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

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Infection with HIV-1 is estimated to affect 850 000 to 950 000 persons in the United States (1). Of those infected, 25% (180 000 to 280 000) are thought to be unaware of their status (1). Almost all patients with untreated HIV infection eventually develop AIDS (2). In the United States, more than 500 000 patients with AIDS have died; approximately 18 000 died in 2003 (3). AIDS is the seventh leading cause of death in persons 15 to 24 years of age and the fifth leading cause in persons 25 to 44 years of age (4). Since 1992, 40 000 new HIV infections have been diagnosed annually (5). Statistical modeling suggests that approximately half of HIV-infected persons in the United States acquire their infection by 25 years of age (6).

Infection with HIV causes immune deficiency to a large extent by decreasing the level and function of CD4 T lymphocytes. In untreated patients with CD4 cell counts less than 0.200×10^9 cells/L, the chance of clinical progression or death over 3 years is approximately 86% (7). A higher HIV-1 viral load also predicts faster disease progression (7--10).

To update its 1996 recommendations, the U.S. Preventive Services Task Force (USPSTF) commissioned a new systematic review of the risks and benefits of testing for anti-HIV antibodies in asymptomatic adolescents and adults (11). Another article in this issue reviews screening in pregnant women (12).

Methods

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

Briefly, we identified relevant studies from MEDLINE (1983 through 30 June 2004) and the Cochrane Clinical Trials Registry (2004, issue 2), reference lists, hand searches of relevant journals, and suggestions from experts (Appendix B, available at www.annals.org). We selected studies that provided evidence on the benefits and harms of screening, risk factor assessment, accuracy of testing, follow-up testing, interventions, acceptability of HIV testing, and cost-effectiveness of screening in outpatient settings in the highly active antiretroviral therapy (HAART) era. For interventions, we focused on studies of HAART (13, 14). We also reviewed studies on the effectiveness of counseling on risky behaviors (15) and prophylaxis against opportunistic infections (16). A separate report (17) reviews the effectiveness of other interventions (immunizations, more frequent Papanicolaou testing, and routine monitoring and follow-up).

We assessed the internal validity and relevance of included studies using predefined criteria developed by the USPSTF (Appendix C, available at www.annals.org) (18, 19). We rated the overall body of evidence for each key question using the system developed by the USPSTF. We used the results of the evidence review to construct an outcomes table estimating the effects of one-time screening for HIV infection in hypothetical cohorts of adolescents and adults. We calculated numbers needed to screen (NNS) and treat (NNT) to prevent 1 case of clinical progression or death or to cause 1 cardiovascular complication for each cohort. The point estimates and 95% CIs for NNS and NNT were based on Monte Carlo simulations.

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Results

Does Screening for HIV Infection in Asymptomatic Adolescents and Adults Reduce Premature Death and Disability or Spread of Disease?

No studies compared clinical outcomes between patients in the general population who were screened or not screened for HIV.

Can Clinical or Demographic Characteristics Identify Subgroups of Asymptomatic Adolescents and Adults at Increased Risk for HIV Infection Compared to the General Population?

A substantial proportion of Americans report behaviors that could put them at risk for HIV infection (Table 1) (20). A recent U.S. telephone survey (n = 33 913) found that 11% of sexually active respondents reported multiple partners within the last year, and 4.2% reported other high-risk behaviors (21). Adolescents (22, 23), men who have sex with men (24), and persons attending sexually transmitted disease clinics also report high rates of recent risky behaviors (25). Even in settings with good access to health care, high-risk behaviors often remain undetected (26) or fail to lead to testing despite identification (27).

The largest (n = 1 281 606) U.S. study found that 20% to 26% of HIV-infected people identified at federally funded testing sites reported no risk factors (28). Other studies in a variety of settings indicated that 7% to 51% of HIV-positive patients reported no risk factors (26, 29--36). The rate of HIV positivity in patients reporting no risk factors was lower in low-prevalence (0.1% to 2.0%) than in high-prevalence (≥5%) sites (0.2% to 0.8% vs. 1.4% to 5.7%) (28).

One good-quality prospective study in a sexually transmitted disease clinic evaluated different methods of selective screening, such as screening only persons with reported risk factors, those with reported risk factors or those in high-prevalence demographic groups, or

screening everybody. In this study, screening only persons who reported risk factors (5.8% of those tested) would have resulted in 74% (79 of 107) missed diagnoses. A broader strategy (70% tested) of also screening persons in high-prevalence demographic groups (black men or persons > 30 years of age) would have resulted in substantially fewer (8%) missed diagnoses (37). Two retrospective studies found that similar selective strategies would have resulted in 33% to 41% of the population being tested and 7% (1 of 14) (38) to 13% (192 of 1474) (39) missed diagnoses. Four U.S. studies in high-prevalence (>1%) settings demonstrated an increased yield after the implementation of routine voluntary HIV screening (40--43).

What Are the Test Characteristics of HIV Antibody Test Strategies?

The use of repeatedly reactive enzyme immunoassay followed by confirmatory Western blot or immunofluorescent assay remains the standard method for diagnosing HIV-1 infection (44, 45). A large study of HIV testing in 752 U.S. laboratories reported a sensitivity of 99.7% and specificity of 98.5% for enzyme immunoassay (45), and studies in U.S. blood donors reported specificities of 99.8% and greater than 99.99% (46, 47). With confirmatory Western blot, the chance of a false-positive identification in a low-prevalence setting is about 1 in 250 000 (95% CI, 1 in 173 000 to 1 in 379 000) (48).

Three rapid (results available in 10 to 30 minutes) HIV tests are in use in the United States; 2 (Uni-Gold Recombigen, Trinity Biotech Plc., Bray, Ireland, and OraQuick Advance, OraSure Technologies, Bethlehem, Pennsylvania) for true point-of-care testing (49), and 1 (Reveal G2, MedMira Laboratories, Inc., Halifax, Nova Scotia, Canada) performed in a laboratory. Three good-quality and 10 fair-quality studies evaluated accuracy of rapid tests on blood specimens against standard HIV testing (50--55). Ten were reported in manufacturer inserts (50--52). Most studies reported the accuracy of rapid tests before confirmatory testing because patients may be notified of results before confirmation is available (56).

For the OraQuick test, 3 good-quality studies found sensitivities ranging from 96% to 100% and specificity greater than 99.9% (53--55). Three fair-quality studies found sensitivities ranging from 99.6% to 100%, with specificity 100% in all (50). For the Uni-Gold and Reveal tests, 7 fair-quality studies reported sensitivities ranging from 94% to 100% and specificities greater than 99% (50, 52). The positive predictive values for the Reveal and Uni-Gold tests were calculated at 25% to 50% in settings with a prevalence of 0.3%, and at 85% to 95% in settings with a prevalence of 5% (57). One good-quality study among 5744 U.S. pregnant women (prevalence, 0.59%) found a positive predictive value of 90% (4 false-positive results) and a negative predictive value of 100% for the OraQuick test using blood (53).

Two large (n = 3570 and n = 4442), good-quality studies of the OraSure Oral Specimen Collection Device (Epitope, Inc., Beaverton, Oregon) measured sensitivities of 99.9% and 99.2% and specificities of 99.9% and 99.2% (58, 59). Urine HIV tests generally appear less accurate than standard testing and are not in widespread use in the United States (60--63). A good-quality (n = 1255) study of the only U.S. Food and Drug Administration--approved home collection kit (Home Access, Home Access Health Corp., Hoffman Estates, Illinois) found that the sensitivity and specificity obtained with use of finger-stick blood spot samples were both 100% compared

to standard testing (64). More than 98% of participants in 2 studies obtained adequate samples for testing (64, 65).

No studies have evaluated the optimal frequency of HIV screening, which partly depends on the incidence and the prevalence of undetected HIV infection in the group being tested (66).

What Are the Harms Associated with Screening?

Information on the frequency and consequences (anxiety, labeling) of false-positive test results is anecdotal (67--69). False- and true-negative results could provide false reassurance if high-risk behaviors are continued.

True-positive HIV test results are associated with important harms, including fears of rejection, abandonment, verbal abuse, and physical assault (70). A substantial proportion (20% to 25%) of Americans continue to agree with stigmatizing statements about HIV (71, 72). Four percent of 142 patients with recently diagnosed HIV infection reported losing a job because of their status, 1% had been asked to move, and 1% had been assaulted (73).

Notification of a positive HIV test result can lead to emotional and psychological distress. On the other hand, receipt of a negative HIV test result is associated with reduced anxiety in at-risk individuals (74). Although earlier studies reported high suicide rates after a positive test result (75--78), no studies have addressed suicide risk after an HIV diagnosis in the HAART era. A large prospective cohort study through 1993 found that suicide rates after routine screening were similar between HIV-positive and HIV-negative military recruits (79). Counseling may reduce distress after a positive test result (80--83).

Both HIV-negative and HIV-positive persons appear to have similar rates of intimate partner violence when matched for high-risk behaviors (84--86). One prospective cohort study found that rates of abuse declined after disclosure of HIV status (87). Several small observational studies did not find an increased rate of partnership dissolution after a positive diagnosis (87--89).

Is Screening Acceptable to Patients?

In the United States, as of 2002 approximately half (43.5%) of persons age 18 to 64 years had been tested at least once for HIV (90). The proportion of tested female adolescents is substantially lower at 25% (91). Among persons reporting high-risk behaviors, recent studies found that 20% to 30% had never been tested (25, 92, 93).

A good-quality systematic review of 62 studies reported that acceptance rates of voluntary HIV testing varied widely (from 11% to 91%) in the United States, even within similar health care settings (94). In general, low-prevalence settings were associated with lower acceptance rates. Higher acceptance rates were associated with the client's perception of HIV risk, acknowledgment of risk behaviors, confidentiality protections, and the provider's belief that testing would be beneficial.

One United Kingdom study of "opt-out" testing (in which an HIV test is considered routine and is performed unless the patient declines) in nonpregnant persons found that uptake increased from 35% to 65% (95). In several studies, anonymous testing was associated with increased testing rates (96--98) or higher mean CD4 cell count at diagnosis (99), although others did not find a clear association (100--102). In Connecticut, testing rates in adolescents doubled after removal of a parental consent requirement (103).

