HIV/STI
Clinical Practice Guideline

This guideline is informational only. It is not intended or designed as a substitute for the reasonable exercise of independent clinical judgment by practitioners, considering each patient’s needs on an individual basis.

Guideline recommendations apply to populations of patients. Clinical judgment is necessary to design treatment plans for individual patients.

Approved by the National Guideline Directors
March 2011
# Table of Contents

Introduction................................................................................................................................... 1

Guideline Summary ...................................................................................................................... 5

Rationale Statements .................................................................................................................... 8

1. Risk Assessment .................................................................................................................... 8
2. HIV/STI Screening ............................................................................................................... 9
3. Patient Counseling ............................................................................................................. 10
4. Screening in Pregnancy ...................................................................................................... 11

Appendix A - GRADE System of Evidence Rating .................................................................. 17

Appendix B - Risk Assessment Tools ..................................................................................... 18

1. Risk Assessment Tools ....................................................................................................... 18
   Problem Formulation 1 ........................................................................................................... 18
   Search Strategy 1 .................................................................................................................. 19

Appendix C – HIV/STI Screening ............................................................................................. 22

2. HIV/STI Screening ............................................................................................................. 22
   Problem Formulation 2 ....................................................................................................... 22
   Search Strategy 2 ................................................................................................................ 23
   Evidence Tables 2 ............................................................................................................... 37

Appendix D - HIV with Concomitant STIs ........................................................................... 56

3. HIV with Concomitant STIs ............................................................................................. 56
   Problem Formulation 3 ....................................................................................................... 56
   Search Strategy 3 ................................................................................................................ 57
   Evidence Tables 3 ............................................................................................................... 69

Appendix E – Patient Counseling ............................................................................................. 110

4. Patient Counseling ............................................................................................................ 110
   Problem Formulation 4 ...................................................................................................... 110
   Search Strategy 4 ............................................................................................................... 111

Appendix F - Population Risk and Intervention Intensity Terminology.................................. 119

Appendix G - USPSTF – Patient Counseling: Evidence Summary and Evaluation ............. 120

Appendix H – Screening in Pregnancy ................................................................................... 126

5. Screening in Pregnancy .................................................................................................... 126
   Problem Formulation 5 .................................................................................................... 126
   Search Strategy 5 ............................................................................................................. 127

Appendix I – HIV Clinician Guide ......................................................................................... 142

Appendix J - Ask Screen Intervene (ASI) .............................................................................. 148

References.................................................................................................................................. 149
Introduction

Kaiser Permanente’s National Guideline Program

The National Guideline Program (NGP) supports the development of a core set of explicit, scientifically-based clinical practice guidelines, practice resources, and evidence synopses to assist Kaiser Permanente (KP) physicians, administrators, and other health care professionals in determining the most effective medical practices.

This core set of evidence-based resources will:
- Create Programwide economies of scale,
- Support ongoing performance improvement activities,
- Consistently provide high quality resources for use in care delivery tools and systems, and
- Increase KP regions’ abilities to leverage clinical guidelines to improve clinical outcomes.

Who are the National Guideline Directors?

The National Guideline Directors group (NGD) oversees the KP National Guideline Program. The NGD selects and approves topics for development of evidence-based knowledge products and is responsible for maintaining the process, including quality assurance and methodological standards, for development of the clinical recommendations for clinical guidance.

What is the Guideline Quality Committee?

The Guideline Quality Committee is a subcommittee of the National Guideline Directors and is comprised of clinical evidence specialists and physician methodologists with expertise in clinical epidemiology, biostatistics, research methods and critical appraisal and synthesis of the medical literature. Final review and approval of all national recommendation, whether internally or externally developed, has been delegated to the Guideline Quality Committee by the National Guideline Directors.

Why is it Important for a Guideline to Be Evidence-Based?

The Kaiser Permanente National Guideline Program (NGP) provides the organization with evidence-based clinical recommendations to support care delivery and optimize the health of Kaiser Permanente (KP) members. When based on a rigorous methodology, clinical practice recommendations are essential tools for improving quality of care; they support KP physicians, other health care professionals, and administrators in their quest to provide the highest quality of care through the consistent delivery of effective clinical practices. When implemented, these practices help to reduce unwarranted variation in care and improve clinical outcomes.
How Are Guidelines Developed?

Clinical recommendations development at Kaiser Permanente follows an evidence-based, systematic, and transparent process. In order to ensure that recommendations are high-quality, relevant, and accurately reflect the body of the evidence, the guideline development process includes the following sequential steps:

- Determine the scope of the clinical content to be addressed in the guideline.
- Develop the key clinical questions, including specification of patient populations, comparative interventions and outcomes.
- Identify and evaluate existing recommendations and guidelines.
- Conduct a comprehensive search of relevant databases and other sources to identify relevant evidence.
- Screen, select and extract data from studies.
- Critically appraise the strengths and limitations of the identified studies.
- Assess, synthesize and grade of the body of evidence.
- Develop recommendations and rationale statements that are consistent with the evidence.
- Review recommendations.
- Approve guideline.
- Disseminate and implement guideline.
- Periodically update the evidence.

For additional information on evidence grading, see Appendix A.

A Guideline Development Team serves as the expert panel that refines and approves the recommendations that make up each guideline. Each GDT includes physician and other clinical experts (such as psychologists, pharmacists, clinical nurse experts, social workers, etc.), evidence analysts, and a methodologist. Each GDT includes the appropriate range of specialties for the guideline topic, with representation from primary care, specialty care, pharmacy, nursing, and health education.

The GDT approves the scope of the recommendations and key clinical questions. The GDT reviews, recommends revisions as appropriate, and endorses completed clinical recommendations.

In addition to their role in developing guideline recommendations, GDT members solicit feedback on draft recommendations and advocate for and seek commitment for guideline adoption in their respective regions.
How Often Are Guidelines Reviewed and Revised?

To keep current with changing medical practices, all guidelines are reviewed, and, if appropriate, revised at least every two years. To develop the HIV/STI Guideline, released in May 2011, a multidisciplinary, interregional GDT first met in July, 2010 to define the scope of the guideline. The Project Management Team then performed systematic reviews of the medical literature on each of the clinical questions identified by the GDT, assembled the evidence, and developed draft recommendations for review by the GDT. All of the recommendations and supporting evidence were reviewed in depth by the GDT in a series of meetings from October, 2010 through December, 2010. The GQ Committee reviewed and approved the guideline in March, 2011.

What Does It Mean for a Guideline to Be Approved and National?

A recommendation that is consistent with the above policies is labeled as “National Guideline Directors Approved.” A National Guideline Directors Approved guideline for which at least 90% of the recommendations are approved by at least six of the eight KP regions is a "National Guideline." On the topics for which they exist, National Guidelines are the preferred evidence source for KP HealthConnect content.

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The Kaiser Permanente (KP) HIV/STI Clinical Practice Guideline is the result of the extensive clinical expertise, collaborative efforts, and outstanding personal contributions of the following participants:

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*There was no conflict of interest for any member of the Guideline Development Team (GDT).*

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Guideline Summary

This guideline is informational only. It is not intended or designed as a substitute for the reasonable exercise of independent clinical judgment by practitioners, considering each patient’s needs on an individual basis.

Guideline recommendations apply to populations of patients. Clinical judgment is necessary to design treatment plans for individual patients.

1. Risk Assessment
   Routinely obtain a thorough sexual history* from all patients ≥ 12 years of age to assess risk behaviors and stratify for appropriate testing.
   - Risk assessment is essential to the evaluation of HIV (human immunodeficiency virus) and/or other STIs (sexually transmitted infections) acquisition and transmission.
   - Risk behaviors include sex with multiple or new partners, sex with high-risk partners, unprotected sex, sex while intoxicated, sex in exchange for money.
   - Higher-risk population groups for STIs in the US might include adolescents and young adults, blacks/African-Americans, Hispanics, men who have sex with men (MSM), military recruits, inmates and former inmates, intravenous drug users (IVDUs) and former IVDUs, sex workers, mentally ill people, mentally disabled people, people living in low-income urban areas, people living in the southern United States, people with a history of an STI, and pregnant women.

2. HIV/STI Screening
   Screen and promptly treat all identified individuals > 12 years of age at risk for the following STIs:†
   - Human immunodeficiency virus (HIV)
   - Neisseria gonorrhea
   - Chlamydia trachomatis
   - Syphilis
   - Hepatitis B
   - Hepatitis C
   - Trichomoniasis (for women)

   NOTE: Evidence suggests the presence of other STIs, including herpes simplex (HSV), increases the risk of HIV transmission and acquisition.

* See Appendix I for more information on obtaining a thorough sexual history.
† The USPSTF recommends against serological screening for herpes simplex virus (HSV) in asymptomatic adolescents and adults (USPSTF Screening for Genital Herpes, 2010).
3. **Patient Counseling**

Provide behavioral counseling and additional risk reduction interventions for all sexually active individuals ≥ 12 years of age at risk for HIV/STI acquisition.

- Behavioral counseling is the provision of education, skills training, and guidance on how to change sexual behavior, delivered alone or in combination with other interventions, intended to promote sexual risk reduction or risk avoidance.\(^{(3),*,†}\)
- High-intensity behavioral counseling may be delivered in primary care settings or in other sectors of the health system after referral from the primary care clinician or system.\(^{(4),‡}\)
- Risk-reduction counseling (e.g., strategies targeting condom use, abstinence, etc.) may be available through various community organizations.
- Strong linkages between the primary care setting and the community may greatly improve the delivery of this service.\(^{(4),‡}\)

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† An example of a behavioral counseling tool is the “Ask, Advise, Agree, Assist, and Arrange” model developed by the CDC (Evidence-Based Methods for Evaluating Behavioral Counseling Interventions. Agency for Healthcare Research and Quality. 1 July 2009). See Appendix I for details.

4. **Screening in Pregnancy**

Screen all pregnant women for HIV antibody, syphilis, and hepatitis B early during each pregnancy. Screen at risk* pregnant women for gonorrhea, Chlamydia and hepatitis C. Retest before 36 weeks in women at risk for exposure to HIV and/or any other STIs during the course of pregnancy.

- Risk factors include HIV infected partner or partner at risk for HIV, new or multiple sex partners during pregnancy, illicit drug use, exchanges sex for money or drugs, history of STI during current pregnancy or one year prior to pregnancy, signs or symptoms of acute HIV infection.^(2),†
- Pregnancy risk for exposure may include a newly diagnosed STI during pregnancy, documented or suspected injection drug use, or partner with known HIV infection.

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* The USPSTF (Recommendations for STI Screening, 2008)\(^5\) recommends that providers determine at risk individuals based on high-risk sexual behavior and age.

Rationale Statements

1. **Risk Assessment**

   Routinely obtain a thorough sexual history* from all patients ≥ 12 years of age to assess risk behaviors and stratify for appropriate testing.

   - Risk assessment is essential to the evaluation of HIV (human immunodeficiency virus) and/or other STIs (sexually transmitted infections) acquisition and transmission.
   - Risk behaviors include sex with multiple or new partners, sex with high-risk partners, unprotected sex, sex while intoxicated, sex in exchange for money.
   - Higher-risk population groups for STIs in the US might include adolescents and young adults, blacks/African-Americans, Hispanics, men who have sex with men (MSM), military recruits, inmates and former inmates, intravenous drug users (IVDUs) and former IVDUs, sex workers, mentally ill people, mentally disabled people, people living in low-income urban areas, people living in the southern United States, people with a history of an STI, and pregnant women.

   **Rationale**

   The Guideline Development Team (GDT) considered other potential approaches to frame this clinical question, including whether performing a risk assessment results in increased and earlier human immunodeficiency virus/sexually transmitted infections (HIV/STI) case finding and thus, a decrease in morbidity and mortality. As medical literature and expert opinion suggests a strong association between risk assessment and decreased HIV/STI morbidity and mortality, the GDT agreed to evaluate the most clinically useful risk assessment tools. An appraisal of HIV/STI risk assessment tools is worthwhile as there remains great variability in obtaining sexual histories and risk assessment in clinical practice, ranging from 15% to 90% in primary care.†,(6)

   As documented in the HIV/STI risk assessment evidence summary (See Appendix B), no trials, recommendation statements, or guidelines were found that identified the most effective HIV/STI risk assessment tool(s). Nonetheless, the GDT agreed that opportunities to identify HIV/STI risk and assist with interventions are often missed by not asking the right questions. As a result, the GDT reached a consensus agreement that despite the absence of a widely-used or recognized risk assessment tool, obtaining a thorough sexual history from all patients ≥ 12 years of age is critical to assessing risk behaviors and stratifying for subsequent testing. The specific tool or process used to achieve a thorough sexual history may be identified at the regional level, on a case by case basis.

