 0.79 (95% CI, 0.24-2.57)</td>
<td>Progression to AIDS: RR, 0.55 (95% CI, 0.29-1.05)</td>
<td>Tuberculosis: RR, 0.54 (95% CI, 0.27-1.09)</td>
<td>Invasive bacterial disease: RR, 0.59 (95% CI, 0.20-1.80)</td>
</tr>
<tr>
<td>SMART</td>
<td>All-cause mortality or opportunistic disease: RR, 0.31 (95% CI, 0.11-0.83)</td>
<td>All-cause mortality: RR, 0.37 (95% CI, 0.11-1.02)</td>
<td>Any AIDS-related event: RR, 0.65 (95% CI, 0.44-0.95)</td>
<td>Tuberculosis: RR, 0.12 (95% CI, 0.08-0.44)</td>
<td>Serious bacterial disease: RR, 0.11 (95% CI, 0.05-0.003)</td>
</tr>
</tbody>
</table>

Abbreviations: HPTN, HIV Prevention Trials Network; NR, not reported; RR, relative risk; SMART, Strategies for Management of Antiretroviral Therapy; START, Strategic Initiatives in Global HIV Trials Strategic Timing of Antiretroviral Treatment.

Data Synthesis

Results were summarized qualitatively. Meta-analysis was not performed because of clinical and methodological heterogeneity among studies. For all KQs, the overall strength of the body of evidence was assessed as high, moderate, low, or insufficient using methods developed by the USPSTF (eMethods 2 in the Supplement). Individual study quality ratings are provided in eTables 1-6 in the Supplement.

Results

Two reviewers independently assessed 4882 unique citations and 348 full-text articles for inclusion (Figure 2). Eighteen new studies (5 RCTs, 11 cohort studies, 2 systematic reviews) and 9 articles were included, and 11 studies (2 RCTs and 9 cohort studies) were carried forward from the prior USPSTF report.

Screening

Key Question 1. What are the benefits of screening for HIV infection in asymptomatic, nonpregnant adolescents and adults on mortality, AIDS and opportunistic infections, quality of life, function, and reduced transmission of HIV and other sexually transmitted infections?

No study met inclusion criteria for KQ1.

Key Question 2. What is the yield (number of new diagnoses per test performed) of screening for HIV infection at different intervals in asymptomatic, nonpregnant adolescents and adults, and how does the screening yield vary in different risk groups?

No study met inclusion criteria for KQ2.

Key Question 3. What are the harms of screening for HIV infection in asymptomatic, nonpregnant adolescents and adults?

No study met inclusion criteria for KQ3.

Treatment Initiation at Higher vs Lower CD4 Cell Count

Key Question 4. What are the effects of initiating ART in adolescents and adults with chronic HIV infection at a higher vs lower CD4 cell count on mortality, AIDS and opportunistic infections, quality of life, function, reduced transmission of HIV and other sexually transmitted infections, and harms?

Effects of ART in reducing risk of mortality and AIDS-associated events in people with advanced immunodeficiency (eg, CD4 cell count <200/mm^3) are well established. The prior USPSTF review included consistent evidence from 2 RCTs (n = 2240) (Table 1) and 4 observational studies (n = 110111)