No clinical trials have evaluated the incremental acceptability of alternative testing (rapid test, home sampling, or oral sampling) compared with standard testing. A recent observational study found that 29% to 69% of patients in different settings accepted rapid testing (104). Another found that all 150 patients being treated for substance abuse who accepted testing chose an oral fluid test over a blood test (105). In studies of patients who accepted home sample collection (106, 107) or oral fluid sampling (108), a substantial proportion (22% to 33% for home sampling and 58% for oral fluid sampling) had not been previously tested.

How Many Newly Diagnosed HIV-Positive Patients Meet Criteria for Antiretroviral Treatment or Prophylaxis against Opportunistic Infections?

In asymptomatic HIV-positive patients, viral load and CD4 cell count testing are used to determine eligibility for HAART and opportunistic infection prophylaxis (13, 16). Antiretroviral therapy is currently recommended for patients with CD4 cell counts less than 0.200×10^9 cells/L. Antiretroviral therapy can also be considered for other asymptomatic patients at high risk for disease progression (CD4 cell count < $0.350 \times$ cells 10^9/L or viral load > 100 000 copies/mL). Interventions are generally less effective in persons with advanced immune deficiency (109), although some benefit is seen (110, 111).

No studies report both CD4 cell count and viral load in newly diagnosed patients. Seven U.S. studies in different settings found that the proportion of patients with CD4 cell counts less than 0.200×10^9 cells /L at diagnosis or when establishing care ranged from 12% to 43%, and the proportion with CD4 cell counts less than 0.500×10^9 cells/L ranged from 46% to 80% (26, 41, 112--116).

Screening could identify a higher proportion of persons whose CD4 cell counts have not decreased below thresholds for interventions. In addition, patients with an adequate response to HAART can safely discontinue prophylaxis against certain opportunistic infections (16). We identified no studies estimating the effects of screening or treatment on the proportion of patients qualifying for different interventions.

How Many HIV-Positive Patients Who Meet Criteria for Interventions Receive Them?

Patients positive for HIV who meet criteria for interventions may not receive them. Ten percent to 44% of tested patients do not have a post-test counseling session or fail to return for test results (117--119), although most (79% to 93%) positive patients are eventually located (30,

120). Two recent studies of routine testing in urgent care centers found that 74% to 82% of patients learned of their positive results (40, 41).

Rapid testing was associated with a higher rate of HIV-positive persons learning their status than was standard testing in an anonymous testing clinic (100% vs. 86%) (121), sexually transmitted disease clinic (97% vs. 79%) (121), and emergency department setting (73% vs. 62%) (122). In noncomparative studies, rapid testing resulted in more than 98% of patients learning their status (104, 123). Of 174 316 persons submitting home samples, 95% to 96% called for results (106).

Patients positive for HIV may delay medical care or not receive care at all. In 1996, 36% to 63% of HIV-positive patients were regularly seeing a non--emergency department provider (124). Studies in the United States found that 17% to 29% of patients had delayed entry into care for at least 3 months (125, 126), and 11% to 39% delayed it for at least 1 year (126--128). A study of rapid testing found that entry into care within 6 months ranged from 100% (in a sexually transmitted disease clinic) to 22% (in a jail) (104).

No prospective studies measured the proportion of newly diagnosed HIV-positive persons who received appropriate treatment. Four large (n = 1411 to 9530) U.S. surveys found that 53% to 85% of HIV-positive patients were receiving antiretroviral therapy according to then-current guidelines (129--132).

How Effective Are Interventions in Improving Clinical Outcomes?

Antiretroviral Agents

Currently, HAART regimens with 3 or more antiretroviral agents, usually from at least 2 different classes, are the standard of care for HIV-infected persons receiving antiretroviral therapy (13, 14). A good-quality systematic review of 54 randomized, controlled trials with 16 684 HIV-infected patients with limited or no antiretroviral experience found that 3-drug therapy was more effective than 2-drug therapy (odds ratio, 0.62 [95% CI, 0.50 to 0.78]) (133). Observational studies indicate that HAART can result in sustained (up to 4 to 5 years) improvements in CD4 cell counts and viral loads (134--136), although long-term clinical outcomes data are not yet available.

Large, good-quality cohort studies from the United States (137--140) and Europe (141--143) parallel the findings of the systematic review regarding the effectiveness of HAART. In addition, studies have consistently found a marked decline in morbidity and mortality among U.S. HIV-infected patients that coincided with the widespread adoption of HAART (138--140, 144--149). In 2 U.S. studies, for example, mortality rates declined from 20.2 (140) and 29.4 (138) per 100 person-years to 8.4 and 8.8 per 100 person-years, respectively.

Few trials have adequately assessed the effect of HAART on quality of life or functional status (such as ability to work) (133). Four fair-quality trials of 3-drug vs. 2-drug regimens reported conflicting results for differences in quality-of-life outcomes (150--153).

The use of HAART could decrease the spread of HIV from infected persons by decreasing viral loads (154). On the other hand, increases in risky behaviors by patients receiving HAART could offset the beneficial effects of viral suppression (155--158). A recent good-quality meta-analysis of 25 studies found no association between receipt of HAART or having an undetectable viral load and unprotected sex (159). Among both seronegative and seropositive persons, however, unprotected intercourse was associated with optimistic *beliefs* about HAART or an undetectable viral load (odds ratio, 1.82 [CI, 1.52 to 2.17]).

No studies have estimated the effects of HAART on horizontal transmission rates. One cohort study found that heterosexual transmission from monogamous zidovudine-treated men was lower than that from untreated men (relative risk, 0.5 [CI, 0.1 to 0.9]) (160). An epidemiologic study estimated that the annual HIV transmission rate from HIV-seropositive persons in the United States declined from 13% in 1987 (the year zidovudine was introduced) to 5.5% in 1989, and has remained steady at approximately 4.2% since 1990 (161). This study was not designed to assess the relative contribution of antiretroviral therapy, changes in high-risk behaviors, or other factors to changes in transmission rates.

Counseling

Because the incidence of new HIV infections has remained steady while mortality due to AIDS has declined, the number of persons living with HIV infection in the United States continues to increase (3). A substantial proportion of HIV-infected persons report behaviors that increase the risk for transmitting infection (15, 24, 126, 162--164). Data on the link between sexual behaviors and reduced risk for HIV transmission are strongest for consistent use of condoms for prevention of heterosexual transmission (165, 166). Good-quality systematic reviews found that testing plus counseling is most effective in reducing risky behaviors among serodiscordant heterosexual couples and those testing HIV-positive, with less evidence for beneficial effects in other populations (167--169). Several recent fair-quality observational studies reported decreased self-reported risky behaviors after patients had HIV testing or received a positive diagnosis (170--173). Some (174--178) but not all (179--182) fair-quality randomized trials found that targeted (tailored to participant needs) or more intensive counseling was associated with greater reductions in risky behaviors than standard or less intensive counseling, but counseling methods varied greatly across trials.

No clinical trials evaluated the impact of testing and counseling compared to no testing and counseling on HIV transmission rates. One prospective U.S. study of 144 serodiscordant heterosexual couples who received counseling and reported reduced risky behaviors found no seroconversion after 193 couple-years of follow-up (183). A prospective African study found that the rate of seroconversion among uninfected female partners of HIV-positive men was 6 to 9/100 person-years, compared with 22/100 person-years in women with untested partners (184). Two observational studies found that testing plus counseling was associated with a moderate (about 33%) decrease in sexually transmitted diseases among those who tested positive but that it increased the risk among those who tested negative (relative risk, 1.27 to 2) (185, 186). Two good-quality randomized, controlled trials found that more interactive counseling was more effective than standard counseling in reducing sexually transmitted disease rates among HIV-

positive women (176) and seronegative heterosexual persons (187), although there were too few new HIV infections to detect differences in HIV rates (187).

No studies have estimated the effects of counseling HIV-positive persons regarding injection drug use behaviors on HIV transmission rates. Although cross-sectional studies found that HIV-positive drug users reported less risky behaviors than those untested or not infected (188--190), 1 randomized trial (191) and 1 prospective study (192) found that testing plus counseling was not associated with decreased drug behaviors. On the other hand, 2 randomized trials found that more intense counseling reduced drug use behaviors more than did standard counseling (174, 193).

Prophylaxis Against Opportunistic Infections

Table 2 summarizes 2 good-quality systematic reviews (194, 195) and 3 clinical trials (196--198) of primary prophylaxis against *Pneumocystis carinii* pneumonia. Prophylaxis was associated with a nonsignificant mortality benefit (194). Several medications used for prophylaxis against *P. carinii* pneumonia are also effective for toxoplasmosis prophylaxis (16, 195).

Two good-quality systematic reviews (199, 200) found that isoniazid prophylaxis was effective at preventing tuberculosis (risk reduced by 60% to 86%) and death (risk reduced by 21% to 23%) in HIV-positive patients with a positive tuberculin skin test result (16).

Table 3 summarizes 4 good-quality placebo-controlled trials (201--203) and 2 head-to-head trials (204, 205) of primary prophylaxis against disseminated *Mycobacterium avium intracellulare* complex infection. Only clarithromycin was associated with a significant mortality benefit (202).

Two placebo-controlled trials of ganciclovir for cytomegalovirus prophylaxis found mixed results for reducing invasive CMV infection, no mortality benefit, and significant adverse events (206, 207).

In Asymptomatic Patients with HIV Infection, Does Immediate Antiretroviral Treatment Result in Improvements in Clinical Outcomes Compared to Delayed Treatment until the Patient Is Symptomatic?

Initiation of HAART in asymptomatic patients must be weighed against potential harms, including effects on quality of life, long-term adverse events, and the development of resistance. Current U.S. guidelines recommend that all asymptomatic patients with CD4 cell counts less than 0.200×10^9 cells/L be offered HAART (13). Recommendations for other asymptomatic patients are less firm.

Twelve observational studies evaluated the risk for disease progression or death in asymptomatic patients initiating HAART at different CD4 cell count thresholds above 0.200×10^9 cells/L. All lasted less than 4 years and could underestimate long-term risks for immediate treatment. Other limitations of studies include not controlling for lead-time bias (208) and not

accounting for important confounders, such as the level of adherence (209) or physician experience (110).

Four fair-quality observational studies controlled for lead-time bias by identifying cohorts of patients at initial CD4 cell count strata and evaluating outcomes according to when they received HAART (210--213). Three U.S. studies found no significant benefit associated with starting HAART at CD4 cell counts between 0.350 and 0.500 $\times 10^9$ cells/L versus between 0.200 and 0.350 $\times 10^9$ cells/L (Table 4) (210, 212, 213). A Swiss study reported a benefit for starting at CD4 cell counts above 0.350 $\times 10^9$ cells/L but did not stratify results of patients starting at CD4 cell counts above or below 0.200 $\times 10^9$ cells/L (211). Six (109, 214--218) of 8 (209, 219) other observational studies that did not control for lead-time bias or used novel methodologic approaches found a benefit or trend toward benefit from initiation of treatment at CD4 counts above versus below 0.350 $\times 10^9$ cells/L.