   Commonly accepted demographic factors that increase HIV/STI risk were identified in a systematic review prepared for the USPSTF on behavioral counseling and HIV/STI risk reduction (Lin et al., 2008).(5) The GDT agreed that these factors reflected those populations most at risk for HIV/STI.

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* See Appendix H for more information on obtaining a thorough sexual history.
2. **HIV/STI Screening**

Screen and promptly treat all identified individuals ≥ 12 years of age at risk for the following STIs:*\(^{2}\),

- Human immunodeficiency virus (HIV)
- Neisseria gonorrhoea
- Chlamydia trachomatis
- Syphilis
- Hepatitis B
- Hepatitis C
- Trichomoniasis (for women)

**NOTE:** Evidence suggests the presence of other STIs, including herpes simplex (HSV), increases the risk of HIV transmission and acquisition.

**Rationale:**

Using statistics provided by the CDC, the GDT choose to investigate seven of the most common STIs in the United States: Human immunodeficiency virus (HIV), Neisseria gonorrhoea, Chlamydia trachomatis, Syphilis, hepatitis B, hepatitis C, and trichomoniasis. The Guideline Development Team (GDT) agreed with the USPSTF’s recommendation against serological screening for herpes simplex virus (HSV) and choose not to include it in this screening recommendation.

A compelling, plausible biological association exists between the presence of other STIs and an increased risk for HIV acquisition and transmission. In turn, the presence of HIV has the potential to alter the management of concomitant STIs. Likely due to heterogeneity between organisms and populations studied, the evidence synthesis found only low-quality evidence to support this association. However, the GDT agreed that there is enough evidence of the association between HIV and concomitant STIs to recommend that all identified individuals ≥ 12 years of age at risk be screened for and promptly treated if diagnosed with the listed STIs. In support of this recommendation the GDT referenced a recent cost-effective analysis showing that expanding HIV screening and treatment simultaneously offers the greatest health benefit with the potential to prevent approximately 212,000 new HIV infections in the United States over a 20 year period.*\(^{7}\),†

There is no strong or consistent evidence regarding the effectiveness of testing methods or the diagnostic accuracy of available tests to make recommendations about which tests to use for specific STIs. Therefore, the GDT leaves decisions regarding HIV/STI tests to local stakeholders.

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* The USPSTF recommends against serological screening for herpes simplex virus (HSV) in asymptomatic adolescents and adults (USPSTF Screening for Genital Herpes, 2010).*\(^{1}\)
3. Patient Counseling

Provide behavioral counseling and additional risk reduction interventions for all sexually active individuals ≥ 12 years of age at risk for HIV/STI acquisition.

- Behavioral counseling is the provision of education, skills training, and guidance on how to change sexual behavior, delivered alone or in combination with other interventions, intended to promote sexual risk reduction or risk avoidance.\(^{(3)\text{,}*,†}\)
- High-intensity behavioral counseling may be delivered in primary care settings or in other sectors of the health system after referral from the primary care clinician or system.\(^{(4)\text{,}‡}\)
- Risk-reduction counseling (e.g., strategies targeting condom use, abstinence, etc.) may be available through various community organizations.
- Strong linkages between the primary care setting and the community may greatly improve the delivery of this service.\(^{(4)\text{,}‡}\)

**Rationale:**

As documented in the human immunodeficiency virus/sexually transmitted infections (HIV/STI) patient counseling evidence summary (see Appendix G), the Guideline Development Team (GDT) chose to use the USPSTF systematic review and recommendations on this topic as the foundation for its recommendations.

The USPSTF found fair to good evidence that moderate to high intensity behavioral counseling conducted in STI clinics effectively reduces STI incidence in at-risk populations. After a review of the evidence that supported this recommendation, the GDT agreed with the USPSTF as the results of moderate to high intensity counseling suggest HIV/STI risk reduction. For sexually active adolescents, there is fair to good evidence that high intensity behavioral counseling conducted in STI clinics effectively reduces STI incidence in at-risk populations. After a review of the evidence that supported this recommendation, the GDT agreed with the USPSTF as the results of moderate to high intensity counseling suggest HIV/STI risk reduction. For sexually active adolescents, there is fair to good evidence that high intensity behavioral counseling effectively reduces STI incidence in primary care settings. No evidence of significant behavioral or biological harms resulting from behavioral counseling was reported in the literature, suggesting the potential harms of counseling are few.

Based on expert opinion, the GDT agreed by consensus to include the provision of risk reduction counseling strategies as well. While counseling on proper condom use and abstinence, for example, may be provided in behavioral counseling, the GDT agreed that a more explicit mention of risk reduction was needed to complete the recommendation.

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† An example of a behavioral counseling tool is the “Ask, Advise, Agree, Assist, and Arrange” model developed by the CDC (Evidence-Based Methods for Evaluating Behavioral Counseling Interventions. Agency for Healthcare Research and Quality. 1 July 2009). See Appendix I for details.
4. Screening in Pregnancy

Screen all pregnant women for HIV antibody, syphilis, and hepatitis B early during each pregnancy. Screen at risk women for gonorrhea, Chlamydia and hepatitis C. Retest before 36 weeks in women at risk for exposure to HIV and/or any other STIs during the course of pregnancy.

- Risk factors include HIV infected partner or partner at risk for HIV, new or multiple sex partners during pregnancy, illicit drug use, exchanges sex for money or drugs, history of STI during current pregnancy or one year prior to pregnancy, signs or symptoms of acute HIV infection.\(^{(2)},\)†
- Pregnancy risk for exposure may include a newly diagnosed STI during pregnancy, documented or suspected injection drug use, or partner with known HIV infection.

**Rationale:**

As documented in the human immunodeficiency virus/sexually transmitted infections (HIV/STI) pregnancy screening evidence summary (See Appendix H), the Guideline Development Team (GDT) chose to use the US Preventive Services Task Force (USPSTF) systematic review and recommendations on this topic as the foundation for its recommendations.

**USPSTF Recommendations and Rationales**

- All pregnant women be screened for HIV. (A recommendation\(^{‡}\))
  - The USPSTF found good evidence that both standard and FDA-approved rapid screening tests accurately detect HIV infection in pregnant women and fair evidence that introduction of universal prenatal counseling and voluntary testing increases the proportion of HIV-infected women who are diagnosed and are treated before delivery. There is good evidence that recommended regimens of combination antiretroviral therapy are acceptable for pregnant women and lead to significantly reduced rates of mother-to-child transmission. Early detection of maternal HIV infection also allows for discussion of elective cesarean section and avoidance of breastfeeding, both of which are associated with lower HIV transmission rates. There is limited evidence of an increase in fetal anomalies or other fetal harm associated with currently recommended antiretroviral regimens (with the exception of efavirenz). Serious or fatal maternal events are rare using currently recommended combination therapies. The USPSTF concluded that the benefits of screening all pregnant women substantially outweigh potential harms.

\(^\ast\) The USPSTF (Recommendations for STI Screening, 2008)\(^{(5)}\) recommends that providers determine at risk individuals based on high-risk sexual behavior and age.


\(^\dagger\) A recommendation - The USPSTF recommends the service. There is high certainty that the net benefit is substantial.
- All pregnant women should be screened for syphilis infection and hepatitis B.
  (A recommendation)
  - **Syphilis** – Evidence indicates that screening tests can accurately detect syphilis infection that when left untreated during pregnancy is associated with stillbirth, neonatal death, bone deformities, and neurologic impairment. Furthermore, the USPSTF found convincing observational evidence that universal screening of pregnant women decreases the proportion of infants with clinical manifestations of syphilis infection. Screening and treatment may result in potential harms, including false-positive results that require clinical evaluation, unnecessary anxiety to the patient, and harms of antibiotic use. However, the USPSTF concluded that the harm from screening is no greater than small. The USPSTF concludes with high certainty that the net benefit of screening is substantial for pregnant women.
  - **Hepatitis B** - With an estimated 24,000 infants born HBV-positive each year in the US, the USPSTF found convincing evidence that universal prenatal screening for HBV infection substantially reduces perinatal transmission of HBV. When left untreated, chronic HBV infections increase long-term morbidity and mortality by predisposing infected persons to cirrhosis of the liver and liver cancer. The current practice of vaccinating all infants against HBV infection and providing postexposure prophylaxis with hepatitis B immune globulin administered at birth to infants of mothers infected with HBV substantially reduces the risk for acquiring HBV infection. The USPSTF found no published studies that describe harms of screening for HBV infection in pregnant women and thus concluded that the potential harms of screening are no greater than small. Additionally, the USPSTF concludes that there is high certainty that the net benefit of screening pregnant women for HBV infection is substantial.
Clinicians should screen all sexually active women, including those who are pregnant, for gonorrhea and Chlamydia infection if they are at increased risk for infection (that is, if they are young or have other individual or population risk factors.) (B recommendation*)

- **Chlamydia Infection** – The USPSTF found fair evidence that nucleic acid amplification tests (NAATs) can identify Chlamydia infection in asymptomatic men and women, including asymptomatic pregnant women, with high test specificity. In low prevalence populations, however, a positive test is more likely to be a false positive than a true positive, even with the most accurate tests available. There are no studies evaluating the effectiveness of screening for Chlamydia infection in pregnant women who are at increased risk. The USPSTF, however, found the following: screening identifies infection in asymptomatic pregnant women; there is a relatively high prevalence of infection among pregnant women who are at increased risk; and there is fair evidence of improved pregnancy and birth outcomes for women who are treated for Chlamydia infection. The USPSTF concluded, therefore, that the benefits of screening pregnant women who are at increased risk are substantial. The USPSTF identified no studies documenting the benefits of screening women, including pregnant women, who are not at increased risk for Chlamydia infection. While recognizing the potential benefit to women identified through screening, the USPSTF concluded the overall benefit of screening would be small, given the low prevalence of infection among women not at increased risk. The USPSTF concluded that the harms of screening for Chlamydia infection are no greater than small, although few studies have been published on this subject. Potential harms include anxiety and relationship problems arising from false positive results and over-treatment. The USPSTF identified the lack of evidence related to potential harms of screening as a gap in the evidence.

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* B recommendation - The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.
- **Gonorrhea** - Women (including pregnant women) and men under the age of 25 - including sexually active adolescents - are at highest risk for genital gonorrhea infection. Risk factors for gonorrhea include a history of previous gonorrhea infection, other sexually transmitted infections, new or multiple sexual partners, inconsistent condom use, sex work, and drug use. Women with asymptomatic gonorrhea infection have high morbidity due to pelvic inflammatory disease, ectopic pregnancy, and chronic pelvic pain. Pregnant women with gonorrhea infection are at risk for preterm rupture of membranes, preterm labor, and chorioamnionitis. There is fair evidence that screening tests can accurately detect gonorrhea infection and good evidence that antibiotics can cure gonorrhea infection. There is fair evidence that screening pregnant women at high risk for gonorrhea, including women at high risk because of younger age, may prevent other complications associated with gonococcal infection during pregnancy, such as preterm delivery and chorioamnionitis. Potential harms of screening and treatment for gonorrhea include false-positive test results, anxiety, and unnecessary antibiotic use. There is insufficient evidence (due to a lack of studies) to quantify the magnitude of these potential harms. The USPSTF judges the magnitude of the potential harms to be small. The USPSTF concludes that the benefits of screening women at increased risk for gonorrhea infection outweigh the potential harms. The prevalence of gonorrhea infection in pregnant women who are not at increased risk for infection is low. The USPSTF could not determine the balance between benefits and harms of screening for gonorrhea in pregnant women who are not at increased risk for infection.

- The USPSTF recommends *against* routine serological screening for herpes simplex virus (HSV) in asymptomatic pregnant women at any time during pregnancy to prevent neonatal HSV infection as well as screening for bacterial vaginosis in asymptomatic pregnant women at low risk for preterm delivery. (D recommendation*)

- **Herpes simplex virus (HSV)** - The USPSTF found fair evidence that screening asymptomatic pregnant women using serological screening tests for HSV antibody does not reduce transmission of HSV to newborn infants. Women who develop primary HSV infection during pregnancy have the highest risk for transmitting HSV infection to their infants. Because these women are initially seronegative, serological screening tests for HSV (enzyme-linked immunosorbent assay [ELISA], immunoblot, and western blot assay [WBA]) do not accurately detect those at highest risk. There is limited evidence that treating seronegative women decreases risk for neonatal infection. There is limited evidence that the use of antiviral therapy in women with a history of recurrent HSV, or performance of cesarean section in women with active HSV lesions at the time of delivery, decreases neonatal herpes infection. There also is limited evidence of the safety of antiviral therapy in pregnant women and neonates.