ratios. Relative risks (RRs) were calculated based on reported event rates, to calculate absolute risk differences (ARDs). RRs and hazard ratios were very similar, and reported results are based on RRs. Two independent investigators assessed the quality of each study as good, fair, or poor using predefined criteria developed by the USPSTF (eMethods 2 in the Supplement). Individual study quality ratings are provided in eTables 1-6 in the Supplement.
Table 2. Cohort Studies of Early vs Delayed Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Source</th>
<th>CD4 Cell Count at ART Initiation, /mm³</th>
<th>All-Cause Mortality, HR/RR (95% CI)</th>
<th>AIDS-Related Events Event, HR/RR (95% CI)</th>
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<tbody>
<tr>
<td>Studies Included in Prior Report</td>
<td></td>
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<tr>
<td>CASCADE Collaboration et al, 45 2011</td>
<td>≥350 to &lt;500 vs no treatment initiation</td>
<td>HR, 0.51 (0.33-0.80)</td>
<td>Progression to AIDS or death HR, 0.75 (0.49-1.14)</td>
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<tr>
<td></td>
<td>≥500 vs no treatment initiation</td>
<td>HR, 1.02 (0.49-2.12)</td>
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<tr>
<td>Kitahata et al, 42 2009</td>
<td>≥350 to 500 vs &lt;350</td>
<td>RR, 0.61 (0.46-0.83)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>&gt;500 vs ≤500</td>
<td>RR, 0.54 (0.35-0.83)</td>
<td></td>
</tr>
<tr>
<td>May et al, 43 2007</td>
<td>≥350 vs &lt;250</td>
<td>HR, 0.34 (0.27-0.44)</td>
<td>Progression to AIDS or death HR, 0.23 (0.19-0.27)</td>
</tr>
<tr>
<td>Ray et al, 44 2010</td>
<td>500 vs 350</td>
<td>HR, 0.99 (0.82-1.19)</td>
<td>Progression to AIDS or death HR, 0.72 (0.64-0.81)</td>
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<tr>
<td></td>
<td>350 vs 200</td>
<td>HR, 0.85 (0.68-1.05)</td>
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<tr>
<td>Sterne et al, 46 2009</td>
<td>&gt;450 to 550 vs ≥350 to 450</td>
<td>HR, 0.93 (0.6-1.40)</td>
<td>Progression to AIDS or death HR, 0.90 (0.76-1.29)</td>
</tr>
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<td>New Studies</td>
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<tr>
<td>Edwards et al, 21 2015</td>
<td>&lt;500 vs &lt;350</td>
<td>5-y follow-up: RR, 0.87 (0.79-0.95)</td>
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<tr>
<td></td>
<td></td>
<td>Ages 18-34 y: RR, 0.95 (0.79-1.15)</td>
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<tr>
<td></td>
<td></td>
<td>Ages 35-44 y: RR, 0.93 (0.82-1.05)</td>
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<tr>
<td></td>
<td></td>
<td>Ages 45-65 y: RR, 0.81 (0.71-0.93)</td>
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<tr>
<td></td>
<td></td>
<td>10-y follow-up: RR, 0.93 (0.86-1.00)</td>
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<td>Ages 18-34 y: RR, 1.00 (0.87-1.15)</td>
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<td></td>
<td></td>
<td>Ages 35-44 y: RR, 0.92 (0.83-1.01)</td>
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<td></td>
<td></td>
<td>Ages 45-65 y: RR, 0.89 (0.80-0.99)</td>
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<tr>
<td>Lima et al, 20 2015</td>
<td>&lt;350 (2007-2012)</td>
<td>Probability, 0.05 (IQR, 0.03-0.08)</td>
<td>AIDS-defining illness Probability, 0.05 (IQR, 0.03-0.08)</td>
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<tr>
<td></td>
<td>≥350 (2007-2012)</td>
<td>Probability, 0.02 (IQR, 0.01-0.04)</td>
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<tr>
<td></td>
<td>&lt;500 (2007-2012)</td>
<td>Probability, 0.05 (IQR, 0.03-0.02)</td>
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</tr>
<tr>
<td></td>
<td>≥500 (2007-2012)</td>
<td>Probability, 0.01 (IQR, 0.01-0.02)</td>
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</tr>
<tr>
<td>Lodi et al, 19 2015</td>
<td>≥500 vs &lt;500</td>
<td>Probability, 0.98 (0.97-0.99)</td>
<td>Progression to AIDS or death RR, 0.94 (0.93-0.94)</td>
</tr>
<tr>
<td></td>
<td>≥500 vs &lt;350</td>
<td>Probability, 0.94 (0.91-0.97)</td>
<td>Progression to AIDS or death RR, 0.83 (0.81-0.85)</td>
</tr>
<tr>
<td></td>
<td>Subgroup of patients with baseline CD4 cell count &gt;500/mm³ vs entire sample: 7.1% vs 4.9%; RR, 1.52 (1.34-1.77)</td>
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<tr>
<td>Lodi et al, 18 2017</td>
<td>≥500 vs &lt;500</td>
<td>General HIV population: RR, 0.97 (0.94-0.99)</td>
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<tr>
<td></td>
<td></td>
<td>General HIV population patients with CD4 cell count ≥500/mm³: RR, 0.76 (0.58-0.97)</td>
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<tr>
<td></td>
<td></td>
<td>VA population: RR, 0.95 (0.93-0.98)</td>
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<tr>
<td></td>
<td></td>
<td>≥500 vs &lt;350</td>
<td>General HIV population: RR, 0.93 (0.87-0.98)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>General HIV population patients with CD4 cell count ≥500/mm³: RR, 0.64 (0.41-0.95)</td>
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<tr>
<td></td>
<td></td>
<td>VA population: RR, 0.90 (0.85-0.95)</td>
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</tbody>
</table>