A randomized clinical trial (the SMART [Strategies for Management of Anti-Retroviral Therapies] study [220]) comparing viral suppression in asymptomatic patients with a CD4 cell count less than 0.350 $\times 10^9$ cells/L with delay until counts decrease below 0.250 $\times 10^9$ cells/L is in progress, with preliminary results expected in 5 to 7 years (221).

What Are the Harms Associated with Antiretroviral Therapy?

Individual antiretroviral drugs, drug classes, and drug combinations are all associated with specific adverse event profiles (13). Retrospective U.S. cohort studies found that 61% of patients had changed or discontinued their initial HAART regimen by 8 months (222) and that the median duration of the initial regimen was less than 2 years (223); 40% to 50% discontinued the initial regimen because of adverse events. Many antiretroviral-associated adverse events, however, are short-term or self-limited, and effective alternatives can often be found (14, 134). Detailed and regularly updated guidelines review adverse events associated with specific antiretroviral drugs, drug classes, and combinations (13). Certain drugs and combinations are not recommended because of associated adverse events.

A recent good-quality systematic review found that 26 of 54 trials of antiretroviral therapy reported drug-related withdrawals, a marker for intolerable or severe adverse events (133). Among trials comparing 3-drug and 2-drug regimens, dropout rates were similar if both regimens either included protease inhibitors or were protease inhibitor--sparing. In a large (n = 1160), good-quality Swiss cohort study of adverse events in clinical practice, 47% of patients reported a clinical adverse event that was probably or definitely attributed to HAART within the previous 30 days (224). Among these, 9% were graded as serious or severe.

The use of HAART is associated with metabolic disturbances (lipodystrophy syndrome, hyperlipidemia, and diabetes) that are related to an increased risk for cardiovascular events (225, 226). The largest prospective study on the risk for cardiovascular events associated with both protease inhibitor--based and non--protease inhibitor--based combination regimens was a good-quality study of 23 468 patients in 11 cohorts (227). It found that the incidence of myocardial infarction increased with longer exposure (adjusted relative rate per year of exposure, 1.26 [227]). The relative risk for the combined outcome of myocardial infarction, invasive

cardiovascular procedures, or stroke was similarly increased, although the event rate was higher (5.7 events/1000 person-years vs. 3.5 events/1000 person-years for myocardial infarction alone) (229). Other studies primarily evaluating the cardiovascular risk associated with protease inhibitors also generally found an increased risk (230--238).

Studies evaluating trends over time reported mixed findings regarding the rate of cardiovascular events in HIV-infected patients since the introduction of HAART. These studies are limited by potential confounding from changes in clinical practice and the demographic characteristics of persons surviving with HIV infection (239--242).

Estimates of the Numbers Needed To Screen and Treat

Table 5 estimates outcomes after 3 years from 1-time screening for HIV in 3 hypothetical cohorts of 10 000 asymptomatic persons (0.3% prevalence, 1% prevalence, and 5% to 15% prevalence [high risk]) (see Appendix Table 1, available at www.annals.org, for base-case assumptions). Because no trials directly compare 3-drug regimens to placebo, we indirectly calculated (Appendix A) a relative risk for clinical progression or death of 0.35 (CI, 0.25 to 0.47) (133). For all cohorts, the number of cases of clinical progression or deaths that were prevented greatly outweighed the number of cardiovascular adverse events caused by antiretroviral therapy. Evidence was insufficient to estimate the effects of screening on transmission rates.

What Is the Cost-Effectiveness of Screening for HIV Infection?

In 2 good-quality studies, the cost-effectiveness of one-time HIV screening in outpatients with 1% prevalence compared to no screening was $38 000 to $42 000 per quality-adjusted life-year (243, 244). One of these studies found that the cost-effectiveness improved to $15 000 per quality-adjusted life-year when secondary transmission benefits were directly incorporated into cost-effectiveness ratios, and they remained less than $50 000 per quality-adjusted life-year even when screened populations had HIV prevalences substantially lower than seen in the general population (243). The other study, which did not directly incorporate secondary transmission benefits into cost-effectiveness ratios, found that the incremental cost-effectiveness of one-time screening in the general population was greater than $100 000 per quality-adjusted life-year (244).

Neither study incorporated long-term cardiovascular risks associated with HAART into their models. The study by Sanders and colleagues found that the model was sensitive to the effects of screening on secondary transmission and the benefits of early identification and therapy.

The 1996 USPSTF guidelines recommended screening persons who report high-risk behaviors (11). Neither of the 2 reviewed studies evaluated the incremental cost-effectiveness of a strategy of screening only higher-risk persons compared to broader screening strategies in different populations. One of the studies found that the incremental cost-effectiveness of testing every 5 years compared to one-time screening exceeded $50 000 per quality-adjusted life-year (243).

Discussion

There is no direct evidence on benefits of screening for HIV infection in the general population. Other evidence obtained for the systematic review (summarized in Table 6) indicates that testing is extremely accurate, a high proportion of patients receive a diagnosis at immunologically advanced stages of disease, and interventions (particularly HAART) are effective in reducing morbidity and mortality in patients with immunologically advanced disease. Although long-term HAART is associated with cardiovascular complications, absolute rates are low.

Reasonable screening strategies might be to screen patients with acknowledged risk factors, all patients in settings with a higher prevalence of HIV infection, or all patients in the general population. Studies that have assessed risk factor assessment to guide screening indicate that targeted screening misses a substantial proportion of HIV-positive patients. On the other hand, universal screening would result in large numbers of patients screened for each clinical outcome prevented.

An important gap in the literature is the inadequate evidence with which to accurately estimate the benefits from identification of HIV-positive patients at earlier stages of disease who do not initially qualify for HAART, particularly since screening could lead to higher rates of earlier diagnosis. In these patients, other interventions, such as counseling to reduce transmission, assume greater relative importance. Despite evidence that knowledge of HIV-positive status reduces some high-risk behaviors, there is insufficient evidence with which to accurately estimate the effects on transmission rates. The relationship between HAART use and beliefs, risky behaviors, and transmission rates also needs to be explored further. The case for screening, particularly in lower-risk populations, would be greatly strengthened by studies showing that identification at earlier stages of disease is associated with decreased transmission rates. When available, results of the SMART trial (221) will provide important information about the effectiveness of HAART in asymptomatic patients with higher CD4 cell counts.

Other studies are needed on methods to improve risk assessment, effects of streamlined or targeted counseling, methods to improve entry into medical care and uptake of recommended interventions, and effects of newer testing and sampling methods. In addition, data with which to estimate the magnitude of screening harms and on methods to minimize their risk are limited. Continued attention to adverse events as patients continue receiving HAART will help clarify long-term risks.

Despite continuing HIV education efforts and the availability of effective interventions, incidence of HIV remains steady in the United States, and HIV infection continues to place an enormous burden on the health care system. Further implementation and evaluation of screening programs could have an important impact on the morbidity and mortality associated with this disease.

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This article and the corresponding recommendations statement are available from the AHRQ Web site (www.preventiveservices.ahrq.gov). The recommendation is also posted on the Web site of the National Guideline Clearinghouse™ (www.guideline.gov).

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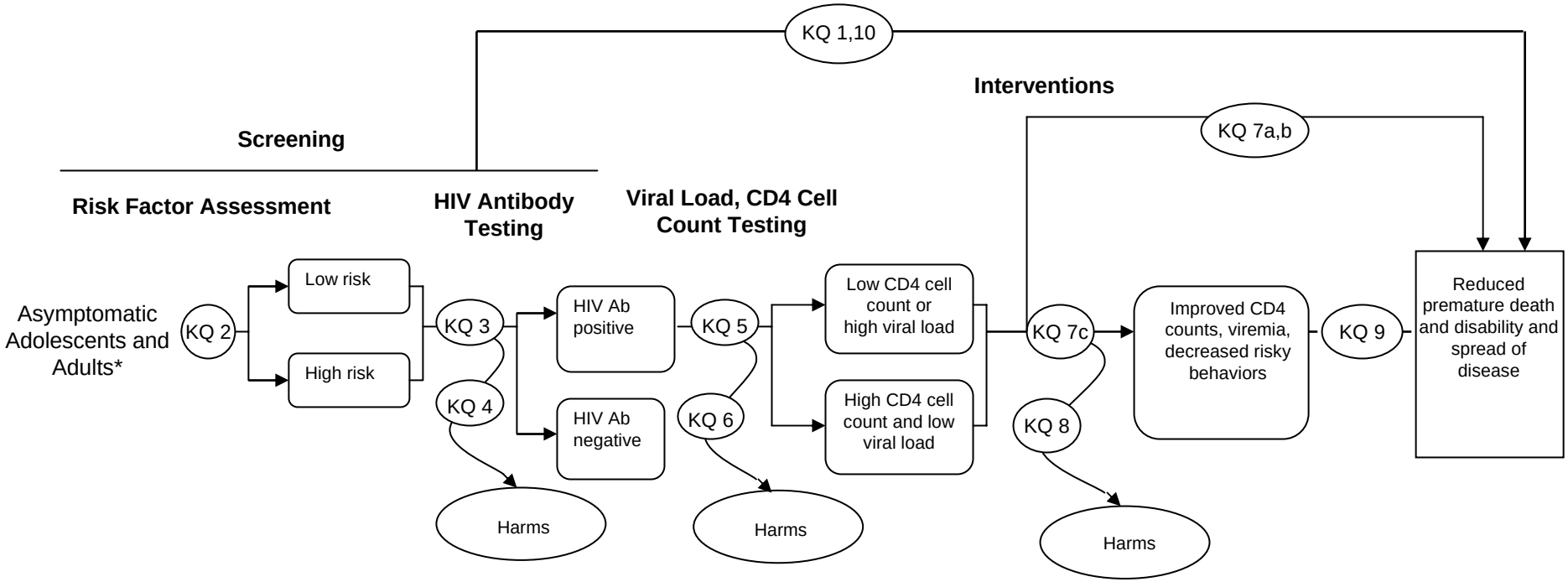
FIGURE 1. SCREENING FOR HUMAN IMMUNODEFICIENCY VIRUS – ANALYTIC FRAMEWORK FOR SCREENING ASYMPTOMATIC ADOLESCENTS AND ADULTS



*Excluding pregnant women, dialysis patients, transplant patients.