* D recommendation - the USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.
**Bacterial vaginosis** - The associations between bacterial vaginosis and adverse pregnancy outcomes, such as preterm delivery, are well documented. Good-quality evidence indicates that screening tests (the Amsel clinical criteria or Gram stain) can detect bacterial vaginosis. No direct evidence indicates that screening for bacterial vaginosis reduces adverse health outcomes in asymptomatic pregnant women at low risk for preterm delivery. Good evidence indicates that treatment of bacterial vaginosis in these women lacks benefit. No direct evidence indicates that screening for bacterial vaginosis reduces adverse health outcomes in asymptomatic pregnant women at high risk for preterm delivery. Evidence from good-quality studies is conflicting with respect to the benefits of treating bacterial vaginosis. Evidence is limited (because studies are lacking) for harms of screening for bacterial vaginosis in asymptomatic pregnant women at low risk for preterm delivery. Evidence is poor (because studies are lacking) for harms of screening for bacterial vaginosis in asymptomatic pregnant women at high risk for preterm delivery. Evidence is fair that false-positive results from screening lead to harms due to treatment. Evidence is poor (because studies are lacking) for harms of screening for bacterial vaginosis in asymptomatic pregnant women at high risk for preterm delivery. Studies on the harms of treatment have conflicting results. The USPSTF concludes that for asymptomatic pregnant women at low risk for preterm delivery, there is moderate certainty that screening for bacterial vaginosis has no net benefit. And, for asymptomatic pregnant women at high risk for preterm delivery, the evidence is conflicting and the balance of benefits and harms cannot be determined.

The GDT agreed with the USPSTF recommendation to screen all pregnant women for HIV, syphilis, and hepatitis B. The GDT made this decision because the evidence indicates that the benefits of screening all pregnant women for these pathogens substantially outweigh potential harms for mother and baby.

The USPSTF also recommends that women (including those who are pregnant) be screened for gonorrhea and Chlamydia if they are at increased risk for infection. As approximately four out of every 100 infants born to HCV-infected mothers become infected with the virus, the GDT agreed by consensus that the benefits of screening pregnant women for hepatitis C outweigh potential harms. As a result, the GDT’s recommendation includes screening at risk pregnant women for gonorrhea, Chlamydia and hepatitis C.

As the USPSTF suggested time frames for re-screening for the pathogens addressed, the GDT agreed that retesting before 36 weeks in women at risk for exposure to HIV and/or any other STIs during the course of pregnancy as vital. The GDT reached this conclusion because it deemed that reassessing a mother’s HIV and/or other STI status throughout pregnancy was a necessity, with substantial benefits to mother and child outweighing potential harms.

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Although the GDT did not develop a recommendation for routine serological screening for herpes simplex virus (HSV) or for bacterial vaginosis, the USPSTF recommends against such screening for HSV in asymptomatic pregnant women at any time during pregnancy to prevent neonatal HSV infection as well as screening for bacterial vaginosis in asymptomatic pregnant women at low risk for preterm delivery. (D recommendation*)

Counseling effectively reduces STI incidence in primary care settings. No evidence of significant behavioral or biological harms resulting from behavioral counseling was reported in the literature, suggesting the potential harms of counseling are few.

Based on expert opinion, the GDT agreed by consensus to include the provision of risk reduction counseling strategies as well. While counseling on proper condom use and abstinence, for example, may be provided in behavioral counseling, the GDT agreed that a more explicit mention of risk reduction was needed to complete the recommendation.

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* D recommendation - the USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.
Appendix A -
GRADE System of Evidence Rating*

The overall quality of evidence for outcomes was assessed using a method developed by the GRADE Working Group, which classified the grade of evidence across outcomes according to the following criteria:

- **High** = Further research is very unlikely to change our confidence on the estimate of effect.
- **Moderate** = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low** = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very Low** = Any estimate of effect is very uncertain.

GRADE also suggests using the following scheme for assigning the “grade” or strength of evidence:

**Criteria for Assessing Grade of Evidence**

**Type of Evidence**
- Randomised trial = high
- Observational study = low
- Any other evidence = very low

**Decrease grade if:**
- Serious (-1) or very serious (-2) limitation to study quality
- Important inconsistency (-1)
- Some (-1) or major (-2) uncertainty about directness
- Imprecise or sparse data (-1)
- High probability of reporting bias (-1)

**Increase grade if:**
- Strong evidence of association – significant risk of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1)
- Very strong evidence of association – significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2)
- Evidence of a dose response gradient (+1)
- All plausible confounders would have reduced the effect (+1)

Last reviewed/revised May 2011

Appendix B - Risk Assessment Tools

1. Risk Assessment Tools

Problem Formulation 1

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>What are the most clinically useful STI risk assessment tools?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>All persons aged ≥ 12 at risk for acquiring HIV/STI</td>
</tr>
<tr>
<td>Health Intervention</td>
<td>Risk assessment tools</td>
</tr>
<tr>
<td>Important Health Outcomes</td>
<td>• Increased and earlier STI case identification</td>
</tr>
<tr>
<td></td>
<td>• Appropriate risk stratification</td>
</tr>
<tr>
<td></td>
<td>• Harms of assessment tools</td>
</tr>
</tbody>
</table>
Search Strategy 1

The search strategy was restricted to systematic reviews, meta-analyses, and RCTs in populations at risk for STI and/or HIV.

<table>
<thead>
<tr>
<th>Database</th>
<th>Terms</th>
<th>Article Type and Limits</th>
<th>Time Frame</th>
<th>No. Included/Total Retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Randomized Controlled Trial, English, Human</td>
<td></td>
<td>1996 to 11/2010</td>
<td>0/0</td>
</tr>
<tr>
<td>Cochrane</td>
<td>STI AND OR HIV AND risk assessment</td>
<td>Systematic Reviews, Clinical Trials</td>
<td>Last Accessed 11/2010</td>
<td>0/0</td>
</tr>
<tr>
<td>Clinical Evidence</td>
<td>STI and/or HIV AND risk assessment</td>
<td>Systematic Reviews, Clinical Trials, Guidelines</td>
<td>Last Accessed 11/2010</td>
<td>1/1</td>
</tr>
</tbody>
</table>

Search Strategy

The GDT considered potential other approaches to frame this clinical question, including evaluating whether performing a risk assessment results in increased and earlier human immunodeficiency virus/sexually transmitted infections HIV/STI case finding and thus, a decrease in morbidity and mortality. As medical literature and expert opinion suggests a strong association between risk assessment and decreased HIV/STI morbidity and mortality, the GDT agreed to evaluate the most clinically useful risk assessment tools. An appraisal of HIV/STI risk assessment tools is worthwhile as there remains great variability in obtain sexual histories and risk assessment in clinical practice, ranging from 15% to 90% in primary care.(6)*

A comprehensive search was conducted in September 2010 (and refreshed in November 2010) to identify RCTs relevant to this problem formulation.

---

RCTs were included in this review if they evaluated risk assessment tools used in sexually active individuals to quantify risk for HIV/STI. One set of recommendations on STI screening from the US Preventive Services Task Force (USPSTF, 2008) was identified and included in this review. Moreover, HIV/STI risk factors presented in a critical review on the use of behavioral counseling for STI risk reduction (Lin et al., 2008) was also included in the review. As the USPSTF is a nationally-renowned and respected source of evidence-based material, the GDT agreed to use its systematic review and recommendations as the foundation for its own recommendations.

Evidence Summary

While no trials, recommendation statements, or guidelines were found that specifically identified the most effective HIV/STI risk assessment tools, the 2008 USPSTF recommendations include commonly accepted demographic factors that increase HIV/STI risk.

2008 USPSTF Discussion of HIV/STI Risk*(3)

- Level of risk and risk factors for STI acquisition can be divided into individual risk factors and population risk factors.
- Individual risk factors are based on an individual's engagement in risky behaviors (e.g., sex with multiple or new partners, sex with high-risk partners, unprotected sex, sex while intoxicated, sex in exchange for money).
- These behaviors are theoretically influenced by an individual's preexisting knowledge, attitudes, skills, self-efficacy, and the presence of environmental factors that promote, reinforce, or inhibit change.
- Risk factors based on an individual's risky behavior are generally considered modifiable.
- Population risk factors are based on the higher than average incidence of STIs in a particular epidemiologic group, or the increased morbidity of STIs in a particular group (e.g., pregnant women).
- Higher-risk population groups for STIs in the US include adolescents and young adults, black/African-American, Hispanics, men who have sex with men (MSM), military recruits, inmates and former inmates, intravenous drug users (IVDUs) and former IVDUs, sex workers, mentally ill persons, mentally disabled persons, persons living in low-income urban areas, persons living in the southern United States, persons with a history of an STI, and pregnant women.

2008 USPSTF Recommendations for STI Screening, Clinical Considerations

Physicians should consider the demographics of the populations they serve in determining which STI screening tests to offer. In addition to evaluating a patient's modifiable behaviors, physicians should consider the patient's nonmodifiable demographics and social situation.

- All communities do not present the same infection risk. In the United States, syphilis and gonorrhea have widely varying prevalence rates. Southern states and many urban centers have higher rates of STIs (CDC, Sexually Transmitted Disease Surveillance, 2005 and 2007 supplements). Even within communities, there is often variability in STI prevalence. This is partially caused by social network and socioeconomic influences (e.g., effects of poverty and discrimination).

- The USPSTF recommends that physicians be aware that in some communities black/African-American and Hispanic men and women (including pregnant women) may be at increased risk of Chlamydia, gonorrhea, and syphilis, irrespective of age or sexual behaviors, and may need to be screened (USPSTF, Screening for Chlamydia infection, 2007; USPSTF, Screening for gonorrhea, 2005; Calogne et al. 2004). When used in this way, race and ethnicity serve as surrogate markers for the underlying social factors that increase STI risk (Holtgrave et al., 2003).

- Research has documented that many social-contextual factors contribute to varying STI prevalence rates within communities. Through a variety of direct and indirect mechanisms, factors in a community (e.g., poverty, discrimination, illicit drug use, male-to-female ratio, incarceration rate, racial segregation) influence sexual behaviors and networks, subsequently affecting the spread of infection. The concepts of social capital (e.g., trust, reciprocity, group membership) and the effect of social groups with common goals may be more predictive of STI risk than more traditional factors such as poverty and income inequalities (Holtgrave et al., 2003).

- When considering screening for STIs, physicians should consult with local public health officials, if possible; and should use national, regional, state, and local epidemiologic data to tailor screening programs based on the community and populations served.

---

### Appendix C – HIV/STI Screening

2. HIV/STI Screening

**Problem Formulation 2**

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>What are the recommended STI screening tests for HIV, gonorrhea, chlamydia, syphilis, trichomonas, and hepatitis B and C?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>All persons aged ≥ 12 at risk for acquiring HIV/STI, including known high-risk groups (such as pregnant women, adolescents, men having sex with men).</td>
</tr>
<tr>
<td><strong>Health Intervention</strong></td>
<td>Screening and appropriate treatment tests</td>
</tr>
</tbody>
</table>
| **Important Health Outcomes** | * Decrease in HIV/STI morbidity and mortality  
* Increased and earlier STI case identification  
* Increased HIV/STI case prevention  
* Benefits/harms of screening (including false negatives/positives)  
* Anxiety, labeling  
* Performance in predicting/proving presence of HIV/STI infection (sensitivity, specificity, positive and negative predictive value) |
### Search Strategy 2