Abbreviations: ART, antiretroviral therapy; CASCADE, Concerted Action on SeroConversion to AIDS and Death in Europe; HR, hazard ratio; IQR, interquartile range; NR, not reported; RR, relative risk; VA, US Department of Veterans Affairs.

(Table 2) that initiation of ART at CD4 cell counts greater than 350/mm³ to 500/mm³ or 550/mm³ was associated with decreased risk of death or AIDS events compared with initiation at lower CD4 cell counts; 1 trial 46 also found early ART associated with substantially decreased risk of HIV transmission. Observational evidence on initiation of ART at CD4 cell counts greater than 500/mm³ did not consistently demonstrate beneficial associations with clinical outcomes (Table 2). 42,44-46 Neither the prior report nor this update found evidence on the effects of early vs later ART initiation on quality of life or function.

New evidence on initiation of ART in people with CD4 cell counts of 350/mm³ to 500/mm³ or 550/mm³ vs delayed initiation was
available from longer-term (up to 5.5 years) follow-up of a trial included in the prior USPSTF report (the HIV Prevention Trials Network [HPTN] 052 study [n = 1701]),13,14 2 new RCTs (n = 6529),13-15 and 3 large (≥1000 participants [total n = 63 478]), fair-quality cohort studies (reported in 4 articles) conducted in the United States, Europe, and Canada18-21 (Table 1 and Table 2; eTables 7-10 in the Supplement).

The new International Network for Strategic Initiatives in Global HIV Trials Strategic Timing of Antiretroviral Treatment (INSIGHT START, or START) trial (n = 4473) randomized ART-naive, HIV-positive participants with CD4 cell counts greater than 500/mm³ at baseline (median, 651/mm³) to immediate ART vs deferred initiation at CD4 cell counts less than 350/mm³. About half of participants were from high-income geographic regions (United States, Europe, and Australia). Mean follow-up duration was 3 years. The other new RCT, the African Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-Infected Adults (TEMRANO ANRS 12136) trial (n = 2056), enrolled people with baseline CD4 cell counts less than 800/mm³ without an indication for ART, based on then-current World Health Organization guidelines.18 Follow-up was 2.5 years. A prespecified subgroup analysis was conducted in people with a CD4 cell count of 500/mm³ or greater at baseline (<40% of trial population). Treatment initiation thresholds for delayed ART varied according to changing World Health Organization guidance. Both trials evaluated a composite primary outcome consisting of mortality, AIDS-defining events, and serious non-AIDS events; neither trial evaluated effects on risk of HIV transmission or other sexually transmitted infections. The START trial was rated good quality and TEMPRANO ANRS 12136 fair quality because of open-label design and changing criteria for initiation of ART. The HPTN 052 trial was previously rated good quality.6

Three new, fair-quality cohort studies enrolled a total of 63 478 participants (Table 2; eTables 9-10 in the Supplement).18-21 Two articles were based on the large HIV Cohorts Analyzed Using Structural Approaches to Longitudinal (HIV-CAUSAL) Collaboration (n = 55 826)16,19 of 12 US and European cohort studies (mean age, 35 years). Three-year data from the HIV CAUSAL Collaboration were included in the prior USPSTF report44; new articles report 7-year outcomes18-21 and subgroup analyses of adults older than 50 years.18 The other 2 studies evaluated cohorts from Canada (n = 4120)20 and the United States (n = 3532).21 All studies reported analyses adjusted for confounders, most commonly age, sex, and HIV viral load at baseline, and focused on effects of ART on mortality and AIDS-associated events.