Figure 1. Screening for HIV---Analytic Framework for Screening Asymptomatic Adolescents and Adults

Key Question (*KQ*) 1: Does screening for HIV infection in asymptomatic adolescents and adults reduce premature death and disability or spread of disease?

KQ 2: Can clinical or demographic characteristics (including specific settings) identify subgroups of asymptomatic adolescents and adults at increased risk for HIV compared to the general population?

KQ 3: What are the test characteristics of HIV antibody test strategies?

KQ 4: What are the harms (including labeling and anxiety) associated with screening? Is screening acceptable to patients?

KQ 5: How many newly diagnosed HIV-positive patients meet criteria for antiretroviral treatment or prophylaxis against opportunistic infections? How many patients who meet criteria for interventions receive them?

KQ 6: What are the harms associated with the work-up for HIV infection?

KQ 7: a) How effective are interventions (antiretroviral treatment, counseling on risky behaviors, immunizations, routine monitoring and follow-up, more frequent Papanicolaou testing, or prophylaxis against opportunistic infections) in improving clinical outcomes (mortality, functional status, quality of life, symptoms, opportunistic infections, or transmission rates)?

KQ 7b) In asymptomatic patients with HIV infection, does immediate antiretroviral treatment result in improvements in clinical outcomes compared to delayed treatment until the patient is symptomatic? c) How well do interventions reduce the rate of viremia, improve CD4 counts, or reduce risky behaviors?

KQ 8: What are the harms associated with antiretroviral therapy?

KQ 9: Have improvements in intermediate outcomes (CD4 counts, viremia, risky behaviors) been shown to reduce premature death and disability or spread of disease?

KQ 10: What is the cost-effectiveness of screening for HIV infection? *Excluding pregnant women, patients undergoing dialysis, and patients receiving transplants.

A separate report (17) reviews KQs 6, 7c, 9, and portions of 7a (immunizations, routine monitoring and follow-up, and more frequent Papanicolaou testing).

Table 1. Asymptomatic Adolescents and Adults at High Risk for HIV Infection

Persons seeking treatment for sexually transmitted diseases*†

Homosexual or bisexual men*†

Past or present injection drug users*†

Persons who exchange sex for money or drugs and their sex partners*†

Women whose past or present sex partners were HIV-infected, bisexual, or injection drug users*†

Persons with a history of transfusion between 1978 and 1985*†

Persons having unprotected vaginal or anal intercourse with >1 sex partner†

* Source: U.S. Preventive Services Task Force, 1996 (11).
† Source: Centers for Disease Control and Prevention, 2001 (21).

Table 2. Effectiveness of Primary Prophylaxis against *Pneumocystis carinii* Pneumonia and Cerebral Toxoplasmosis in HIV-Infected Patients

Regimen Comparison	Relative Risk (95% CI)			Source, Year (Reference)
	Pneumocystis carinii Pneumonia	Cerebral Toxoplasmosis	Mortality Outcomes	
Any primary prophylaxis vs. placebo	0.39 (0.27–0.55)	Not reported	0.87 (0.60–1.25)	Ioannidis et al., 1996*† (194)
Trimethoprim–sulfamethoxazole vs. aerosolized pentamidine	0.59 (0.45–0.76)	0.78 (0.55–1.11)	0.88 (0.74–1.06)	Bucher et al., 1997* (195)
	0.58 (0.45–0.75)	Not reported	0.99 (0.80–1.22)	Ioannidis et al., 1996*† (194)
Dapsone-based regimen vs. aerosolized pentamidine	0.90 (0.71–1.15)	0.72 (0.54–0.97)	1.07 (0.90–1.27)	Bucher et al., 1997* (195)
	0.93 (0.72–1.19)	Not reported	0.98 (0.86–1.12)	Ioannidis et al., 1996*† (194)
Trimethoprim–sulfamethoxazole vs. dapsone-based regimen	0.49 (0.26–0.92)	1.17 (0.68–2.18)	1.08 (0.88–1.25)	Bucher et al., 1997* (195)
	0.61 (0.34–1.10)	Not reported	0.95 (0.82–1.11)	Ioannidis et al., 1996*† (194)
Atovaquone vs. dapsone	0.81 (0.58–1.12)	1.18 (0.26–5.30)	1.25 (0.98–1.59)	El-Sadr et al., 1998 (196)
Dapsone vs. pyrimethamine–sulfadoxine	0.87 ($P > 0.05$)	1.07 ($P > 0.05$)	1.15 (not significant)	Payen et al., 1997 (197)
Azithromycin vs. rifabutin in patients already receiving *P. carinii* prophylaxis	0.42 (0.24–0.76)	Not reported	Not reported	Dunne et al., 1999 (198)

* Systematic review.
† Includes studies of secondary prophylaxis.

Table 3. Effectiveness of Primary Prophylaxis against Disseminated *Mycobacterium avium intracellulare* Infection in HIV-Positive Patients*

Regimen Comparison	Disseminated *Mycobacterium avium intracellulare* Infection (95% CI)	Mortality (95% CI)	Source, Year (Reference)
Azithromycin vs. placebo	HR, 0.34 (*P* = 0.004)	HR, 1.02 (*P* = 0.955)	Oldfield et al., 1998 (201)
Clarithromycin vs. placebo	HR, 0.31 (CI, 0.18–0.53)	HR, 0.75 (0.58–0.97)	Pierce et al., 1996 (202)
Rifabutin vs. placebo	RR, 0.43 (0.26–0.70) RR, 0.47 (0.29–0.77)	RR, 0.68 (0.43–1.06)	Nightingale et al., 1993 (Studies 023 and 027) (203)
Clarithromycin vs. rifabutin	RR, 0.56 (0.37–0.85)	RR, 0.97 (0.78–1.20)	Benson et al., 2000 (204)
Azithromycin vs. rifabutin	HR, 0.53 (0.34–0.85)	No differences	Havlir et al., 1996 (205)
Clarithromycin + rifabutin vs. rifabutin	RR, 0.43 (0.27–0.69)	No differences	Benson et al., 2000 (204)
Azithromycin + rifabutin vs. rifabutin	HR, 0.28 (0.16–0.49)	No differences	Havlir et al., 1996 (205)
Azithromycin + rifabutin vs. azithromycin	HR, 0.53 (0.29–0.95)	No differences	Havlir et al., 1996 (205)
Clarithromycin + rifabutin vs. clarithromycin	RR, 0.79 (0.48–1.31)	No differences	Benson et al., 2000 (204)

* HR = hazard ratio; RR = relative risk.

Table 4. Studies Evaluating When to Initiate Antiretroviral Therapy in HIV-Infected Patients That Controlled for Lead-Time Bias

CD4 Cell Count at Which HAART Was Started, $\times 10^9$ *cells/L*	Clinical Progression or Mortality	Mortality (95% CI)	Source, Year (Reference)
0.501–0.750 vs. <0.500	Not reported	RR, 1.20 (0.17–8.53)	Palella et al., 2003 (210)
0.351–0.500 vs. 0.200–0.350	Not reported	RR, 0.61 (0.22–1.67)	Palella et al., 2003 (210)
	HR, 0.95 (*P* = 0.897)	Not reported	Ahdieh-Grant et al., 2003 (212)
0.350–0.499 vs. <0.350	*P* = 0.21, log-rank test	*P* = 0.10, log-rank test	Sterling et al., 2003 (213)
>0.350 vs. <0.350	HR, 0.28 (0.12–0.68)	HR, 0.20 (0.07–0.52)	Opravil et al., 2002 (211)
0.350–0.499 vs. <0.200	HR, 0.37 (*P* = 0.003)	Not reported	Ahdieh-Grant et al., 2003 (212)
0.201–0.350 vs. <0.200	Not reported	RR, 0.27 (0.14–0.55)	Palella et al., 2003 (210)
	HR, 0.39 (*P* < 0.001)	Not reported	Ahdieh-Grant et al., 2003 (212)

*HAART = highly active antiretroviral therapy; HR = hazard ratio; RR = relative risk.

Table 5. Outcomes of Counseling and One-Time Screening for HIV Infection Ater 3 Years

in 10,000 Asymptomatic Adolescents and Adults

Results	Prevalence, 0.3%	Prevalence, 1%	Prevalence, 5%–15% (High Risk)
Persons screened, *n*	10 000	10 000	10 000
Persons identified as HIV-positive, *n*	30	100	500–1500
Patients receiving test results, *n*	24–28	79–93	400–1400
Partners identified as HIV-positive, *n*	2–6	6–21	32–320
Total HIV-positive patients identified, *n*	26–34	85–114	426–1720
Patients with CD4 cell count < 0.200×10^9 cells/L, *n*	3–15	10–49	51–740
Cases of clinical progression or deaths prevented over 3 y with HAART, *n*	0.7–8.2	2–28	12–410
NNS_B to prevent 1 clinical progression or death over 3 y	1210–13 800	360–4140	24–830
NNT_B with HAART to prevent 1 clinical progression or death over 3 y	1.8 (95% CI, 1.5–2.2)	1.8 (95% CI, 1.5–2.2)	1.8 (95% CI, 1.5–2.2)
NNC_B, NNS_B, or NNT_B to prevent 1 horizontal transmission over 3 y	Unable to calculate	Unable to calculate	Unable to calculate
Cardiovascular or cerebrovascular events caused by HAART over 3 y, *n*	0.006–0.6	0.02–2	0.1–30
NNS_H to cause 1 cardiovascular or cerebrovascular event over 3 y	16 900–1 580 500	5100–474 400	340–95 000
NNT_H with HAART to cause 1 cardiovascular or cerebrovascular event over 3 y	69 (95% CI, 21–257)	69 (95% CI, 21–257)	69 (95% CI, 21–257)

*NNC_B = number needed to counsel for benefit; NNS_B = number needed to screen for benefit; NNS_H = number needed to screen for harm; NNT_B = number needed to treat for benefit; NNT_H = number needed to screen for harm.