<table>
<thead>
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<th>Database</th>
<th>Terms</th>
<th>Article Type and Limits</th>
<th>Time Frame</th>
<th>No. Included/Total Retrieved</th>
</tr>
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<td>OVID Medline</td>
<td>(exp HIV Infections or exp Chlamydia Infections/ or exp Chlamydia trachomatis/ or exp Gonorrhea/ or Neisseria gonorrhoeae/ or exp Syphilis/ or exp Hepatitis B/ or exp Hepatitis C/ or exp Trichomonas vaginalis/ or exp Trichomonas Vaginitis/ or *Sexually Transmitted Diseases/di or Trichomonas vagin$.ti,ab or Syphilis Serodiagnosis/ or syphilis.ti,ab or AIDS Serodiagnosis or (HIV or AIDS).ti, ab or (Hepatitis adj c).ti, ab or (Hepatitis adj B).ti,ab or (gonorrhea or gonorrhoea).ti,ab or chlamydia$.ti,ab) AND (exp Mass Screening/ or (test$ or diagnos$ or screen$ or detect$).ti,ab)</td>
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<td>26/38</td>
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<td></td>
<td>RCTs</td>
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</tr>
<tr>
<td>OVID</td>
<td>(Human immunodeficiency virus infection/ or Chlamydia trachomatis/ or chlamydiasis/ or gonorrhea/ or Neisseria gonorrhoeae/ or syphilis/ or hepatitis B/ or hepatitis C/ or trichomoniasis/ or Trichomonas vaginalis/ or Trichomonas vagi$ti,ab or syphilis$ti,ab or (HIV or AIDS)$ti,ab or (Hepatitis adj c)$ti,ab or (Hepatitis adj B)$ti,ab or (gonorrhea or gonorrhoea)$ti,ab or chlamydia$ti,ab) AND (mass screening/ or (test$ or diagnose$ or screen$ or detect$)$ti,ab) OR (*Human immunodeficiency virus infection/di or *Chlamydia trachomatis/di or chlamydiasis/ or *gonorrhea/di or *Neisseria gonorrhoeae/di or *syphilis /di or *hepatitis B/di or *hepatitis C/di or *trichomoniasis/di or *Trichomonas vaginalis/di</td>
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<td>------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>CENTRAL</td>
<td>(exp HIV Infections or exp Chlamydia Infections/ or exp Chlamydia trachomatis/ or exp Gonorrhea/ or Neisseria gonorrhoeae/ or exp Syphilis/ or exp Hepatitis B/ or exp Hepatitis C/ or exp Trichomonas vaginalis/ or exp Trichomonas Vaginitis/) AND (mass screening/ or (test* or diagnos* or screen* or detect*):ti,ab,kw)</td>
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<td>5/11</td>
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<td>CDSR</td>
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<td>systematic reviews</td>
<td>5/2010</td>
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<td>Terms</td>
<td>Article Type and Limits</td>
<td>Time Frame</td>
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<td>----------</td>
<td>-----------------------------------------------------------------------</td>
<td>------------------------------</td>
<td>------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>DARE</td>
<td>(exp HIV Infections or exp Chlamydia Infections/ or exp Chlamydia trachomatis/ or exp Gonorrhea/ or Neisseria gonorrhoeae/ or exp Syphilis/ or exp Hepatitis B/ or exp Hepatitis C/ or exp Trichomonas vaginalis/ or exp Trichomonas Vaginitis/) AND (mass screening/ or (test* or diagnos* or screen* or detect*):ti,ab,kw)</td>
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<td>5/2010</td>
<td>4/4</td>
</tr>
<tr>
<td>HTA</td>
<td>(exp HIV Infections or exp Chlamydia Infections/ or exp Chlamydia trachomatis/ or exp Gonorrhea/ or Neisseria gonorrhoeae/ or exp Syphilis/ or exp Hepatitis B/ or exp Hepatitis C/ or exp Trichomonas vaginalis/ or exp Trichomonas Vaginitis/) AND (mass screening/ or (test* or diagnos* or screen* or detect*):ti,ab,kw)</td>
<td>systematic reviews</td>
<td>5/2010</td>
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<td>Article Type and Limits</td>
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<td>------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>TRIP</td>
<td>(HIV or Chlamydia trachomatis or Gonorrhea or gonorrhoea or Syphilis or Hepatitis B or Hepatitis C or Trichomonas vaginalis/ AND (test* or diagnos* or screen* or detect*))</td>
<td>systematic reviews</td>
<td>5/2010</td>
<td>0 unique</td>
</tr>
<tr>
<td></td>
<td></td>
<td>guidelines</td>
<td>5/2010</td>
<td>0 unique</td>
</tr>
</tbody>
</table>

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects online database; HTA: Health Technology Assessment online database; OVID Medline and OVID Embase: Medline and Embase via the Ovid platform; RCTs: randomized controlled trials; TRIP: TRIP online database.

**Search Strategy**

The GDT considered a different approach to frame this clinical question, specifically whether screening for human immunodeficiency virus/sexually transmitted infections HIV/STI results in reduced morbidity and mortality. As medical literature and expert opinion strongly suggests that screening after exposure to infection leads to reduced HIV/STI morbidity and mortality, the GDT agreed to instead evaluate the effectiveness and diagnostic accuracy of screening tests for HIV, gonorrhea, Chlamydia, syphilis, trichomonas, and hepatitis B and C.

The literature review for this clinical question was completed through a collaborative effort with Kaiser Permanente’s Care Management Institute (CMI) and the British Medical Journal’s (BMJ) Evidence Center. The BMJ Evidence Center is world-renowned and responsible for building and supporting a wide range of evidence-based resources, including literature reviews, journal articles, and clinical reference tools.
The structure of this question was such that each study design required multiple database searches for each of the seven included pathogens - HIV, gonorrhea, chlamydia, syphilis, trichomonas, hepatitis B and C. These pathogens were selected based on many factors including incidence, prevalence, and increase in risk of HIV acquisition, transmission and impact on disease progression within the US population. In 2009, the Centers for Disease Control (CDC) and Prevention reported the following – a total of 1,244,180 cases of sexually transmitted Chlamydia trachomatis, the largest number of cases ever reported to CDC for any condition; a total of 301,174 cases of gonorrhea, which corresponds to a rate of 99.1 cases per 100,000 population; a total of 13,997 cases of syphilis, the highest number of cases reported since 1995 and corresponds to a rate of 4.6 cases per 100,000 population; and NHANES data from 2001 to 2004 indicated an overall prevalence of 3.1% of trichomonas cases. The CDC also reports that at the end of 2006, an estimated 1,106,400 persons in the US were living with HIV infection, with 21% undiagnosed, while figures for the number of persons living with hepatitis B and C are approximately 800,000 to 1.4 million and 2.7 to 3.9 million for both pathogens, respectively.

As the Search Strategy 2 illustrates, each pathogen required 16 separate searches across seven databases, resulting in 112 separate searches in total.

To increase efficiency, BMJ performed searches for systematic reviews (SRs) and guidelines for all pathogens first and then appraised the results. Where an existing SR with suitable methodology and scope was found, it was used as a basis for limiting the search for primary studies to those published after the search date of the chosen SR. Where no suitable SR was identified, BMJ limited the primary study search to the agreed start date of 2000 through May/June 2010.

**Evidence Summary**
Problem Formulation 2 evaluated the effectiveness of HIV/STI screening as well as the diagnostic characteristics of specific tests. The results of both assessments are included below.

**Effectiveness of Screening**

- **HIV**: There is limited evidence from two observational studies that rapid HIV testing may increase the rate of people receiving positive test results (very low-quality evidence), and may also potentially increase the rate of patients needing medical care after rapid testing (very low-quality evidence). No studies that evaluated other HIV testing methods were found.

- **Chlamydia trachomatis**: There is insufficient evidence to assess the effectiveness of *C. trachomatis* screening in high-risk populations and primary care/ambulatory clinic settings. One retrospective analysis indicated that *C. trachomatis* testing and treatment may reduce long-term risk of ectopic pregnancy (very low-quality evidence).

- **Gonorrhea**: No studies evaluating the effectiveness of gonorrhea testing in high-risk patients attending primary care or ambulatory clinic facilities were identified.

- **Hepatitis B**: No studies evaluating the effectiveness of hepatitis B testing in high-risk patients attending primary care or ambulatory clinic facilities were identified.

- **Hepatitis C**: No studies evaluating the effectiveness of hepatitis C testing in high-risk patients attending primary care or ambulatory clinic facilities were identified.
- **Syphilis**: One observational study provided limited evidence that adding regular, intensive syphilis testing to routine HIV outpatient follow-up in an area with high syphilis prevalence significantly increased testing rates and detection of early syphilis (very low-quality evidence). Event rates were too low to determine whether affected patients had a higher risk of HIV treatment failure, and the study did not examine clinical outcomes.

- **Trichomonas**: No studies were identified that evaluated the effectiveness of trichomonas testing in high-risk patients attending primary care or ambulatory clinic facilities.

**Diagnostic Accuracy**

- **HIV**: Eleven observational studies examined the diagnostic accuracy of rapid HIV testing and HIV assays conducted in high-risk groups (very low-quality evidence). Sensitivity and specificity of rapid HIV tests against EIA-based reference standards ranged between 80% and 100%, whereas the sensitivity of the WHO-recommended two-rapid test algorithm fell below 35% against Western Blot. One study demonstrated a sensitivity of 75% with p24 assay against Western Blot, whereas another study showed high sensitivity (95% to 100%) with five HIV testing strategies using dried blood spots (EIAx3 parallel; EIA+Pepti-Lav 1-2 parallel; Gelatine Particle Assays; Gelatine Particle Assays+Pepti-Lav 1-2 parallel; Gelatine Particle Assays+filtration parallel) compared with the reference strategy of serum-based triple EIA. Specificity in these studies was above 97.5%.

- **Chlamydia trachomatis**: Fifteen studies examined the diagnostic accuracy of Chlamydia testing with EIA, a range of nucleic acid amplification tests (NAATs, for example, polymerase chain reaction (PCR), transcription mediated amplification (TMA), System *C. trachomatis* amplified-DNA assay (SDA), ligase chain reaction (LCR), DNA Probe, direct immunofluorescent antibody (DFA) and rapid tests), conducted mainly in STI clinic settings (all very low-quality evidence). Of these, three studies found unsatisfactory levels of sensitivity (40% to 81%) and wide-ranging specificity (56% to 100%) with different EIAs against reference standards of culture, TMA NAAT or concordance of at least 2/3 methods used. Eleven studies evaluated the diagnostic accuracy of different NAATs and demonstrated consistently high specificity but wide-ranging results for sensitivity (ranging from 25% to 100% with PCR; 59% to 100% with TMA; 41% to 95% with SDA; 78% to 84% with LCR). Two studies showed conflicting results for the diagnostic accuracy of DNA Probe. One study reported very low sensitivity (6% to 9%) and specificity of around 90% with a Russian manufactured DFA against LCR as reference standard. Two studies found low levels of sensitivity (31% to 83%) and specificity of over 95% with rapid tests (Chlamydia Rapid Test or Clearview Chlamydia MF) against a PCR reference standard.

- **Gonorrhea**: Thirteen studies found consistently high specificity but unsatisfactory sensitivity with single-test microscopy (around 30% in women, 75% in men) (very low-quality evidence) or culture (32% to 71%) (low-quality evidence), and high sensitivity with the combination of microscopy plus culture (98%) and with NAATs, especially symptomatic patients and using endocervical, urethral or rectal swabs (moderate-quality evidence). Sensitivity of NAATs tended to fall below 90% only when using pharyngeal or urine samples (especially in women), and in studies conducted in asymptomatic patients.

- **Hepatitis B**: No studies were found evaluating the diagnostic accuracy of hepatitis B testing in high-risk patients attending primary care or ambulatory clinic facilities.
- **Hepatitis C:** The evidence is scarce on hepatitis C screening outside chronic liver disease, hemodialysis or blood donor populations. One observational US study in adults attending an STI clinic suggested that the positive predictive value of EIA (overall 84%) was higher in intravenous drug users (97%) but considerably lower in low-risk groups (27%) against confirmation with recombinant immunoblot assay (very low-quality evidence).

- **Syphilis:** Eight studies conducted mainly in STI clinic settings examined the diagnostic accuracy of syphilis testing with EIA and a range of rapid tests (low-quality evidence). There is limited evidence from single studies for high diagnostic accuracy with EIA (≥ 98%) and for low sensitivity with finger-prick based rapid testing using VisiTect (57%). Blood-based rapid testing for primary syphilis—especially using serum samples—was associated with higher sensitivity in five studies (ranging from 73% to 100%), even when carried out by less-skilled personnel, and with specificity of at least 92%.

- **Trichomonas:** Eighteen observational studies—including nine studies conducted in the USA—examined the diagnostic accuracy of trichomonas testing using culture, Pap smear, point-of-care pH and Whiff tests, EIA, rapid immunochromatographic tests and PCR conducted in high-risk groups, mainly symptomatic women in STI clinic settings (very low-quality evidence for all methods). Only two PCR studies provided evidence on trichomonas testing in men. Numerous studies have confirmed that the current gold standards (culture and wet mount microscopy) have low sensitivity (39% to 72%) but near 100% specificity, with culture proving slightly more sensitive than wet mount in vaginal swabs but not in urine samples. In four studies, Pap smear showed also low sensitivity (31% to 63%) paired with high specificity. There was limited evidence from a single study that combination of point-of-care testing with vaginal pH and Whiff tests may be characterised by moderate sensitivity (83%) and low specificity (44%). Although sensitivity reached 95% in a single study on EIA, it showed a specificity of only 83%. In three US studies, rapid immunochromatographic tests (especially OSOM) were more sensitive than wet mount and displayed comparable specificity (sensitivity 83%; specificity 97%). Five studies showed some promising results with PCR (around 90% sensitivity in vaginal swabs and male urine samples; specificity between 86% and 97%) but more research is needed to come to a conclusive assessment on the best type of PCR to use.
Results

Effectiveness of Screening

A. Chlamydia Trachomatis (C. trachomatis) Screening
There is insufficient evidence to assess the effectiveness of C. trachomatis screening in a primary care or ambulatory clinic setting. Two systematic reviews (Low 2009, Gottlieb 2010)\(^{11, 12}\) were selected for analysis but between them included only one registry-based retrospective cohort study that met inclusion criteria. (Anderson 2005)\(^{13}\) (very low-quality evidence). Please refer to Evidence Table 2.4 for details.