Immediate vs Delayed ART in People With Baseline CD4 Cell Count Greater Than 500/mm³

Two new RCTs found initiation of ART at baseline CD4 cell counts greater than 500/mm³ more beneficial than delayed initiation (Table 1; eTables 7-8 in the Supplement).13,15 In START, early ART was associated with decreased risk of the primary composite outcome of all-cause mortality, serious AIDS-related events, and serious non-AIDS-related events after a mean of 3 years (1.8% vs 4.1%; RR, 0.44 [95% CI, 0.31 to 0.63]; ARD, −2.3% [95% CI, −3.2% to −1.3%]), compared with initiation at CD4 cell counts less than 350/mm³.13,15 When outcomes were disaggregated, immediate ART was associated with reduced risk of serious AIDS-related events, tuberculosis, and serious bacterial infection. Associations with all-cause mortality and AIDS-related mortality favored immediate ART but were not statistically significant; there were only 5 cases of AIDS-related mortality.13 Results for the primary outcome were similar when analyses were stratified by geographic region (high or low income, P = .55 for interaction), age (>35 years, >35 years), sex, race, baseline HIV viral load, smoking status, and cardiovascular risk. In TEMPRANO ANRS 12136, in a prespecified subgroup analysis of patients with CD4 cell counts of 500/mm³ or greater at baseline, immediate ART was associated with decreased risk of the primary composite outcome of all-cause mortality, progression to AIDS, AIDS-defining cancer, or non-AIDS-defining invasive bacterial disease after 2.5 years (5.3% vs 9.2%; RR, 0.57 [95% CI, 0.35 to 0.95]; ARD, −3.9% [95% CI, −7.4% to −0.4%]).19 Associations with all-cause mortality, progression to AIDS, tuberculosis, and invasive bacterial disease also favored immediate ART but were not statistically significant (Table 1). Results were similar when adjusted for study center and concomitant isoniazid use.

The new cohort studies also found initiation of ART at CD4 cell counts greater than 500/mm³ associated with beneficial effects on clinical outcomes. An analysis of the HIV-CAUSAL Collaboration (n = 55 826; median baseline CD4 cell count, 376/mm³) found ART initiation at CD4 cell counts less than 350/mm³ associated with increased risk of the composite end point of progression to AIDS or death (8.5% vs 7.1%; RR, 1.20 [95% CI, 1.17 to 1.23]) after 7 years, compared with immediate initiation (Table 2).19 Associations with immediate ART were stronger in the subgroup of patients with baseline CD4 cell count greater than 500/mm³ (71% vs 4.9%; RR, 1.52 [95% CI, 1.34 to 1.77]). Initiation of ART at CD4 cell counts less than 350/mm³ was also associated with slightly increased risk of all-cause mortality compared with immediate initiation in the whole sample (4.2% vs 4.0%; RR, 1.06 [95% CI, 1.03 to 1.10]). Findings were similar in an HIV-CAUSAL analysis that focused on patients older than 50 years (n = 9599).18 Another cohort study (n = 4120) found that in 2007 to 2012, ART initiation at CD4 cell counts of 500/mm³ or greater was associated with lower probability of mortality (0.01 [interquartile range (IQR), 0.01-0.02]) and AIDS-related morbidity (0.01 [IQR, 0.00-0.01]) than initiation at CD4 cell counts less than 500/mm³ (0.05 [IQR, 0.03-0.08] and 0.03 [IQR, 0.01-0.04], respectively) or less than 350/mm³ (0.05 [IQR, 0.03-0.08] and 0.05 IQR, 0.03-0.08, respectively) (Table 2).

Immediate vs Delayed ART in People With Baseline CD4 Cell Count of 350/mm³ to 500/mm³

The prior USPSTF report6,7 included 1.7-year results from the HPTN 052 trial (n = 1763), which enrolled persons with baseline CD4 cell count 350/mm³ to 550/mm³.40 Longer follow-up from HPTN 052 is now available. At mean 2.1 years follow-up, initiation of ART at CD4 cell counts of 350/mm³ to 550/mm³ was associated with decreased risk of AIDS-related events (4.5% vs 7.0%; RR, 0.65 [95% CI, 0.44 to 0.95]), mostly due to tuberculosis events (1.9% vs 3.9%; RR, 0.49 [95% CI, 0.28 to 0.88]), vs initiation at CD4 cell counts less than 250/mm³. Effects on the primary composite outcome (death, serious AIDS events, and serious non-AIDS events) (6.4% vs 8.8%; RR, 0.73 [95% CI, 0.53 to 1.02]), all-cause mortality, and AIDS-related mortality favored early ART (Table 1) but were not statistically significant. HPTN 052 also found that at 5 years (n = 1701), early ART remained associated with decreased risk of any HIV transmission to uninfected partners (2.1% vs 6.6%; RR, 0.32 [95% CI, 0.19
to 0.53) as well as virologically linked transmission (0.3% vs 4.9%; RR, 0.07 [95% CI, 0.02 to 0.22]); almost all of the effect was attributable to fewer virologically linked cases (Table 1). A new US-based cohort study (n = 3532) found that relative to initiation of ART at CD4 cell counts less than 500/mm³, initiation at counts less than 200/mm³ was associated with greater risk of 10-year all-cause mortality (RR, 1.25 [95% CI, 1.08 to 1.44]) than initiation at counts less than 350/mm³ (RR, 1.08 [95% CI, 1.00 to 1.16]) (Table 2). However, the confidence intervals for the risk estimates overlapped and there was no test for statistical significance for the difference.