Table 6. Summary of Findings of Systematic Evidence Review*

Question Number	Key Question	Level and Type of Evidence	Overall Evidence for the Link	Findings
1	Does screening for HIV in asymptomatic adolescents and adults reduce premature death and disability and spread of disease?	None	Not applicable	No controlled studies or observational studies link screening directly to health outcomes.
2	Can clinical or demographic characteristics (including specific settings) identify a subgroup of asymptomatic adolescents and adults at increased risk for HIV compared to the general population?	II-2. Cohort and cross-sectional studies	Good	The strongest risk factors for HIV infection from multiple large observational studies are intravenous drug use, male to male sex, and high-risk sexual behaviors. The largest U.S. study found that in federally funded testing sites, 20%–26% of HIV-positive patients reported no risk factors (28). In high-risk settings, several observational studies found that targeted screening based on broad criteria could increase the yield of screening but would still miss 7%–13% of positive patients while testing a much higher proportion (37--39).
3	What are the test characteristics of HIV antibody test strategies?	Studies of diagnostic test accuracy	Good for standard and OraQuick rapid test†; fair for other testing and collection methods	Standard testing is associated with a sensitivity and specificity >99% (45--47). Initial studies indicate that FDA-approved rapid tests are associated with similar diagnostic test accuracy, but data from clinical settings are limited for rapid tests other than OraQuick on blood specimens (50--55). Home sampling and oral specimen sampling appear to have diagnostic accuracy similar to that of standard testing (58, 59, 64), but urine specimens may be associated with lower accuracy (60--63).
4	What are the harms (including labeling and anxiety) associated with screening? Is screening acceptable to patients?	Studies of diagnostic test accuracy II-2; cohort and cross-sectional studies for harms of screening and acceptability	Good for false-positive rates and false-negative rates; fair to good for harms from screening and acceptability of testing	False-positive results appear rare with standard testing, even in low-prevalence settings (1 of 250 000 blood donors) (48). False-positive results from rapid tests could occur if results are given before confirmatory testing. False-negative results could occur during the window period before seroconversion and provide false reassurance. True-negative results could also provide false reassurance in patients practicing high-risk behaviors. True-positive results are associated with social consequences, anxiety, and labeling, but these harms are difficult to measure. Violence is very frequent in HIV-infected persons, but the impact of screening is not clear. Larger or more recent observational studies have not clearly shown that disclosure increases partner dissolution (87--89), intimate partner violence (84--86), or suicide risk (79). Acceptance rates vary widely even in similar settings (10%–97%) and may be improved by the availability of newer screening methods (rapid tests, noninvasive samples, home-based collection, on-site testing) (94). An opt-out testing policy increased testing rates in 1 study (95).

5	How many newly diagnosed HIV-positive patients meet criteria for antiretroviral treatment or prophylaxis against opportunistic infections? How many patients who meet criteria for interventions receive them?	II-2. Cohort and cross-sectional studies	Fair for proportion of patients qualifying for intervention at treatment (little information on initial viral load); good for proportion receiving interventions	Seven U.S. studies found that 12%–43% of patients are diagnosed with CD4 cell counts below 0.200×10^9 cells/L, and 46%–80% with CD4 cell counts below 0.500×10^9 cells/L (26, 41, 112--116). No studies reported initial CD4 cell counts and viral loads in asymptomatic patients. No studies estimated the effects of screening on the proportion of patients qualifying for interventions or the effects of HAART on the proportion of patients qualifying for prophylaxis. A substantial proportion of HIV-positive patients do not receive or decline care. An estimated 36%–63% of infected patients were receiving care at least once every 6 months in 1996 (124); 38%–58% with positive test results do not return for initial post-test counseling (although about 90% are eventually located) (30, 117--120), and 53%–85% of infected patients who met guidelines for antiretroviral treatment were receiving them (129--132). Patients with lower CD4 cell counts and higher viral loads appear to have poorer response to antiretroviral therapy, but data on long-term outcomes are lacking.
6	What are the harms associated with the work-up for HIV infection?	None	Not applicable	No evidence.

7a	1. How effective is antiretroviral treatment in improving clinical outcomes (mortality, functional status, quality of life, symptoms, opportunistic infections, or transmission rates)?	I, II-2. Randomized, controlled trials; large cohort studies	Good for clinical progression and death; fair for quality of life and spread of disease	HAART is associated with improved clinical outcomes (clinical progression and death) compared to 2-drug therapy (OR, 0.62 [95% CI, 0.51–0.70]) and other less intense regimens (133). Quality-of-life outcomes from HAART have not been well studied. Beneficial effects of HAART on reducing horizontal transmission by reducing viral load may be offset by increases in risky behaviors (154--159), but there was insufficient evidence with which to estimate the effects of HAART on transmission rates.
	2. How effective is counseling on risky behaviors in reducing transmission rates?	II. Cohort studies	Fair	Few data address the effects of counseling and testing on HIV transmission rates in the United States. In Africa, uninfected women's knowledge of the HIV-positive status of their male partner was associated with a reduction in transmission by about 50% (184). Several observational studies indicate that sexually transmitted disease rates decline after an HIV diagnosis but may increase in persons testing negative (185, 186). Interactive HIV counseling and testing was more effective than standard didactic counseling and testing in reducing sexually transmitted disease rates in 1 large, good-quality randomized trial, although there were too few cases to determine whether it was more effective at reducing new HIV infections (187). There is insufficient evidence with which to estimate effects of counseling on drug behaviors and transmission rates.
	3. How effective are immunizations in improving clinical outcomes (mortality, functional status, quality of life, symptoms, opportunistic infections)?	I, II-2. Randomized, controlled trials; large cohort studies	Fair for pneumococcal, influenza, and hepatitis B vaccinations; poor for others	In 1 randomized trial from Uganda, pneumococcal vaccination was associated with an increased risk for all-cause pneumonia (HR, 1.89 [95% CI, 1.1–3.2]) (253), although long-term follow-up found an unexpected survival advantage (HR, 0.84 [CI, 0.7–1.0]) (254. Observational studies mostly found a benefit from vaccination, particularly in patients with higher CD4 cell counts (255--259). Influenza vaccination was associated with a lower risk for symptomatic respiratory illness (49% vs. 29%; $P = 0.04$) in a clinical trial of HIV-infected patients in a military clinic (260). Hepatitis B vaccination was associated with a lower risk for acute hepatitis B in 1 observational study of HIV-infected persons (261). No studies had clinical outcomes of other immunizations in HIV-positive patients.
	4. How effective is prophylaxis against opportunistic infections in improving clinical outcomes (mortality, functional status, quality of life, symptoms, opportunistic infections, or transmission rates)?	I, II-2. Randomized, controlled trials; large cohort studies	Good overall	Good-quality systematic reviews found that chemoprophylaxis against PCP reduced the risk for PCP (RR, 0.39 [95% CI, 0.27–0.55]) and was associated with a nonsignificant mortality benefit (RR, 0.87 [CI, 0.60–1.25]) (194, 195). Some medications effective for PCP prophylaxis were also effective for toxoplasmosis prophylaxis. Two good-quality systematic reviews found that prophylaxis was effective at preventing active tuberculosis (risk reduced by 60%–86%) and death (risk reduced by 21%–23%) in patients with a positive skin test result (199, 200) Multiple randomized, controlled trials found that chemoprophylaxis was effective for preventing disseminated *Mycobacterium avium*

				intracellulare infection, and may be associated with a mortality benefit (HR, ~0.75) (201--206). In 2 randomized trials of ganciclovir, prophylaxis against CMV in patients who are positive for CMV antibody may prevent invasive CMV disease but does not appear associated with a significant mortality benefit (206, 207).
7b	In asymptomatic patients with HIV infection, does immediate antiretroviral treatment result in reduced rates of premature death or disability compared to delayed treatment until symptomatic?	II-2. Cohort studies	Fair	Large observational studies that controlled for lead-time bias consistently found that starting HAART at CD4 cell counts > 0.350 $\times 10^9$ cells/L is associated with better clinical outcomes than starting at a count < 0.200 $\times 10^9$ cells (210--213). The optimal CD4 cell count at which to start HAART in patients with counts between 0.200 and 0.350 $\times 10^9$ cells is unclear. Observational studies that have controlled for lead-time bias did not control for other potentially important confounders (such as level of adherence or physician experience).
7c	How well do interventions reduce the rate of viremia, improve CD4 cell counts, or reduce risky behaviors?	I, II-2. Randomized, controlled trials; large cohort studies	Good	A fair-quality systematic review of HAART regimens found a rate of viral load suppression to <50 copies/mL at 48 wk of 47% overall (95% CI, 43%–51%) (262). Observational studies found that 40%–50% of patients reached and maintained CD4 cell counts > 0.500 $\times 10^9$ cells during HAART after 4–5 y (263, 264), and 47% had a viral load < 50 copies/mL after 6 y (265). Two good-quality systematic reviews found that HIV counseling and testing are associated with decreases in risky sexually behaviors in persons testing positive, but the strength of the association varied according to the group studied (168, 169). The strongest association was in heterosexual couples and in those testing positive. More intense or targeted counseling was more effective than standard counseling in several randomized trials (174--178).

8	What are the harms associated with antiretroviral therapy?	I, II-2. Randomized, controlled trials; large cohort studies	Good	In numerous clinical trials and observational studies, HAART regimens were associated with clinically significant short-term adverse events. Many patients can be switched to effective alternative regimens. Specific antiretroviral drugs and combinations are associated with specific adverse event profiles. A large, good-quality prospective cohort study found that the incidence of myocardial infarction and cardiac or cerebrovascular events increased with longer exposure to HAART (adjusted RR per year, 1.26 [95% CI, 1.12–1.41] and 1.26 [CI, 1.14–1.38], respectively) for the first 4 y, but the overall rate was low at 3.5 and 5.7 events, respectively, per 1000 person-years (228, 229).
9	Have improvements in intermediate outcomes (CD4 cell counts, viremia, risky behaviors) been shown to reduce premature death and disability or spread of disease?	I, II-2. Randomized, controlled trials; large cohort studies	Good for CD4 cell count or viral load and clinical progression and transmission risk; fair for behavior changes and transmission risk	A large collaborative analysis of 13 cohort studies found that 6-mo CD4 cell count and viral load were strongly, independently associated with clinical outcomes in patients starting HAART (266). Observational studies found that low viral load was strongly correlated with decreased risk for HIV transmission in heterosexual couples (267), but data from patients treated with HAART are lacking. Condoms have been shown to be associated with decreased risk for transmission from HIV-infected persons (165,166). In mixed populations of infected and uninfected drug users, lower rates of HIV infection were associated with decreased risky drug use behaviors, participation in needle exchange programs, and participation in drug treatment programs (268--270).