- The first review (Low 2009)\(^{11}\) examined the effectiveness of register-based and opportunistic C. trachomatis screening interventions and identified six reviews, five RCTs, one non-RCT and one time trend study, of which no studies met our inclusion criteria.

- The second review (Gottlieb 2010)\(^{12}\) examined the effectiveness of screening and treatment to prevent sequelae in women with C. trachomatis and, among other studies, identified one registry-based retrospective cohort study which met our inclusion criteria (Anderson 2005).\(^{13}\) The study evaluated the risk of long-term complications (ectopic pregnancy and birth rate) in women with at least one diagnosed and treated C. trachomatis screening, and found that the risk of ectopic pregnancy was significantly reduced in women with \(\geq 1\) positive C. trachomatis tests compared with women with only negative test results (aHR = 0.55, 95% CI: 0.31 to 0.96), and showed no difference in birth rates between groups (aHR = 0.92, 95% CI: 0.84 to 1.00). The authors concluded that detection and subsequent treatment of Chlamydia infection put women in a far more advantageous situation than women who were not diagnosed and treated.

B. Gonorrhea Testing
No studies evaluating the effectiveness of gonorrhea testing in high-risk patients attending primary care or ambulatory clinic facilities were identified.

C. Hepatitis B Screening
There are no studies evaluating the effectiveness of hepatitis B testing in high-risk patients attending primary care or ambulatory clinic facilities.

D. Hepatitis C Screening
There is insufficient evidence to assess the effectiveness of hepatitis C screening in primary care or ambulatory clinic settings.

- One systematic review (Chou 2004)\(^{14}\) identified no studies comparing outcomes between patients in the general adult population who were screened and not screened for hepatitis C infection. Data on harms of screening were extremely scarce and none of the identified studies met our inclusion criteria. Please refer to Evidence Table 2.7 for details.
E. Syphilis Screening

One observational study reported in two articles (Winston 2003, Cohen 2005)\textsuperscript{(15, 16)} was selected for analysis and evaluated the effects of regular syphilis screening in HIV patients attending routine follow-up in an outpatient STD clinic with high syphilis prevalence (very low-quality evidence). Please refer to Evidence Table 2.8 for details.

- Winston et al. evaluated the records of 2,670 UK-based HIV outpatients during the first year of adding three-monthly syphilis testing with the Venereal Disease Research Laboratory (VDLR; Oxoid carbon antigen) and Treponema Pallidum Particle Agglutination (TPPA; Serodia) tests to the routine computerized blood order sets used for HIV follow-up care. Among the 4,515 syphilis samples of 2,266 patients, 26 asymptomatic people were identified with early syphilis. These cases represented 29% of all people treated at the clinic for early syphilis and 50% of cases in the HIV positive cohort. Compared with data from the year prior to introducing intensive syphilis screening, testing rates had increased 28-fold from 3% to 85%.

- Cohen et al. analyzed data of 2,655 HIV positive patients in the second year of the intensive syphilis testing program at the same STD clinic. Among the 6,081 syphilis samples of 2,389 patients, 40 asymptomatic people were identified as having early syphilis, representing 36% of all people treated at the clinic for early syphilis and 56% of cases in the HIV positive cohort. Compared with the previous year, the early syphilis event rate had increased significantly from 2.8 (95% CI: 1.8 to 4.0) to 7.3 per 1,000 patient years (95% CI: 5.2 to 9.9; \( p = 0.05 \)); testing rates had further increased to 90% of HIV outpatients (30-fold versus 3% prior to the intervention).

- Overall, adding regular, intensive syphilis testing to routine HIV outpatient follow-up in an area with high syphilis prevalence significantly increased testing rates and detection of early syphilis. Event rates were too low to determine whether affected patients had a higher risk of HIV treatment failure.

F. Trichomonas Vaginalis Testing

No studies evaluating the effectiveness of trichomonas testing in high-risk patients attending primary care or ambulatory clinic facilities were identified.
Diagnostic Accuracy

A. Gonorrhea Tests


- Although specificity was consistently high with all tests, sensitivity was unsatisfactory with single-test microscopy or culture, and tended to fall below 90% with NAATs when using pharyngeal or urine samples (especially in women) and in asymptomatic patients. Please refer to Evidence Table 2.9 for details.

- Three studies assessed the diagnostic accuracy of microscopy with and without culture compared with different reference standards, and found disquietingly low sensitivity with single-test microscopy (Forni 2009, Shipitsyna 2008, Ho 2009).\(^{(26, 29, 30)}\) Forni et al. reported low sensitivity of microscopy to detect rectal gonorrhea in culture-positive asymptomatic men having sex with men (MSMs) (29%). Compared with PCR NAAT, Shipitsyna et al. demonstrated that sensitivity of microscopy was also low in symptomatic patients, especially in women (sensitivity in women: 31.8%; in men: 75%), with a specificity of 100%. When combining microscopy with culture in an STI clinic setting, Ho et al. reported a sensitivity of 97.6% and specificity of 99.6% versus an NAAT reference standard.

- Five studies evaluated the diagnostic accuracy of single-test culture against NAAT or gene sequencing reference standards, and found unsatisfactory rates of sensitivity and high specificity (Ota 2009, Shipitsyna 2008, Hjelmevoll 2008, Darwin 2002, Moncada 2004).\(^{(20, 23, 27, 28, 30)}\) Compared with NAAT, Ota et al. found that culture failed to detect any cases of pharyngeal gonorrhea and had a sensitivity of 41% in detecting rectal gonorrhea in MSMs attending a clinic for STI screening or testing. In symptomatic adults attending dermatovenereological dispensaries, Shipitsyna et al. demonstrated similar sensitivities of 31.8% in women and 50% in men, with a specificity of 100% versus porA pseudogene and 16S rRNA gene sequencing. Against the same reference standard and in people with suspected gonorrhea attending an STI clinic, Hjelmevoll et al. reported a sensitivity of 71%, with a specificity of 100%. In a sixth study combining culture with microscopy in an STI clinic setting, Ho et al. reported a sensitivity of 97.6% and specificity of 99.6% versus an NAAT reference standard (Ho 2009).\(^{(26)}\)

Of these, four studies assessed transcription-mediated amplification (TMA) NAAT and showed high rates of sensitivity and specificity, especially in symptomatic patients and using endocervical, urethral or rectal swabs. Ho et al. found that sensitivity was 100%, and specificity 98.4% compared with culture. Sensitivity ranged from 87.5% to 100% and specificity from 98.1 to 99.6% compared with culture plus ligase chain reaction (LCR) NAAT, depending on sample method (higher with endocervical swab than in urine) and presence of symptoms (Gaydos 2003).\(^{(21)}\) Moncada et al. demonstrated a sensitivity of 99.2% and specificity of 98.6% versus a reference standard of culture confirmed with sugar utilization tests, fluorescent antibody, or Haemophilus-Neisseria identification. Ota et al. reported significantly higher diagnostic accuracy compared with that of culture, with sensitivity of 95% for pharyngeal gonorrhea and of 100% for other sites (urethral, rectal), and a specificity of consistently over 98% versus the reference standard of a confirmed positive second run using a different sampling method or strand displacement amplification (SDA) NAAT.

Four studies evaluated SDA NAAT and found consistently high diagnostic accuracy other than with urine samples in women (Ota 2009, Cosentino 2003, Chan 2000, Van der Pol 2001).\(^{(18, 19, 24, 27)}\) Ota et al. reported significantly higher diagnostic accuracy compared with culture, with sensitivity of 93.1% a specificity of over 98% versus the reference standard of a confirmed positive second run using a different sampling method or TMA NAAT. Two studies compared SDA versus culture confirmed with additional tests including gram staining, oxidase test, and Gonocheck II, and reported sensitivity of over 96% and specificity of over 94% (Cosentino 2003, Van der Pol 2001)\(^{(19, 24)}\) although one of the studies found that using urine samples in women resulted in lower sensitivity ranging from 83.7 to 86.5% (Van der Pol 2001)\(^{(24)}\) Chan et al. compared SDA NAAT versus PCR, resolving inconsistencies with in-house PCRs, and found high sensitivity (100%) and specificity (99.2 and 99.9% in women and men respectively) with SDA NAAT using urine samples.
• Four studies examined polymerase chain reaction (PCR) NAAT in mainly STI clinic settings and found high diagnostic accuracy other than with urine samples in women and potentially asymptomatic men (van Doornum 2001, Martin 2000, Hjelmevoll 2008, Chan 2000)(18, 22, 25, 28) Against culture as reference standard, van Doornum et al. reported sensitivity between 95.2% and 100% with PCR using endocervical/urethral swabs or male urine but lower sensitivity using urine samples in women (66.7%). Specificity ranged from 97.4 to 99.4%. Martin et al. assessed the diagnostic accuracy of two PCRs (98.8% concordance) against culture confirmed with glucose utilization profiles. High diagnostic accuracy was shown in women using endocervical swabs independent of symptom presence and in symptomatic men independent of sampling method (urethral, urine), with sensitivity ranging from 92.4 to 98.1%, and specificity between 98.8 and 99.9%. Urine sampling in women and testing asymptomatic men resulted in lower sensitivity (urine in women: 64.8%; urethral in asymptomatic men: 73.1%; urine in asymptomatic men: 42.3%), with high specificity (99 to 99.9%). In a study of adults with suspected gonorrhea, Hjelmevoll et al. demonstrated 100% sensitivity and specificity with PCR against the reference standard of culture confirmed with sequencing of the 16S rRNA gene and the entire porA pseudogene. Chan et al. compared SDA NAAT versus PCR, resolving inconsistencies with in-house PCRs, and found high sensitivity (100% and 96.2% in women and men respectively) and specificity (98.4 and 99.1% in women and men respectively) with PCR using urine samples.

• Two studies assessed LCR NAAT in mainly STI clinic settings and found high sensitivity of over 95% and specificity close to 100%. van Doornum 2001, Moncada 2004) Against culture as reference standard, van Doornum et al. reported a sensitivity of LCR of 100% for female endocervical swab and urine samples, and male urethral swab samples, while for male urine samples the sensitivity was 95.2%; the specificity was 100% for all types of specimens. Moncada et al. demonstrated a sensitivity of 96.1% and specificity of 99.7% with LCR versus a reference standard of culture confirmed with sugar utilization tests, fluorescent antibody, or Haemophilus-Neisseria identification.

• DNA probe was assessed by one study in high-risk women attending an STI clinic (Darwin 2002). Compared against culture confirmed with direct fluorescent assay, the authors demonstrated a sensitivity of 92.2% and specificity of 99.8%.

B. Hepatitis B Testing
No studies evaluating the diagnostic accuracy of hepatitis B testing in high-risk patients attending primary care or ambulatory clinic facilities were identified.
C. Hepatitis C Testing

- There is a paucity of evidence on hepatitis C screening outside chronic liver disease, hemodialysis or blood donor populations.
  - One systematic review (Chou 2004)\(^{14}\) examined the diagnostic accuracy of hepatitis C testing but identified no studies in primary care or ambulatory clinic settings. One additional observational study found that the positive predictive value of EIA decreased rapidly in low-risk subgroups among 3,367 people attending an STD clinic (Gunn 2003).\(^{31}\) Please refer to Evidence Table 2.7 for details.

D. HIV Tests


- Four studies assessed the diagnostic accuracy of oral (or finger-prick) rapid HIV testing compared with an EIA-based reference standard (Debattista 2007, Zelin 2008, Pascoe 2009, Stekler 2009).\(^{33, 37, 41, 42}\)
  - They found that OraQuick ADVANCE had high sensitivity (ranging from 80 to 100%) and specificity (ranging from 80 to 100%). False positive rates were reported in two studies, ranging from 1/176 (0.6%) to 1/47 (2%) (Debattista 2007, Zelin 2008).\(^{33, 37}\) False negative values were slightly higher with 4/176 (2.2%) and 3/47 (6%).

- Three studies evaluated the WHO-recommended two-test algorithm, a parallel testing strategy using two blood-based rapid HIV tests (Determine HIV-1/2 and UniGold; or Determine HIV-1, Capillus HIV-1/2) against a reference standard (Fiscus 2007, Karim 2007, Klarkowski 2009).\(^{35, 36, 39}\)
  - Compared with Western Blot, sensitivity was reported in one study as low as 33%, with specificity at 98% (Fiscus 2007);\(^{35}\) with false positive rates ranging between 1% (Fiscus 2007)\(^{35}\) and 3.3% (Klarkowski 2009).\(^{39}\) The two-test strategy in Karim et al. 2007 increased the detection of acute HIV infection by 39.1% compared with RNA PCR.