Harms of Immediate vs Delayed ART

Two RCTs (n = 4950) found no evidence of an increased risk of cardiovascular events with early vs delayed ART, although data were limited by small numbers of events (eTable 8 in the Supplement). The START, HPTN 052, and TEMPRANO ANRS 12136 trials also found no significant differences between early vs delayed initiation of ART and risk of other harms, such as liver disease, renal disease, and new-onset diabetes. Few adverse events were reported and some risk estimates were imprecise.

Longer-Term Harms of Treatment

Key Question 5. What are the longer-term harms (≥2 years) associated with currently recommended ART regimens?

The prior USPSTF report focused on longer-term cardiovascular harms of ART. Details on evidence reviewed for this update on longer-term cardiovascular and additional harms are reported in eTables 11-13 in the Supplement.

Cardiovascular Events

The prior USPSTF report found mixed evidence on the risk of long-term cardiovascular events with abacavir use based on 4 cohort studies, including the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) observational study, and evidence of no increased cardiovascular risk associated with efavirenz use. A meta-analysis of 26 trials (total n = 9868) published since the prior report found no association between ART containing abacavir vs ART without abacavir and risk of myocardial infarction (odds difference, 0.008% [95% CI, −0.26% to 0.27%]). Three observational studies (n = 75 548), including D:A:D, found no significant association between use of efavirenz and death from suicide or suicidal ideation. Use of protease inhibitors, but not nonnucleoside reverse transcriptase inhibitors, was associated with higher risk of non-AIDS-defining cancers (rate ratio, 1.03/y [95% CI, 1.01/y to 1.05/y]).

Fracture

A cohort study (n = 11 820) found ever using tenofovir associated with increased risk of fracture (incidence rate ratio, 1.40 [95% CI, 1.15 to 1.70]) but no association between cumulative exposure to tenofovir and risk of fracture (incidence rate ratio per 5 years of exposure, 1.08 [95% CI, 0.94 to 1.25]).

Neuropsychiatric Events

A systematic review of 42 randomized and quasi-randomized trials (n = 8466 exposed to efavirenz; mean duration, 78 weeks) found efavirenz associated with an increased risk of severe neuropsychiatric adverse events vs ritonavir-boosted atazanavir (RR, 2.4 [95% CI, 1.5 to 3.8]), dolutegravir (RR, 16.7 [95% CI, 2.0 to 137.8]), and maraviroc (RR, 5.3 [95% CI, 1.6 to 18.1]). Three observational studies (n = 75 548), including D:A:D, found no significant association between use of efavirenz and death from suicide or suicidal ideation. Use of protease inhibitors, but not nonnucleoside reverse transcriptase inhibitors, was associated with higher risk of non-AIDS-defining cancers (rate ratio, 1.03/y [95% CI, 1.01/y to 1.05/y]).

Non-AIDS Mortality

An analysis of a European cohort (EuroSIDA [n = 12 069]) found no association between longer-term (>2 years) exposure to ART and risk of non-AIDS-related deaths after a median of 5.4 years.

Discussion

As in previous USPSTF reviews on this topic, there remains no direct evidence on clinical benefits and harms of screening for HIV infection vs no screening or the yield of repeat or alternative screening strategies. Table 3 summarizes the other evidence reviewed in this update.