10	What is the cost-effectiveness of screening for HIV infection?	Cost-effectiveness analyses	Good	Two good-quality cost-effectiveness analyses found that the cost-effectiveness of screening for HIV infections compared to no screening in settings with 1% prevalence was $38 000 to $42 000 per quality-adjusted life-year (243, 244). One study found that when transmission benefits were incorporated into estimates, cost-effectiveness remained less than $50 000 per quality-adjusted life-year in settings with prevalences lower than that in the general population (243). Neither study evaluated the incremental cost-effectiveness of universal screening compared to targeted screening strategies in different populations.

* CMV = cytomegalovirus; FDA = U.S. Food and Drug Administration; HAART = highly active antiretroviral therapy; HR = hazard ratio; OR = odds ratio; PCP = *Pneumocystis carinii* pneumonia; RR = relative risk.
† OraSure Technologies, Bethlehem, Pennsylvania.

Appendix Table. Base-Case Assumptions for Outcomes Tables (Table 5) of Counseling and One-Time Screening for HIV Infection

Base-Case Assumptions	Values Used in Outcomes Table	Source, Year (Reference)
Prevalence of HIV infection	Average-risk: 0.3% High-risk: 5%–15%	CDC, 2003 (3) McQuillan et al., 1997 (271) Valleroy et al., 2000 (272) Holmberg, 1996 (273)
Yield of partner notification (newly diagnosed HIV infection per index patient)	0.08–0.23	Macke and Maher, 1999 (274) CDC, 2003 (275)
Accuracy of standard testing	≥99%	Weber et al., 1995 (276) McAlpine et al., 1994 (277) CDC, 1990 (45) CDC, 1988 (46)
Proportion of HIV-positive patients who receive test results	79%–93%	Erickson et al., 1990 (30) Hightow et al., 2003 (120) CDC, 2004 (40) Molitor et al., 1999 (119)

Proportion of patients who would qualify for treatment (assuming only patients with CD4 count < 0.200 × 10^9 cells/L treated)	12%–43%	Samet et al., 2001 (112) Katz et al., 1992 (113) Luby et al., 1994 (114) Hutchinson et al., 1991 (115) Klein et al., 2003 (26)
Proportion of patients qualifying for antiretroviral therapy who would receive it	53%–85%	Stall et al., 2001 (129) Cunningham et al., 2000 (130) Kaplan et al., 1999 (131) McNaghten et al., 2003 (132)
3-y risk for clinical progression or death in untreated patients with CD4 count < 0.200 × 10^9 cells/L	86% (95% CI, 77%–93%)	Mellors et al., 1997 (7)
Relative risk for clinical progression or death with HAART compared to no treatment	0.35 (95% CI, 0.25–0.47)	Calculated from Jordan et al., 2002 (133)
Background rate of myocardial infarction (cases per 3 person-years)	0.00158 (95% CI, 0.000508–0.00487)	Calculated from Friis-Moller, 2003 (227)
Relative risk for myocardial infarction with HAART after 2–4 y compared to no treatment	7.73 (95% CI, 2.42–24.71)	Calculated from Friis-Moller, 2003 (227)
Background rate of cardio- or cerebrovascular (myocardial infarction, stroke, or invasive cardiovascular procedure) events (cases per 3 person-years)	0.0037 (95% CI, 0.0018–0.00770)	Calculated from Writing Group of the DAD Study, 2004 (229)

Relative risk for cardiovascular or cerebrovascular events with HAART after 2–4 y compared to no treatment	5.00 (95% CI, 2.31–10.82)	Calculated from Writing Group of the DAD Study, 2004 (229)
Relative risk for spread of disease	Unable to estimate	

* CDC = Centers for Disease Control and Prevention; DAD = Data collection of Adverse events of anti-HIV Drugs; HAART = highly active antiretroviral therapy.

Appendix A. Methods

Scope of Evidence Synthesis

The analytic framework in the Figure shows the target populations, interventions, and intermediate and health outcome measures we examined. The analytic framework was developed in consultation with the USPSTF and was refined after review by 6 content experts. We considered screening to be testing for HIV infection in asymptomatic persons or those with mild, nonspecific symptoms (such as fatigue) that are not predictive because they are so common. We excluded children (<13 years of age) because the prevalence of HIV in this population is low (9.3 per 100 000 population) and because most were infected vertically (3). We excluded other specific populations such as patients who had undergone transplantation, patients with known chronic viral hepatitis, and patients undergoing hemodialysis. In these groups, treatment considerations, adverse effects from treatment, and natural history may differ from those in the general population of HIV-infected persons; such patients are also usually excluded from clinical trials. We excluded patients with occupational exposures and blood donors because of consensus regarding testing for HIV infection in these situations. We excluded studies of HIV-2 infection because it is rare in the United States and its natural history differs substantially from that of HIV-1 infection.

Our review considered the standard screening strategy for HIV-1 infection to be an office-based venipuncture for anti-HIV enzyme-linked immunosorbent assay, followed by confirmatory Western blot for positive test results (46, 245). We also considered rapid tests, home-based sampling, and tests using saliva or urine specimens. Viral load plus CD4 cell count testing was considered the standard work-up to determine the stage of infection and eligibility for interventions in infected patients (13, 14, 16, 246).

We evaluated recommended HAART regimens, prophylaxis against opportunistic infections, immunizations, Papanicolaou testing, counseling to reduce risky behaviors, and routine monitoring and follow-up. We excluded interventions not recommended for antiretroviral-naive patients or those not known to be effective. These include enfuvirtide; structured treatment interruptions; sequential initiation of therapy with antiretroviral drugs; induction-maintenance regimens; hydroxyurea; interleukin-2; acyclovir; and prophylaxis against candidiasis, histoplasmosis, coccidioidomycosis, herpes simplex virus infection, or cryptococcosis (13, 16). We also did not consider resistance testing in antiretroviral-naive patients to be a routine intervention. Although the presence of primary antiretroviral drug resistance is increasing, resistance testing has mainly been studied in patients in whom a regimen has already failed. In patients with untreated chronic HIV infection, current U.S. guidelines either do not recommend routine resistance testing (13) or do not give firm recommendations (247).

For outcomes, we were particularly interested in reviewing literature on the benefit of early interventions in asymptomatic, treatment-naive patients. Clinical outcomes that we evaluated were mortality, AIDS-related opportunistic infections, spread of disease, and quality of life or functional status. For counseling, we included rates of sexually transmitted diseases as clinical markers of high-risk behaviors. Intermediate outcomes were loss of detectable viremia,

improvement in CD4 cell counts, and changes in risky behaviors. We also reviewed harms from screening, work-up, and treatment. For harms from treatment, we focused on the long-term risk for cardiovascular complications and intolerable (causing discontinuation of therapy with the drug) side effects from HAART. Although interventions for chronic HIV infection, particularly HAART, are associated with many clinically significant short-term side effects, many are tolerable or patients can be switched to effective alternative regimens. In addition, intention-to-treat analyses of clinical outcomes incorporate the effects of intolerable or serious side effects (248). We did not include antiretroviral resistance as a separate outcome because its effects are seen in other intermediate (CD4 cell count, viral load) and clinical outcomes.

Methods

Literature Search and Strategy

We searched the topic of HIV in the MEDLINE and Cochrane Library databases. Most searches were done from 1983 (the year that HIV was characterized) through 30 June 2004. For searches on antiretroviral therapy, we electronically searched these databases from 1998, the year that HAART was first recommended in U.S. guidelines (249); we supplemented these searches by an electronic search for systematic reviews of antiretroviral therapies from 1983. We performed a total of 13 searches covering the areas of risk factor assessment, screening tests, work-up, and interventions. Appendix B presents detailed electronic search strategies and results. Periodic hand searching of relevant medical journals, the Centers for Disease Control and Prevention Web site, and reviews of reference lists supplemented the electronic searches.

Content experts who reviewed the draft report identified additional citations. For rapid HIV tests, we included unpublished studies reported in manufacturer inserts. Other unpublished material was not included. Abstracts were not included in systematic searches, but major abstracts cited in reference lists or presented at recent conferences were included. We also obtained reviews, policy statements, and other papers with contextual value.

Inclusion and Exclusion Criteria

Papers were selected for full review if they were about HIV infection, were relevant to key questions, and met inclusion criteria. We also included cost-effectiveness analyses of HIV screening in outpatient settings in the HAART era. For all key questions, articles were limited to those that evaluated the general adult and adolescent population with chronic HIV infection. We excluded studies that included only overtly symptomatic patients or those with end-stage disease. Although the population of interest was persons with unsuspected HIV infection who would be identified by screening, we included studies of patients with a broad spectrum of chronic HIV disease to get a picture of the effects of screening and treatment in patients with different degrees of immune deficiency. We included studies performed in the United States, Australia, Canada, and countries of western Europe, in which the epidemiology and management of chronic HIV infection are similar. When important studies for a specific key question had been done only in other countries, we included these as well. We excluded studies of nonhuman subjects and those without original data. We considered non--English-language papers if they reported on clinical trials and an abstract was available in English. We searched for relevant systematic reviews for all key questions. A separate report lists additional key question--specific inclusion criteria (17).

Data Extraction and Synthesis

We used predefined criteria from the USPSTF to assess the internal validity of included systematic reviews, trials, and observational studies, which we rated as "good," fair," or "poor." We also rated the applicability of each study to the population that would be identified by screening. The rating system was developed by the USPSTF and is described in detail elsewhere (18) and summarized in Appendix C. For included trials and systematic reviews, we abstracted information about setting, patients, interventions, and outcomes. For intervention studies, when available we abstracted intention-to-treat results in which missing data were classified as treatment failures (248). We rated the overall body of evidence for each key question using the system developed by the USPSTF. We also rated studies evaluating cost-effectiveness of HIV screening in the HAART era using criteria developed by the USPSTF for evaluation of cost-effectiveness analyses (Appendix C) (19).

Methods for Outcomes Table

Table 5 estimates the outcomes after 3 years from one-time screening for HIV in 3 hypothetical cohorts of 10 000 adolescents or adults. We limited our time horizon to 3 years because longer studies on the clinical benefits from HAART are not yet available. We excluded areas from this table in which reliable data to estimate the clinical magnitude of benefit or harm were not available, such as harms from screening (anxiety, labeling, violence, suicide, partnership dissolution) and decreased transmission from counseling or other interventions. We also had insufficient data with which to estimate the impact of screening on earlier diagnosis of HIV and the proportion of patients qualifying for different interventions. Because short-term adverse events from HAART are usually self-limited, and effective alternative regimens are usually available, we focused on the long-term cardiovascular harms of HAART. We calculated numbers needed to screen and treat to prevent 1 case of clinical progression (new category B or C event) or death and to cause 1 cardiovascular event (myocardial infarction, invasive cardiovascular procedure, or stroke). Data from clinical trials were insufficient to separate clinical outcomes by severity.