- One of these studies also examined the diagnostic accuracy of Antigen p24 assay in adults with acute STIs (Fiscus 2007),\(^{35}\) and found that sensitivity was 75%, and specificity 99.6% compared with Western Blot. An ultrasensitive version of the assay increased these to 88% and 100% respectively.

- Teague et al. compared two blood-based rapid tests and reported higher false positive rates with INSTI compared with Determine rapid test (FPV: 12/91 [13%] compared with none).

- Sarge-Njie et al. assessed the diagnostic accuracy of five HIV testing strategies using dried blood spots (ELISA\(_\times3\) parallel; ELISA+Pepti-Lav 1-2 parallel; Gelatine Particle Assays; Gelatine Particle Assays+Pepti-Lav 1-2 parallel; Gelatine Particle Assays+filtration parallel) compared with the reference strategy of serum-based triple ELISA in people attending a Genito-Urinary Clinic in The Gambia. They found comparably high sensitivities (ranging from 95% [95% CI: 83.1 to 99.4%] to 100%) and specificities with all test strategies (97.5% [95% CI: 93.7 to 99.3%] to 100%).\(^{32}\)

- Two studies demonstrated high concordance between two assays (BED-CEIA and Vironostika LS) in distinguishing between chronic and acute HIV infection (Priddy 2007 and Truong 2009).\(^{34, 38}\)
### Evidence Tables 2

#### Screening Tools

**Evidence Table 2.1: Diagnostic Accuracy of HIV Tests**

<table>
<thead>
<tr>
<th>Name Design</th>
<th>N</th>
<th>Age</th>
<th>% Female</th>
<th>Reference Standard</th>
<th>Add'l Variable 1</th>
<th>Add'l Variable 2</th>
<th>Test</th>
<th>Se</th>
<th>Sp</th>
<th>FP</th>
<th>FN</th>
<th>Comment</th>
<th>Risk of Bias assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarge-Njie et al, 2006 Prospective diagnostic study Funded by the Medical Research Council (UK), National AIDS Control Programme (The Gambia), and the United Nations Development Programme.</td>
<td>201 adults at Genito-Urinary Clinic in The Gambia tested, 200 samples analysed</td>
<td>Not reported.</td>
<td>Not reported.</td>
<td>3-ELISA serum ICEHIV 1.0.2 assay; Wellcozyme HIV Recombinant; ICEHIV-2 ELISA (all Murex Biotech Ltd., Dartford, UK); 40/200 HIV-positive; 24/40 HIV-1 positive; 12/40 HIV-2 positive; 4/40 dual positive</td>
<td>n/a</td>
<td>n/a</td>
<td>3-ELISA dried blood spot</td>
<td>97.5%</td>
<td>100%</td>
<td>0</td>
<td>1/200</td>
<td>2 HIV-1 single infections misdiagnosed as being dual positive</td>
<td>Unclear</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>ELISA + Pepti-Lav 1-2 parallel</td>
<td>100%</td>
<td>100%</td>
<td>0</td>
<td>0</td>
<td>1 HIV-1 single infection misdiagnosed as being dual positive</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Gelatine Particle Assays</td>
<td>100%</td>
<td>97.5%</td>
<td>0</td>
<td>4/200</td>
<td>7 HIV-1 and 2 HIV-2 single infections misdiagnosed as being dual positive</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Gelatine Particle Assays + Pepti-Lav 1-2 parallel</td>
<td>100%</td>
<td>100%</td>
<td>0</td>
<td>0</td>
<td>1 HIV-1 single infection misdiagnosed as being dual positive</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Gelatine Particle Assays + filtration parallel</td>
<td>Cutoff ≥ 20,480: 95% Cutoff ≥ 5120: 97.5%</td>
<td>100%</td>
<td>1/200</td>
<td>0</td>
<td>Cutoff ≥ 20,480: 2 HIV-1 single infections misdiagnosed as being dual positive; and 1 dual sample was misdiagnosed as being single HIV-1 positive</td>
<td></td>
</tr>
<tr>
<td>Debattista et al, 2007 Prospective diagnostic study Funded by the Communicable Diseases Unit, Queensland Health.</td>
<td>354 MSM at an ambulatory sexual health clinic/inner city sexual health clinic in Brisbane, Australia</td>
<td>Not reported.</td>
<td>0%</td>
<td>AxSYM Combo Ag/Ab blood test (Abbott Laboratories, Abbott Park, IL, USA)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Orasure (OraSure Technologies, Beaverton, OR, USA) Oral fluid test</td>
<td>99.4%</td>
<td>97.6%</td>
<td>1/176</td>
<td>4/176</td>
<td>False negative - sample had been stored for longer than the recommended 6 weeks. False positive cut off absorbency was 0.509.</td>
<td>High</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oral Fluid Vironostika HIV-1 EIA</td>
<td>not reported</td>
<td>not reported</td>
<td>not reported</td>
<td>not reported</td>
<td>Used as confirmatory testing.</td>
<td></td>
</tr>
</tbody>
</table>

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care management institute

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National HIV/STI Clinical Practice Guideline
<table>
<thead>
<tr>
<th>Name Design</th>
<th>N</th>
<th>Age</th>
<th>% Female</th>
<th>Reference</th>
<th>Add'l Variable 1</th>
<th>Add'l Variable 2</th>
<th>Test</th>
<th>Se</th>
<th>Sp</th>
<th>FP</th>
<th>FN</th>
<th>Comment</th>
<th>Risk of Bias assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiscus et al. 2007</td>
<td>1450 attendees of the Kamuzu Central Hospital</td>
<td>not reported</td>
<td>34%</td>
<td>Western Blot</td>
<td>Blood rapid tests x2: (Determine HIV-1/2, UniGOLD)</td>
<td>33% (7/21 acute infections)</td>
<td>98%</td>
<td>14/1450</td>
<td>14/1450</td>
<td></td>
<td></td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Karim et al. 2007</td>
<td>245 high-risk sex workers, HIV negative at baseline</td>
<td>not reported</td>
<td>RNA PCR (Cobas AmpliScreen Multiprep HIV-1 test version 1.5 and the Cobas AmpliPrep/Cobas Amplicor HIV-1 Monitor Test, version 1.5 (Roche Diagnostics, Branchburg, New Jersey, USA), ELISA</td>
<td>Blood rapid tests x2: (Determine HIV-1 Capillus HIV-1/HIV-2 test)</td>
<td>not reported</td>
<td>not reported</td>
<td>not reported</td>
<td>60.8% (14/23) of HIV positive cases Increased detection of acute HIV infection (39.1%). PCR on negative test results only RNA PCR cut-off for positivity was &gt;1000 copies.</td>
<td>High</td>
<td></td>
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<tr>
<td>Zslim et al. 2008</td>
<td>820 samples from patients attending GUM clinics, HIV prevalence 5.73%</td>
<td>median age 31yrs</td>
<td>15%</td>
<td>ELISA</td>
<td>Oral Rapid test (OraQuick ADVANCE Rapid HIV-1/2)</td>
<td>93.64% (96% CI 82.46-96.66)</td>
<td>99.87% (99.28-100%)</td>
<td>3/47</td>
<td>3/47</td>
<td>3 false negatives due to observer error. PPV = 97.76% (98.27-99.94) NPV = 99.61% (98.87-99.92)</td>
<td>Unclear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name Design</td>
<td>N</td>
<td>Age</td>
<td>% Female</td>
<td>Reference Standard</td>
<td>Add'l Variable 1</td>
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<td>FN</td>
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<td>Risk of Bias assessment</td>
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<tr>
<td>Truong 2009</td>
<td>15,010</td>
<td>15% &gt;25 yrs, 44% 25-34 yrs, 41% &lt;35 yrs</td>
<td>0</td>
<td>EIA (Vironostika HIV-1)</td>
<td>n/va</td>
<td>n/va</td>
<td>Assay (BED-CEIA)</td>
<td>not reported</td>
<td>not reported</td>
<td>not reported</td>
<td>not reported</td>
<td>Chronic vs. recent infection High agreement between tests = 90% concordance. HIV estimated by: (#recent infections/uninfected)*100% (365/170) Kappa 0.77</td>
<td>High</td>
</tr>
<tr>
<td>Priddy et al. 2007</td>
<td>2202 high risk adults</td>
<td>median age 30yrs</td>
<td>40.8%</td>
<td>Pooled NAAT + RT-PCR or EIA + WB</td>
<td>n/va</td>
<td>n/va</td>
<td>Assay (BED-CEIA)</td>
<td>not reported</td>
<td>not reported</td>
<td>not reported</td>
<td>not reported</td>
<td>Chronic vs. recent infection High agreement between tests, kappa = 0.85 (95% CI 0.67 - 1.00)</td>
<td>High</td>
</tr>
<tr>
<td>Klarkowski 2009</td>
<td>2864</td>
<td>Not reported:</td>
<td>60%</td>
<td>Western Blot</td>
<td>n/va</td>
<td>n/va</td>
<td>Organics Immunocob Combirm HIV tests (OIC-HIV)</td>
<td>not reported</td>
<td>not reported</td>
<td>7/212</td>
<td>3.3% (95% CI 1.3-6.7)</td>
<td></td>
<td>Unclear</td>
</tr>
<tr>
<td>Teague 2009</td>
<td>Unclear number of high risk adults</td>
<td>Not reported.</td>
<td>Not reported.</td>
<td>BiCRAAD (Bio-Rad Laboratories Ltd, Hemel Hempstead, UK)</td>
<td>n/va</td>
<td>n/va</td>
<td>Blood Rapid test INSTI</td>
<td>not reported</td>
<td>not reported</td>
<td>1291</td>
<td>not reported</td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Pascoe et al. 2009</td>
<td>591 adults</td>
<td>median age 36 yrs for male, 34 for females</td>
<td>79.9%</td>
<td>EIA/Western Blot</td>
<td>n/va</td>
<td>n/va</td>
<td>Oral Rapid test (OraQuick ADVANCE) Test 2</td>
<td>100%</td>
<td>100%</td>
<td>not reported</td>
<td>not reported</td>
<td>118 positive results with INSTI rapid test. (of which only 91 samples available) Prevalence 0.9%</td>
<td>High</td>
</tr>
<tr>
<td>Name Design</td>
<td>N</td>
<td>Age</td>
<td>% Female</td>
<td>Reference Standard</td>
<td>Add'l Variable 1</td>
<td>Add'l Variable 2</td>
<td>Test</td>
<td>Se</td>
<td>Sp</td>
<td>FP</td>
<td>FN</td>
<td>Comment</td>
<td>Risk of Bias assessment</td>
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<tr>
<td>Stekler 2009 Seattle, USA Cohort study Sep 2003-June 08 Funded by National Institutes of Health (K23 AI-65243, CFAR Laboratory Core Grant AI-27757, and AI-38858). Gen-Probe Incorporated and Abbott Diagnostics provided support for subsets of laboratory tests.</td>
<td>14,005 specimens taken from men who have sex with men attending STD clinics. Oraquick offered to high-risk men only.</td>
<td>0%</td>
<td>EIA + p-NAAT</td>
<td>n/a</td>
<td>n/a</td>
<td>Oral or finger-prick Rapid test (OraQuick ADVANCE)</td>
<td>80%</td>
<td>80%</td>
<td>not reported</td>
<td>not reported</td>
<td>PPV = 98.1%, NPV = 99.4%</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 2.2: Downstream Effects of HIV Rapid Screening