New data extend evidence on effectiveness of ART to people with CD4 cell counts greater than 500/mm³, expanding on previous findings of a strong association between initiation of ART at CD4 cell counts of 350/mm³ to 500/mm³ or 550/mm³ and reduced risk of death or AIDS-related illness and substantially reduced risk of sexual transmission of HIV infection, compared with initiation at lower CD4 cell counts. New data also found effects of ART initiation at CD4 cell counts greater than 350/mm³ were sustained. Other systematic reviews on timing of ART found insufficient evidence to determine effects of initiation of ART at CD4 cell counts greater than 500/mm³.
Table 3. Summary of Evidence

<table>
<thead>
<tr>
<th>No. of Studies, No. of Participants, Study Design</th>
<th>Summary of Findings by Outcome</th>
<th>Consistency/Precision, Reporting Bias</th>
<th>Overall Risk of Bias/Quality</th>
<th>Other Limitations</th>
<th>Strength of Evidence</th>
<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>IQR1: Benefits of HIV Screening vs No Screening</td>
<td>No studies</td>
<td>NA NA NA NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>IQR2: Yield of Repeat vs 1-Time HIV Screening or of HIV Screening at Different Intervals</td>
<td>No studies</td>
<td>NA NA NA NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>IQR3: Harms of HIV Screening vs No Screening</td>
<td>No studies</td>
<td>NA NA NA NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>IQR4: Effects of Immediate vs Delayed ART</td>
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### CD4 cell count ≥500/mm³

- 2012 USPSTF review: 4 observational studies (n = 74,563) (Continued)

- New evidence: 4 studies (2 RCTs [n = 67,460] and 2 observational studies [n = 59,946])

- Two new RCTs found initiation of ART at CD4 cell counts >500/mm³ associated with decreased risk of death, AIDS events, or serious non-AIDS events (RR, 0.44 [95% CI, 0.31-0.63] and RR, 0.57 [95% CI, 0.35-0.95]).

- Four observational studies in the prior USPSTF review found inconsistent evidence on effects of initiation of ART in patients with CD4 cell counts >500/mm³ associated with decreased risk of death, AIDS events, or serious non-AIDS events.

- One RCT reported that ART drugs were provided by industry.

- Two RCTs found initiation of ART at CD4 cell counts >500/mm³ associated with lower risk of death and AIDS-related events vs delayed initiation.

- A new RCT was open-label and changed criteria for initiation of ART in the delayed therapy group over the course of the trial to match revisions to WHO recommendations and conducted a prespecified subgroup analysis of patients with baseline CD4 cell counts >500 mm³ (41% of study population).

- Median CD4 cell count was 6.71 mm³ in one trial, and in the other trial baseline CD4 cell count ranged from 500/mm³ to 8.70 mm³ (average CD4 cell count not reported in the subgroup of patients with count ≥500/mm³ at baseline).

- Patients were randomized between 2006 and 2013 in the RCTs.

- Observational studies were conducted in US and European cohorts.

(continued)
Table 3. Summary of Evidence (continued)

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>KQ5: Long-Term Harms of ART</strong></td>
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<td>2012 USPSTF review: 4 observational studies (n &gt;60 500)</td>
<td>Cardiovascular harms: a meta-analysis of 26 trials found no association between abacavir use and risk of myocardial infarction, but 2 observational studies found abacavir associated with increased risk (RR, 1.98 [95% CI, 1.72-2.29] and OR, 1.50 [95% CI, 1.26-1.79])</td>
<td>Some inconsistency between RCT and observational data regarding cardiovascular risks of abacavir; findings reasonably precise</td>
<td>Fair</td>
<td>All studies were observational</td>
<td>Low to moderate</td>
<td>Studies evaluated components of ART regimens rather than complete regimens, potentially limiting applicability to current regimens; difficult to account for potential interactions between ART drugs and patients switching ART regimens in analyses</td>
</tr>
<tr>
<td>New evidence: 11 studies (2 systematic reviews [n = 18 334], 2 trials [n = 2296], and 8 observational studies in 16 articles [n = approximately 134 225*] including longer-term follow-up from a large observational study included in the prior review)</td>
<td>Neuropsychiatric harms: a systematic review of randomized and quasi-randomized trials found efavirenz associated with increased risk of neuropsychiatric adverse events vs other antiretroviral agents</td>
<td>No reporting bias detected</td>
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<td>Hepatic harms: an observational study found tenofovir associated with increased risk of end-stage liver disease or hepatocellular carcinoma and found emtricitabine associated with decreased risk</td>
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<td>Renal harms: 2 observational studies found tenofovir associated with increased risk of chronic kidney disease, and 2 observational studies found ritonavir-boosted atazanavir and protease inhibitors associated with renal adverse events</td>
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<td>Fracture: a cohort study found ever using tenofovir associated with increased risk of fracture (IRR, 1.40 [95% CI, 1.15-1.70]) but no association between cumulative exposure to tenofovir and risk of fracture (IRR per 5 y of exposure, 1.08 [95% CI, 0.94-1.25])</td>
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Abbreviations: ART, antiretroviral therapy; IRR, incidence rate ratio; KQ, key question; NA, not applicable; OR, odds ratio; RCT, randomized clinical trial; RR, relative risk; USPSTF, US Preventive Services Task Force; WHO, World Health Organization.