Several assumptions made our estimates on the benefits of screening conservative. First, we focused on the effects of HAART. For some interventions (for example, most immunizations, more frequent Papanicolaou testing, routine monitoring and follow-up, and counseling), data were insufficient to estimate the magnitude of benefit. For others, such as prophylaxis against opportunistic infections, the magnitude of benefit from HAART substantially outweighs the benefit from other interventions, and successful treatment with HAART would also reduce the proportion of patients requiring prophylaxis by increasing CD4 counts. Second, we assumed that only asymptomatic patients with CD4 cell counts less than 0.200×10^9 cells/L would routinely receive HAART because they are at highest risk for clinical progression, evidence for clinical benefits of treatment is strongest in this group, and recommendations are less firm for asymptomatic patients with higher CD4 cell counts. Third, we estimated benefits only for the first 3 years after screening, although HAART is likely to be beneficial beyond that time period. Methods for Calculating Relative Risk for Clinical Progression or Death during HAART Compared to No Treatment (Used in Outcomes Table)

Because no clinical trials have directly evaluated the relative risk for clinical progression or death associated with HAART (antiretroviral therapy with 3 drugs) compared to no treatment in HIV-infected persons, we calculated this relative risk indirectly from data provided in a systematic review of clinical trials of 1-drug therapy versus no antiretroviral agents, 2-drug versus 1-drug therapy, and 3-drug versus 2-drug therapy in antiretroviral-naive persons (133). Bucher and colleagues (250) proposed a method for indirect treatment comparisons to estimate odds ratios from 2 sets of clinical trials; we adapted this method to calculate the relative risk indirectly from the 3 sets of trials. Bucher and colleagues' method has been shown to usually agree with results of direct treatment comparisons (251). For this calculation, let RR_{MN}, RR_{DM} and RR_{TD} denote relative risk for clinical progression or death on 1-drug therapy versus no antiretroviral drugs, 2-drug versus 1-drug therapy and 3-drug versus 2-drug therapy, respectively. The relative risk for clinical progression or death during 3-drug therapy versus no antiretroviral agents (RR_{TN}) is given by:

$$RR_{TN} = RR_{MN} \times RR_{DM} \times RR_{TD}. \quad (1)$$

To calculate the (1 −α)% CI for RR_{TN}, it is usual to use the natural log scale:

$$\log(RR_{TN}) = \log(RR_{MN}) + \log(RR_{DM}) + \log(RR_{TD}) \quad (2).$$

The variance of log relative risk is given as:

$$\mathrm{Var}(\log(RR_{TN})) = \mathrm{var}(\log(RR_{MN})) + \mathrm{var}(\log(RR_{DM})) + \mathrm{var}(\log(RR_{TD})). \quad (3)$$

by assuming independence among $\log(RR_{MN})$, $\log(RR_{DM})$ and $\log(RR_{TD})$. Since $\log(RR_{TN})$ is approximately normally distributed, the (1 −α)% CI for RR_{TN} are

$$\left(RR_{TN}\exp\left(-Z_{\alpha/2}\mathrm{sqrt}(\mathrm{var}(\log(RR_{TN})))\right),\ RR_{TN}\exp\left(Z_{\alpha/2}\mathrm{sqrt}(\mathrm{var}(\log(RR_{TN})))\right)\right). \quad (4)$$

Jordan and colleagues (133) reported the rates for clinical progression or death from clinical trials of 1-drug therapy vs. no antiretroviral agents (15 studies), 2-drug vs. 1-drug therapy (16 studies) and 3-drug versus 2-drug therapy (9 studies). In our analysis, we obtained estimates of RR_{MN} and var(log(RR_{MN})) from a meta-analysis of the 15 trials comparing 1-drug therapy versus placebo. Similarly, we estimated RR_{DM} and var(log(RR_{DM})) from a meta-analysis of the 16 trials comparing 2-drug versus 1-drug therapy; and we obtained estimates of RR_{TD} and var(log(RR_{TD})) from a meta-analysis of the 9 studies of 3-drug versus 2-drug therapy. The assumption of independence between $\log(RR_{MN})$, $\log(RR_{DM})$ and $\log(RR_{TD})$ should be adequately satisfied because each value was estimated from different trials. We calculated an overall estimate of RR_{TN} and its corresponding 95% CI by plugging these estimates into formulas (1) through (4). For each meta-analysis, tests for heterogeneity indicated statistically significant variation among studies, so we used a random-effects model to combine studies and calculate the estimates of RR_{MN}, RR_{DM} and RR_{TD}. Estimates obtained by using a fixed-effects model, however, were similar to those from a random-effects model. Bucher and colleagues (250) used a fixed-effects model to combine studies. Jordan and colleagues (133) also used a fixed-effects approach to estimate odds ratios for 1-drug therapy versus placebo, 2-drug versus 1-drug therapy, and 3-drug versus 2-drug therapy.

Methods for Calculating 3-Year Risk for Cardiovascular Complications

The background rate (cases per 3 person-years) and relative risk for myocardial infarction and cardiovascular and cerebrovascular events (myocardial infarction, stroke, or invasive cardiovascular procedures) associated with combination antiretroviral therapy after 2 to 4 years compared to no exposure were calculated on the basis of raw data from the Data collection on Adverse events of anti-HIV Drugs (DAD) study (Figure; we used outcomes for no antiretroviral treatment and combined outcomes for 2 to 3 and 3 to 4 years of exposure) according to standard statistical methods (228, 229).

Methods To Calculate Numbers Needed To Screen and Treat

Calculations of numbers needed to screen for benefit (NNS_B) and numbers needed to treat for benefit (NNT_B) were based on estimates from different sources in the literature (Appendix Table). The indicated range of estimates and variation associated with estimates were incorporated in the calculations by using Monte Carlo simulations and are reflected by the ranges in the calculated NNS_B and NNT_B.. The sampling distributions of the estimates used in the simulations were either the underlying distribution on which the calculation of 95% CI was based, or one that best approximated the point estimate and CI. For example, if the estimate was a rate or proportion, the logit of the rate or proportion was sampled assuming an approximately normal distribution; it was then transformed back to its original scale. For relative risks, we assumed that the log of relative risk was approximately normally distributed. The log of the relative risk was sampled from the normal distribution and then transformed back to relative risk. In each iteration of the Monte Carlo simulation, one sample of each proportion, relative risk, or other estimate was drawn to calculate the NNS_B and NNT_B. The point estimates and 95% CI of NNS_B and NNT_B were based on 1 000 000 samples. Similar calculations were performed to calculate numbers needed to screen for harm (NNS_H) and numbers needed to treat for harm (NNT_H). A simple program using R statistical language was written to perform simulations and calculate summary statistics (278).

Appendix B. Search Strategies

Immunization---Database: MEDLINE (1996 to Present)
1. exp hiv infections/ or exp hiv/
2. exp Viral Hepatitis Vaccines/
3. exp Influenza Vaccine/
4. exp Bacterial Vaccines/
5. 2 or 3 or 4
6. 1 and 5
7. exp IMMUNIZATION/
8. exp Immunization Programs/
9. 7 or 8
10. exp HEPATITIS/
11. exp INFLUENZA/
12. exp PNEUMONIA/
13. 10 or 11 or 12
14. 1 and 9 and 13
15. 6 or 14
16. exp Evaluation Studies/
17. exp Epidemiologic Studies/
18. Comparative Study/
19. 16 or 17 or 18
20. 15 and 19
21. limit 15 to (clinical trial or guideline or meta analysis or multicenter study or practice guideline)
22. 20 or 21
23. limit 22 to (human and english language)
24. from 23 keep 1-206
Prophylaxis---Database: MEDLINE (1996 to Present)
1. exp AIDS-Related Opportunistic Infections/pc [Prevention & Control]
2. prophyla$.mp.
3. exp HIV Infections/co [Complications]
4. exp AIDS-Related Opportunistic Infections/
5. 2 and (3 or 4)
6. 1 or 5
7. limit 6 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
8. from 7 keep 1-396
Counseling---Database: MEDLINE (1996 to Present)
1. exp HIV Infections/ or exp HIV/
2. exp COUNSELING/
3. 1 and 2
4. exp impulsive behavior/ or risk reduction behavior/ or risk-taking/
5. 1 and 4
6. 3 or 5
7. exp Evaluation Studies/

8. Comparative Study/
9. exp Epidemiologic Studies/
10. 7 or 8 or 9
11. 6 and 10
12. limit 6 to (clinical trial or guideline or meta analysis or multicenter study or practice guideline)
13. 11 or 12
14. limit 13 to (human and english language)
15. from 14 keep 1-1272

Risk Factors---Database: MEDLINE (1996 to Present)

1. exp RISK/
2. exp HIV Infections/mo, ep, eh, et, tm, pc [Mortality, Epidemiology, Ethnology, Etiology, Transmission, Prevention & Control]
3. 1 and 2
4. limit 3 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
5. exp HIV/
6. 1 and 5
7. limit 6 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
8. 4 or 7
9. exp Evaluation Studies/
10. Comparative Study/
11. exp Epidemiologic Studies/
12. 9 or 10 or 11
13. (3 or 6) and 12
14. limit 13 to (human and english language)
15. from 8 keep 1-573

Screening---Database: MEDLINE (1996 to Present)

1. exp AIDS Serodiagnosis/
2. exp HIV SERONEGATIVITY/ or exp HIV ANTIGENS/ or exp HIV/ or exp HIV SEROPREVALENCE/ or exp HIV SEROPOSITIVITY/ or exp HIV ANTIBODIES/
3. exp Mass Screening/
4. 2 and 3
5. 1 or 4
6. exp "Sensitivity and Specificity"/
7. 5 and 6
8. ae.fs.
9. exp stress, psychological/
10. Life Change Events/
11. exp prejudice/ or prejudic$.mp.
12. 8 or 9 or 10 or 11
13. 5 and 12
14. exp diagnostic errors/
15. 5 and 14
16. 7 or 13 or 15