<table>
<thead>
<tr>
<th>Author &amp; Title</th>
<th>Search Database / Method</th>
<th>Study Characteristics</th>
<th>Results</th>
<th>Conclusions/ Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hutchinson et al. (2006)</td>
<td>Databases: Medline, Embase, and AIDSLine</td>
<td>N: 15 studies providing 17 effect sizes for receipt of positive HIV result (21,096); incl 5 studies on rapid testing in STD clinics (13,476) of which 2 RCTs (3297 and 761) (Metcalf 2005, Spielberg 2005) and 1 observational study (1581) (Spielberg 2005) met our inclusion criteria; Spielberg 2005 was subsequently excluded as the published full text article did not provide data on STD clinics</td>
<td>Receipt of positive HIV test result: Alternative HIV-CT, especially rapid testing, significantly increased access to positive HIV test results compared with conventional testing [all studies: RR 1.61, 95%CI 1.36–1.90; 5 studies on rapid testing in STD clinics: RR 1.82, 95%CI 1.30–2.54; 2 studies meeting our inclusion criteria: RR 1.43 (Metcalf 2005) and reported as 3.09 (Kendrick 2005; could not be confirmed after review of full text version, see absolute results in row below).</td>
<td>The review concluded that rapid testing, lead to substantial increases in receipt of test results. Compared with conventional HIV-CT, patients were around 1.8 times more likely to receive results with rapid testing conducted in STD clinics. The rate of false-positive test results was low (&lt; 1%). The analysis may underestimate effect sizes that might be expected with newer rapid HIV tests because most of the included studies used the SUDS rapid test, which required phlebotomy and processing of a serum specimen in a laboratory. On the other hand, significant heterogeneity was present in the pooled analyses, and larger effect sizes reported in studies with non-randomized than with randomized designs.</td>
</tr>
<tr>
<td></td>
<td>Other sources: Abstracts of International AIDS Conferences (2000, 2002, and 2004) and the CDC's National HIV Prevention Conferences (2003 and 2005); references in retrieved articles; contact with experts and authors</td>
<td>Setting: STD clinics (all included studies), emergency departments, HIV testing, and outreach venues (needle exchanges, bath houses, mobile health vans)</td>
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<tr>
<td></td>
<td>Search period: March 1990 to May 2005</td>
<td>Location: U.S.</td>
<td></td>
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<tr>
<td></td>
<td>Search terms: Not reported.</td>
<td>Inclusion criteria: Types of studies Published English</td>
<td></td>
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<tr>
<td></td>
<td>Reported outcomes/outcome measures: Receipt of HIV test results and acceptance of testing</td>
<td>Language articles, abstracts, and unpublished studies (if providing sufficient detail for effect size computation) of primary studies with control or comparison group</td>
<td></td>
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<tr>
<td></td>
<td>Method: - Meta-analyses of test type; study setting, sero status and study design with rapid testing - Assessment of publication bias using Begg's funnel plot - No information on study funding reported</td>
<td>Types of interventions Voluntary HIV counseling and testing (HIV-CT) interventions that included rapid, oral fluid, urine or home testing as an alternative to serum EIA testing; or another alternative that eliminated a return visit for test results</td>
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<td>Exclusion criteria: Mandatory HIV-CT and those conducted in perinatal or occupational exposure settings.</td>
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<tr>
<td>Author &amp; Title</td>
<td>Search Database / Method</td>
<td>Study Characteristics</td>
<td>Results</td>
<td>Conclusions/ Limitations</td>
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<tr>
<td>Roberts et al. (2007) Outcomes of Blood and Oral Fluid Rapid Testing: A Literature Review, 2000-2006.</td>
<td>Databases: PubMed, Sociological Abstracts, PsychInfo</td>
<td>N: 26 studies incl 2 RCTs of which 2 observational studies met our inclusion criteria (41514 eligible, 5468 tested for HIV)</td>
<td>Receipt of positive HIV test result: 13 studies reported results, 2 of which met our inclusion criteria: CDC2001, 3887/39537 patients tested for HIV. Introduction of rapid testing increased the number of HIV patients being tested (2,787/19,911 vs. 1,100/19,626); rapid testing increased the rate of people being notified of their HIV status (65/74 [74%] vs. 29/47 [60%]). Kendrick 2005, 1581/1977 patients tested for HIV. More patients opted for rapid testing (1372 vs. 209); rapid testing increased the number of people being notified of their HIV status compared with conventional testing (37/37 [100%] vs. 16/19 [84%]).</td>
<td>Many people who test rapidly receive their test results, an improvement on conventional testing where failure to return for HIV test results is common. The studies did not assess how many of the people receiving their preliminary rapid test results return for confirmatory testing. There is some evidence that more people may make enter into medical care after rapid testing but evidence is scarce on the rate of people remaining in care.</td>
</tr>
<tr>
<td></td>
<td>Other sources: References in retrieved articles</td>
<td>Population: In all studies: persons who use injection drugs, men who have sex with men, pregnant women</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Search period: January 2000 to June 2006</td>
<td>Age: Not reported</td>
<td>Entry into medical care: 13 studies reported results, 2 of which met our inclusion criteria: CDC2001: Introduction of rapid testing increased the absolute number but not the rate of people entering into medical care (26/55 [47%] vs. 13/28 [46%]). Kendrick 2005: Rapid testing increased the rates of patients attending a first appointment (36/37 [97%] vs. 16/19 [84%]) and of those remaining in care after rapid testing compared with conventional testing (30/37 [81%] vs. 13/19 [68%]).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Search terms: Rapid, HIV, test</td>
<td>Setting: STD clinics (both included studies), labor and delivery units, jail</td>
<td>Adverse effects: Not reported.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reported outcomes/outcome measures: Client acceptance rates, rates of clients receiving results, rate of entry into medical care for those found to be HIV positive, efficacy of prevention counseling</td>
<td>Location: U.S. (both included studies) and 7/26 foreign countries</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Method: - No meta-analyses or assessment of publication bias conducted</td>
<td>Inclusion criteria: Types of studies English language articles published in peer reviewed journals, conducted in human populations Types of interventions Blood and oral rapid HIV testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- No information on study funding reported</td>
<td></td>
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</tbody>
</table>
### Evidence Table 2.3: Effects of Acute HIV Screening in Pregnant Women on Mother-to-Infant Transmission

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion &amp; Exclusion Criteria</th>
<th>Age and Gender</th>
<th>Limitations / Biases</th>
<th>Intervention</th>
<th>Duration</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patterson et al. (2007)</td>
<td>Prospective: 187,135 people tested at publicly funded sites in North Carolina, U.S. who had received antibody-negative or indeterminate results with EIA plus Western Blot but positive with pooled NAAT. Retrospective: Records of 6 infants reported as HIV-positive in the same study period.</td>
<td>Not reported.</td>
<td>Low rate of events allowing no statistical analysis; results not reported for negative vs. indeterminate antibody-negative tests; no confirmatory testing of antibody and HIV RNA-negative samples for acute HIV (potentially missing other acute HIV cases).</td>
<td>Adding pooled NAAT (Procleix HIV-1 assay [GenProbe, San Diego, California, USA], theNuclisens HIV-1 EasyQassay, or the Nuclisens HIV-1 QL assay [bioMe’rieux]) to HIV antibody screening with EIA (Vironstika HIV-1 enzyme immunoassay [bioMe’rieux] plus Western blot analysis (WB, Bio-Rad, Hercules, California, USA), followed by HAART for all patients diagnosed with acute HIV.</td>
<td>2.5 years (November 2002 to April 2005)</td>
<td>Number of HIV antibody-positive patients. Number of patients diagnosed with acute HIV infection. Number of mother to child HIV transmissions from acute HIV infections. HIV test status of mothers whose infants had been tested HIV-positive</td>
<td>Number of antibody-positive patients: 428/187,135 Number of HIV-infected people who had tested antibody-negative but HIV RNA-positive (false negatives): 15/443 (3.4%) Number of infants infected with HIV whose mothers had been diagnosed with acute HIV and treated with HAART: 0/5 HIV status of mothers whose infants had been diagnosed with HIV during the same study period: Mothers with chronic HIV: 3/6 (2/3 not attending routine antenatal care, 1/3 not compliant with HAART) Mothers with acute HIV: 3/6 (tested at nonpublic sites with no HIV RNA retesting of antibody-negative samples)</td>
</tr>
</tbody>
</table>
### Evidence Table 2.4: Chlamydia Screening

<table>
<thead>
<tr>
<th>Author &amp; Title</th>
<th>Search Database / Method</th>
<th>Study Characteristics</th>
<th>Results</th>
<th>Conclusions/ Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low et al. (2009)</td>
<td>Databases and search period: Cinahl, Cochrane Controlled Trials Register, Database of Abstracts of Research Effectiveness, Embase, Medline, PsyCINFO and SIGLE Jan 1999-Oct 2007</td>
<td>N: 6 reviews, 5 RCTs, 1 non-RCT and 1 time trend study, of which no studies met our inclusion criteria</td>
<td>N/A</td>
<td>- No RCTs on the effects of opportunistic C. trachomatis screening in non-pregnant women, pregnant women in antenatal clinics or men.</td>
</tr>
<tr>
<td></td>
<td>Other sources: Hand search of reference lists of included articles</td>
<td>Inclusion criteria: Types of studies Systematic reviews, RCTs, non-RCTs and observational time trend studies if they included data from at least two time points before the introduction of the intervention</td>
<td></td>
<td>- No RCTs evaluating infertility in women or men, ectopic pregnancy, adverse pregnancy outcomes, neonatal morbidity or mortality.</td>
</tr>
<tr>
<td></td>
<td>Search terms: exp chlamydia infections, exp chlamydia trachomatis, exp chlamydia, exp chlamydia pneumonia, Chlamydia adj infection$, exp pelvic inflammatory disease, exp mass screening, screening, national chlamydia screening programme, humans and yr=&quot;1990 - 2007&quot;, exp chlamydiasis, exp health screening, chlamydia</td>
<td>Types of interventions Register-based and opportunistic chlamydia screening interventions</td>
<td></td>
<td>- No trials examining the effects of &gt;1 round of any screening intervention.</td>
</tr>
<tr>
<td></td>
<td>Outcome measures: Primary outcomes Pelvic inflammatory disease, ectopic pregnancy, infertility, adverse pregnancy outcomes, neonatal infection, chlamydia prevalence</td>
<td></td>
<td>- No trials reporting harms of C. trachomatis screening.</td>
<td></td>
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<tr>
<td></td>
<td>Methods: - Narrative approach but planned to combine the results of &gt;1 trials using the same intervention in a meta-analysis using a random effect model. - Heterogeneity due to between trial variation examined using I2 statistics</td>
<td></td>
<td>- Areas for future research: high quality RCTs of multiple rounds of screening with biological outcome measures.</td>
<td></td>
</tr>
<tr>
<td>Author &amp; Title</td>
<td>Search Database / Method</td>
<td>Study Characteristics</td>
<td>Results</td>
<td>Conclusions/ Limitations</td>
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</table>
| Gottlieb et al. (2010)  
Screening and treatment to prevent sequelae in women with Chlamydia trachomatis genital infection: how much do we know?  
Funding:  
Not reported. | Databases and search period:  
Medline  
1960-March 2008  
Other sources:  
Hand search of reference lists of included articles | N: 2 RCTs, 5 cohort studies with untested control groups and, 4 ecological studies (total 20,762 women); of which one registry-based retrospective cohort study met our inclusion criteria (18452 tests in 13,693 women) (Anderson 2005) | Risk of ectopic pregnancy:  
Increased risk of ectopic pregnancy in women with 1 or more prior infection compared with women with negative tests only: HR 1.82, 95% CI 1.27–2.60;  
Large effect in women with 2 or more ectopic pregnancies: HR 2.96, 95%CI 1.58–5.56. | For SR:  
Only few and methodologically flawed studies were identified on the effectiveness of C. trachomatis screening. Gaps in the evidence include populations at lower risk, asymptomatic patients, > 1 round of screening, optimal frequency of screening, benefit of screening for recurrent infection, different types of screening approaches.  
For Anderson 2005:  
Outcomes not assessed in women never tested for C. trachomatis; no systematic screening; less sensitive tests used; undetected infections at other times likely; did not control for sociodemographic factors, sexual behavior, contraceptive use, desire to conceive etc.; birth rates cannot necessarily be extrapolated to infertility |
| Method:  
- No meta-analysis  
- No assessment of publication bias | Age:  
<43 years  
Setting:  
Anderson 2005: Registry data with unique ID to link test results with pregnancy outcome in hospital  
Location:  
Anderson 2005: Denmark |
| Outcome measures:  
Primary outcomes  
Effectiveness of screening and treatment to prevent sequelae in already infected women  
Method:  
- No meta-analysis  
- No assessment of publication bias | Inclusion criteria:  
Types of studies  
Original, prospective studies, registry-based retrospective cohort studies and ecological studies |
| Types of participants  
Women who had not given birth or experienced an ectopic pregnancy before their first C. trachomatis test  
Types of interventions  
C. trachomatis screening interventions | Types of participants  
Women who had not given birth or experienced an ectopic pregnancy before their first C. trachomatis test  
Types of interventions  
C. trachomatis screening interventions | Types of participants  
Women who had not given birth or experienced an ectopic pregnancy before their first C. trachomatis test  
Types of interventions  
C. trachomatis screening interventions |
## Evidence Table 2.5: Hepatitis B Screening