* The number of participants in D:A:D cohort publications ranged from 23 905 to 49 717, depending on year of follow-up and outcome.

on clinical outcomes but were conducted before the publication of the recent trials.54,55

Understanding long-term harms of ART is important because patients are started on ART earlier and typically continue it indefinitely. As in the 2012 USPSTF report,7 new evidence regarding abacavir and cardiovascular harms remains mixed, with a discrepancy between shorter-term randomized trials (no increased risk)38 and longer-term observational studies (increased risk).23,25 A recent systematic review also noted a discrepancy between randomized trials and observational studies.56 A new analysis found no association between the currently used protease inhibitor atazanavir and risk of cardiovascular events.24 Data from randomized trials found no association between early vs later initiation of ART and increased risk of cardiovascular events.13,41 with 1 trial finding ART initiation at CD4 cell counts greater than 350/mm33 associated with a potential protective effect. Because HIV infection is itself associated with increased cardiovascular risk, effects of ART on mitigating cardiovascular risk may be greater in people with more advanced disease.57

Data are also available on other long-term harms. Although a systematic review found efavirenz associated with an increased risk of severe neuropsychiatric adverse events compared with other antiretroviral medications,39 other studies found no clear association between efavirenz use and suicidal ideation or death from suicide.32,34,35 Long-term data on neuropsychiatric adverse events associated with integrase inhibitors is limited. Some new evidence also indicates that long-term hepatic, renal, and bone (fracture) adverse events are associated with certain antiretroviral medications.28,31,33,36,37 The clinical effect of such adverse events depends on their reversibility, their severity, and the availability of effective alternative ART regimens. Abacavir and efavirenz are not recommended as part of initial ART in most people with HIV, although they are recommended in certain clinical situations.8

No clinical study evaluated the yield of repeat vs 1-time screening or of screening at different intervals. Modeling studies suggest that repeat screening as frequently as once every 3 months may be cost-effective in high-risk individuals, depending on testing...
frequency, HIV incidence, HIV risk category, test assay, and other factors. A recent Centers for Disease Control and Prevention systematic review found insufficient evidence to support general recommendations on screening more frequently than annually in men who have sex with men but noted suggestive findings from mathematical models that more frequent screening could prevent some new HIV infections and be cost-effective.

**Limitations**

This review had several limitations. First, inclusion was restricted to English-language articles, although no non-English-language studies that would have met inclusion criteria were identified. Second, it was not possible to formally assess for publication bias with graphical or statistical methods because of small numbers of studies; however, eligible unpublished trials were not identified in searches on ClinicalTrials.gov. Third, observational studies, which are susceptible to bias and confounding, were included, although results focused on studies that performed statistical adjustment for potential confounding. Fourth, some studies were conducted in resource-poor and high-prevalence settings, which could reduce applicability to US practice. Fifth, studies of long-term harms of ART often did not specify the regimen used or analyze effects of specific antiretroviral drugs rather than the regimen as a whole, some evidence on long-term harms of ART apply to drugs not considered first-line options, and analyses have difficulty in accounting for ART regimen switches.

**Conclusions**

In nonpregnant adolescents and adults there was no direct evidence on the clinical benefits and harms of screening for HIV infections vs no screening, or the yield of repeat or alternative screening strategies. New evidence extends effectiveness of ART to asymptomatic individuals with CD4 cell counts greater than 500/mm³ and shows sustained reduction in risk of HIV transmission at longer-term follow-up, although certain ART regimens may be associated with increased risk of long-term harms.