17. exp Evaluation Studies/
18. Comparative Study/
19. exp longitudinal studies/
20. 17 or 18 or 19
21. 16 and 20
22. limit 16 to (clinical trial or guideline or meta analysis or multicenter study or practice guideline or review)
23. 22 or 21
24. limit 23 to (human and english language)
25. limit 23 to (human and abstracts)
26. 24 or 25
27. from 26 keep 1-247

Antiviral Drugs---Database: MEDLINE (1998 to Present)

1. exp HIV Infections/dt [Drug Therapy]
2. exp HIV/de [Drug Effects]
3. 1 or 2
4. exp Reverse Transcriptase Inhibitors/ad, tu
5. exp HIV Protease Inhibitors/ad, tu
6. exp anti-hiv agents/ad, tu
7. 4 or 5 or 6
8. 3 and 7
9. limit 8 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
10. exp Reverse Transcriptase Inhibitors/ae, ct, to, po
11. exp HIV Protease Inhibitors/ae, ct, to, po
12. exp anti-hiv agents/ae, ct, to, to
13. 10 or 11 or 12
14. 3 and 13
15. limit 14 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
16. 14 and exp epidemiologic studies/
17. 14 and (exp evaluation studies/ or exp comparative study/)
18. 16 or 17
19. limit 18 to (human and english language)
20. 15 or 19
21. limit 9 to yr = 1998-2003
22. from 21 keep 1-1157

Adverse Effects---Database: MEDLINE (1998 to Present)

1. exp HIV Infections/dt [Drug Therapy]
2. exp HIV/de [Drug Effects]
3. 1 or 2
4. exp Reverse Transcriptase Inhibitors/ad, tu
5. exp HIV Protease Inhibitors/ad, tu
6. exp anti-hiv agents/ad, tu
7. 4 or 5 or 6
8. 3 and 7

9. limit 8 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
10. exp Reverse Transcriptase Inhibitors/ae, ct, to, po
11. exp HIV Protease Inhibitors/ae, ct, to, po
12. exp anti-hiv agents/ae, ct, to, to
13. 10 or 11 or 12
14. 3 and 13
15. limit 14 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
16. 14 and exp epidemiologic studies/
17. 14 and (exp evaluation studies/ or exp comparative study/)
18. 16 or 17
19. limit 18 to (human and english language)
20. 15 or 19
21. limit 9 to yr=1998-2003
22. from 21 keep 1-1157
23. limit 20 to yr = 1998-2003
24. from 23 keep 1-732
25. from 24 keep 1-732

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

1. exp HIV/
2. viral load.mp. or Viral Load/
3. VIREMIA/
4. exp HIV Infections/
5. 1 or 4
6. 2 or 3
7. 5 and 6
8. (exp leukocyte count/ and cd4.mp.) or exp cd4 lymphocyte count/
9. exp "pathological conditions, signs and symptoms"/ or disease progression/
10. 7 and 8 and 9
11. exp "sensitivity and specificity"/
12. 10 and 11
13. exp epidemiologic studies/
14. 10 and 13
15. limit 10 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
16. limit 14 to (human and english language)
17. 15 or 16
18. from 17 keep 1-232

Maternal---Database: MEDLINE (1996 to Present)

1. exp HIV/ or exp HIV INFECTIONS/
2. exp Anti-HIV Agents/ad, ae, po, ct, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Contraindications, Therapeutic Use, Toxicity]
3. exp Reverse Transcriptase Inhibitors/ad, ae, po, ct, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Contraindications, Therapeutic Use, Toxicity]

4. exp HIV Protease Inhibitors/ad, ae, po, tu, ct, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Contraindications, Toxicity]
5. 1 and (2 or 3 or 4)
6. exp Disease Transmission, Vertical/
7. exp HIV Infections/tm
8. pregnancy complications/ or exp pregnancy complications, infectious/
9. exp Pregnancy/
10. 6 or 7
11. 8 or 9
12. 10 and 11
13. 5 and 12
14. limit 13 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
15. exp Evaluation Studies/
16. Comparative Study/
17. exp Epidemiologic Studies/
18. 15 or 16 or 17
19. 13 and 18
20. limit 19 to (human and english language)
21. 14 or 20
22. from 21 keep 1-373

Cesarean---Database: MEDLINE (1996 to Present)

1. exp HIV/ or exp HIV INFECTIONS/
2. exp Anti-HIV Agents/ad, ae, po, ct, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Contraindications, Therapeutic Use, Toxicity]
3. exp Reverse Transcriptase Inhibitors/ad, ae, po, ct, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Contraindications, Therapeutic Use, Toxicity]
4. exp HIV Protease Inhibitors/ad, ae, po, tu, ct, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Contraindications, Toxicity]
5. exp cesarean section/
6. 1 and (2 or 3 or 4 or 5)
7. exp Disease Transmission, Vertical/
8. exp HIV Infections/tm
9. pregnancy complications/ or exp pregnancy complications, infectious/
10. exp Pregnancy/
11. 7 or 8
12. 9 or 10
13. 11 and 12
14. 6 and 13
15. limit 14 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
16. exp Evaluation Studies/
17. Comparative Study/
18. exp Epidemiologic Studies/
19. 16 or 17 or 18
20. 14 and 19

21. limit 20 to (human and english language)
22. 15 or 21

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

1. exp HIV Infections/
2. exp HIV/
3. 1 or 2
4. exp "Costs and Cost Analysis"/
5. 3 and 4
6. Comparative Study/
7. exp Evaluation Studies/
8. exp epidemiologic study characteristics/
9. 5 and (6 or 7 or 8)
10. limit 9 to (human and english language)
11. exp Mass Screening/
12. 9 and 11
13. 5 and 11
14. limit 13 to (human and english language)
15. ec.fs.
16. 3 and 15
17. 16 and 11
18. limit 17 to (human and english language)
19. 14 or 18
20. from 19 keep 1-179

Systematic Reviews---Database: PubMED

1. hiv/de [mh] OR hiv infections/dt [mh]
2. anti hiv agents[pa] OR reverse transcriptase inhibitors[pa] OR hiv protease inhibitors [pa]
3. #1 OR #2
4. evaluation studies[mh] OR epidemiologic studies[mh] OR comparative study [mh]
5. #3 AND #4
6. tu[sh] OR ad[sh] OR ae[sh] OR to[sh] OR po[sh] OR ct[sh]
7. #5 AND #6
8. #7 AND systematic [sb]
9. #8 AND Limits: Publication Date from 1989 to 1997, English, Human

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

((systematic review$ OR systematic literature review$ OR meta-analysis.pt. OR meta-analysis.ti. OR metaanalysis.ti. OR meta-analyses.ti. OR evidence-based medicine OR (evidence-based AND (guideline.tw. OR guidelines.tw. OR recommendations)) OR (evidenced-based AND (guideline.tw. OR guidelines.tw. OR recommendation$)) OR consensus development conference.pt. OR health planning guidelines OR guideline.pt. OR cochrane database syst rev OR acp journal club OR health technol assess OR evid rep technol assess summ OR evid based nurs OR evid based ment health OR clin evid) OR ((systematic.tw. OR systematically OR critical.tw. OR (study.tw. AND selection.tw.) OR (predetermined OR inclusion AND criteri$.tw.) OR exclusion criteri$ OR main outcome measures OR standard of care) AND (survey.tw. OR surveys.tw. OR overview$ OR review.tw. OR reviews OR search$ OR handsearch OR analysis.tw. OR critique.tw. OR appraisal OR (reduction AND risk AND (death

OR recurrence))) AND (literature.tw. OR articles OR publications.tw. OR publication.tw. OR bibliography.tw. OR bibliographies OR published OR unpublished OR citation OR citations OR database OR internet.tw. OR textbooks.tw. OR references OR trials OR meta-analysis.mh. OR (clinical.tw. AND studies) OR treatment outcome)) NOT (case report.ti. OR case report.mh. OR editorial.ti. OR editorial.pt. OR letter.pt. OR newspaper article.pt.))

Appendix C. USPSTF Quality Rating Criteria

Diagnostic Accuracy Studies

Criteria

1. Screening test relevant, available for primary care, adequately described.
2. Credible reference standard, performed regardless of test results.
3. Reference standard interpreted independently of screening test.
4. Indeterminate results handled in a reasonable manner.
5. Spectrum of patients included in study.
6. Sample size.
7. Administration of reliable screening test.

Definition of Ratings Based on Above Criteria

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

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

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

Randomized, Controlled Trials and Cohort Studies

Criteria

1. Initial assembly of comparable groups: randomized, controlled trials---adequate randomization, including concealment and statement of whether potential confounders were distributed equally among groups; cohort studies---consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
2. Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination).
3. Important differential loss to follow-up or overall high loss to follow-up.
4. Measurements: equal, reliable, and valid (includes masking of outcome assessment).
5. Clear definition of interventions.
6. Important outcomes considered.
7. Analysis: adjustment for potential confounders for cohort studies, or intention-to-treat analysis for randomized, controlled trials.

Definition of Ratings Based on Above Criteria

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

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

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

Case-Control Studies

Criteria

1. Accurate ascertainment of cases.
2. Nonbiased selection of case-patients and controls, with exclusion criteria applied equally to both.
3. Response rate.
4. Diagnostic testing procedures applied equally to each group.
5. Measurement of exposure accurate and applied equally to each group.
6. Appropriate attention to potential confounding variable.

Definition of Ratings Based on Above Criteria

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

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

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

Cost-Effectiveness Analyses: Criteria

Framing

1. Are interventions and populations compared appropriate?
2. Is the study conducted from the societal perspective?
3. Is the time horizon clinically appropriate and relevant to the study question?

Effects

1. Are all important drivers of effectiveness included?
2. Are key harms included?
3. Is the best available evidence used to estimate effectiveness?
4. Are long-term outcomes used?
5. Do effect measures capture preferences or utilities?

Costs

1. Are all appropriate downstream costs included?
2. Are charges converted to costs appropriately?
3. Are the best available data used to estimate costs?

Results

1. Are incremental cost-effectiveness ratios presented?
2. Are appropriate sensitivity analyses performed?

Quality criteria for cost-effectiveness analyses were based on those developed by the USPSTF (19), which, in turn, are based on recommendations of the Panel on Cost-Effectiveness in Health and Medicine (252). We used the criteria to guide our categorization of studies as good, fair, or poor. We assigned quality grades on the basis of a subjective assessment of study design and quality of data inputs.