<table>
<thead>
<tr>
<th>Author &amp; Title</th>
<th>Search Database / Method</th>
<th>Study Characteristics</th>
<th>Results</th>
<th>Conclusions/ Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chou et al. (2004)</td>
<td>Databases: Medline (1989 through to February 2003), Cochrane Clinical Trials Registry (2002, Issue 2)</td>
<td>N: No RCTs or longitudinal cohort studies comparing outcomes between patients in the general adult population who were screened and not screened for hepatitis C infection. 2 small trials on harms of hepatitis C screening none of which met our inclusion criteria. Age: Adults.</td>
<td>N/A</td>
<td>No direct evidence found on benefits of screening for hepatitis C infection in the general adult population, and no studies have adequately assessed the potential harmful effects of screening for HCV infection, such as anxiety, labeling, or damage to close relationships.</td>
</tr>
<tr>
<td></td>
<td>Other sources: References in retrieved articles, periodic hand searches of relevant journals; contact with experts.</td>
<td>Inclusion criteria: Types of studies: Clinical trials or observational studies that evaluated clinical outcomes in patients screened and not screened for hepatitis C infection. Types of participants: General adult population with chronic hepatitis C infection. Exclusion criteria: Studies that focused only on patients with end-stage liver disease, cirrhosis, or hepatocellular cancer, and on persons with HCV who had undergone transplantation; studies of pregnant patients, children, or those with end-stage renal disease, occupational exposure or HIV infection; studies of nonhuman subjects and studies without original data; foreign language papers unless clinical trials with English abstract.</td>
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<tr>
<td></td>
<td>Search terms: For screening: MeSH terms hepatitis C and hepacivirus combined with the terms mass screening, hepatitis C antibodies, predictive value of tests, and sensitivity and specificity and the text words antibody testing.</td>
<td>Reported outcomes/outcome measures: Harm, premature death and disability.</td>
<td></td>
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</tbody>
</table>
### Evidence Table 2.6: Hepatitis B Screening

<table>
<thead>
<tr>
<th>Author &amp; Title</th>
<th>Search Database / Method</th>
<th>Study Characteristics</th>
<th>Results</th>
<th>Conclusions/ Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin et al. (2007)</td>
<td>Databases: Cochrane Database of Systematic Reviews, PubMed core clinical journal subset (previously known as the Abridged Index Medicus). The authors expanded their search to include noncore journals, when the search revealed few articles. Databases: Cochrane Database of Systematic Reviews, PubMed core clinical journal subset (previously known as the Abridged Index Medicus). The authors expanded their search to include noncore journals, when the search revealed few articles. Other sources: Reference list of recent reviews and clinical guidelines Search period: 1 January 2001 to 5 March 2008 Search terms: hepatitis B, pregnancy, screening, and mass screening Reported outcomes/outcome measures: Benefits and harms of screening for HBV infection on pregnant women Method: - No meta-analyses - No assessment of publication bias</td>
<td>N: 1 SR (Lee 2006, see row below) although it assessed the effectiveness of Hepatitis B vaccination rather than screening Age: Not reported Setting: Not specified Inclusion criteria: Types of studies English-language articles only Benefits: RCTs, meta-analyses, SRs. Harms: SRs, meta-analyses, RCTs, cohort studies, case–control studies and large case series Types of interventions Hepatitis B vaccination Exclusion criteria: - No new RCTs of prenatal screening or newborn prophylaxis for Hepatitis B infection. - No new studies describing false-positive screening rates or downstream events associated with false-positive test results. - The review might suffer from publication bias, since the search was limited to English language.</td>
<td>Benefits of hepatitis B testing: No new evidence. Harms of hepatitis B testing: No new evidence.</td>
<td></td>
</tr>
<tr>
<td>Author &amp; Title</td>
<td>Search Database / Method</td>
<td>Study Characteristics</td>
<td>Results</td>
<td>Conclusions/ Limitations</td>
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</tr>
<tr>
<td>Lee et al. (2006) Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: Systematic review and meta-analysis.</td>
<td>Databases: The Cochrane Neonatal Group Controlled Trials Register, The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Central Register of Controlled Trials in The Cochrane Library, MEDLINE and EMBASE. Other sources: Authors of trials, pharmaceutical companies, hand searches.</td>
<td>N: 29 RCTs none of which evaluated the benefits of Hepatitis B screening. Participants: Newborn infants of either gender born to HBsAg positive mothers. Setting: Not indicated. Inclusion criteria: Types of studies: RCTs irrespective of blinding, publication status, or language. Types of interventions: 1. PDV or RV versus placebo or no intervention 2. Hepatitis B immunoglobulin versus placebo or no intervention 3. PDV or RV plus hepatitis B immunoglobulin versus placebo, no intervention, PDV, or RV. Exclusion criteria: Non-RCTs; participants other than newborn infants of HBsAg positive mothers.</td>
<td>Benefits of hepatitis B testing: No evidence. Studies assessed only effectiveness of Hepatitis B vaccination: Hepatitis B vaccine versus placebo or no intervention: Compared with placebo or no intervention, hepatitis B vaccination significantly decreased the risk of hepatitis B occurrence (relative risk 0.28, 95% confidence interval 0.20 to 0.40; four trials). Recombinant vaccine (RV) versus plasma derived vaccine (PDV): Recombinant vaccine and plasma derived vaccine showed no significant difference in hepatitis B occurrence (1.00, 0.70 to 1.42; four trials). High dose versus low dose vaccine: High dose vaccine and low dose vaccine showed no significant difference in hepatitis B occurrence (plasma derived vaccine 0.97, 0.55 to 1.68; three trials; recombinant vaccine 0.78, 0.31 to 1.94; one trial). Hepatitis B immunoglobulin versus placebo or no intervention: Overall, hepatitis B immunoglobulin significantly decreased the risk of hepatitis B occurrence in infants (0.52, 0.44 to 0.63; 11 trials). Multiple versus single injection of hepatitis B Immunoglobulin: Multiple hepatitis B immunoglobulin plus plasma derived vaccine versus single hepatitis B immunoglobulin injection plus plasma derived vaccine did not significantly reduce the risk of hepatitis B occurrence (0.87, 0.30 to 2.47; two trials; 12 = 0%). Vaccination plus hepatitis B immunoglobulin versus placebo or no intervention: Compared with placebo or no intervention, plasma derived vaccine plus hepatitis B immunoglobulin significantly reduced hepatitis B occurrence (0.08, 0.03 to 0.17; three trials). Harms of hepatitis B testing: No meta-analysis due to poor reporting in included studies in which intervention group adverse events had occurred in.</td>
<td>This study suffers from the following limitations: 1. Some analyses include few trials and a small number of newborn infants. 2. Though the authors did not find association between methodological quality and results, the possibility of bias still exists as most trials were of low methodological quality. 3. Publication bias cannot be excluded although the authors did not find asymmetries in funnel plots. 4. The authors indicated that, when contacted, only few of the authors of the original studies responded while others claimed to have lost data. 5. Most trials reported only surrogate outcomes (hepatitis B surface antigen status or antibody levels to hepatitis B surface antigen) and not long-term clinical outcomes.</td>
</tr>
</tbody>
</table>

Funding:
Tri-Service General Hospital, Taiwan; Copenhagen Trial Unit, Copenhagen University Hospital, Denmark; SC Van Foundation, Denmark; and Public Health Laboratory Service, United Kingdom.

Reported outcomes/outcome measures:
Primary outcome: measure: occurrence of hepatitis B, defined as a blood specimen positive for hepatitis B surface antigen, hepatitis B e antigen, or antibody to hepatitis B core antigen. Secondary outcome measures: antibody levels to hepatitis B surface antigen < 10 IU/l and adverse events.

Method:
- Meta-analyses performed using Review Manager 4.2; data analysis with random-effects and fixed-effect models.
- Begg's and Egger's methods used to assess publication and other bias.
### Evidence Table 2.7: Diagnostic Accuracy of Hepatitis C Screening

<table>
<thead>
<tr>
<th>Author &amp; Title</th>
<th>Search Database / Method</th>
<th>Study characteristics</th>
<th>Results</th>
<th>Conclusions/ Limitations</th>
</tr>
</thead>
</table>
| Chou et al. (2004) | **Databases:** Medline (1989 through to February 2003), Cochrane Clinical Trials Registry (2002, Issue 2)  
**Other sources:** References in retrieved articles, periodic hand searches of relevant journals, contact with experts  
**Search terms:** For screening: MeSH terms hepatitis C and hepatitis virus combined with the terms mass screening, hepatitis C antibodies, predictive value of tests, and sensitivity and specificity and the text words antibody testing.  
**Reported outcomes/outcome measures:** Diagnostic accuracy, harm, premature death and disability | N: 1 SR (7 studies on sensitivity of third-generation ELISA vs. PCR or RIBA; 3 studies on RIBA [4674 patients with chronic liver disease or undergoing hemodialysis]) and 3 additional studies (2616 patients with acute/chronic liver disease or blood donors) on third-generation EIA vs. PCR, none of which met our inclusion criteria | N/A | No studies in primary care or ambulatory clinic settings. People with chronic liver disease or undergoing hemodialysis: “Screening can accurately detect chronic HCV infection... Using viremia as the reference standard, sensitivity of third-generation ELISA testing appears to be 94% or higher. Limited data found a specificity of 97% or greater using viremia as the reference standard.” |

Funding: Agency for Healthcare Research and Quality under a contract to support the work of the U.S. Preventive Services Task Force.
### Evidence Table 2.8: Effects of Syphilis Screening

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion &amp; Exclusion Criteria</th>
<th>Age and Gender</th>
<th>Limitations / Biases</th>
<th>Intervention</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
</table>
| Winston et al. (2003)      | **Inclusion:** HIV positive individuals attending for routine care at the Kobler Clinic, Chelsea and Westminster Hospital, London, UK. **Included for analysis:** Asymptomatic patients with early syphilis **Excluded:** Symptomatic patients or suspected of having syphilis at time of screening. | Mean age 40 years; 2139/2443 (88%) male.                                              | Low event rates of early syphilis affecting conclusions on HIV treatment failure; known syphilis outbreak in the area of the clinic (between 1996 and 2001, new diagnoses of infectious syphilis increased from 122 cases to 715 cases, mainly in MSWs and HIV-infected individuals in Manchester, Brighton and London, UK). | Adding 3-monthly syphilis testing with the Venereal Disease Research Laboratory (VDLR; Oxioid carbon antigen) and Treponema Pallidum Particle Agglutination (TPPA; Serodia) tests to routine computerized blood order sets used for HIV follow-up care (previously offering yearly testing). | 1 year (May 2001 to April 2002)                      | Syphilis testing rates: Increased compared with previous year (2266/2670 [84%] vs. 3%).  
Median time since most recent syphilis screening: 6 months  
Proportion of early syphilis cases seen at the clinic whose condition was detected through screening intervention: 26/88  
Proportion of HIV patients whose early syphilis was detected through screening intervention: 26/52  
Early syphilis event rates: 2.8 per 1000 patient years (95%CI 1.8 to 4.0)  
Detection of early syphilis cases with VDLR compared with TPPA: 20 vs. 6  
HIV treatment failure rate: Significantly higher than overall departmental rate: 37% vs. 17%; p=0.03 |
| Cohen et al. (2005)        | **Inclusion:** HIV positive individuals attending for routine care at the Kobler Clinic, Chelsea and Westminster Hospital, London, UK. **Included for analysis:** Asymptomatic patients with early syphilis **Excluded:** Symptomatic patients or suspected of having syphilis at time of screening. | Reported for patients with early syphilis: Mean age 40 years; 3940 (97.5%) male.         | Low event rates of early syphilis affecting conclusions on HIV treatment failure; known syphilis outbreak in the area of the clinic. | Adding 3-monthly syphilis testing with the Venereal Disease Research Laboratory (VDLR; Oxioid carbon antigen) and Treponema Pallidum Particle Agglutination (TPPA; Serodia) tests to routine computerized blood order sets used for HIV follow-up care (previously offering yearly testing). | 2 years (May 2001 to 30 April 2003; comparing second year data vs. first year data) | Syphilis testing rates: Increased compared with previous year (2389/2655 [90%] vs. 2266/2670 [84%]).  
Median time since most recent syphilis screening: Decreased compared with previous year (3 months [IQR 1.7–4.3] vs. 6 months)  
Proportion of all early syphilis cases seen at the clinic whose condition was detected through screening intervention: No significant difference compared with previous year: 40/112 (36%) vs. 26/88 (29%); p=0.357  
Proportion of all early syphilis cases seen at the clinic whose condition was detected through screening intervention: No significant difference compared with previous year: 40/71 (56%) vs. 26/52 (50%); p=0.486  
Early syphilis event rates: Significantly increased compared with previous year (7.3 per 1000 patient years [95%CI 5.2 to 9.9] vs. 2.8 per 1000 patient years [95%CI 1.8 to 4.0]; p=0.05)  
Detection of early syphilis cases with VDLR compared with TPPA: 27 vs. 13  
HIV treatment failure rate: No significant difference compared with previous year: 25.8% vs. 37%; p=0.409  
No significant difference compared with overall departmental rate: 25.8% vs. 17%; p=0.273 |
**Evidence Table 2.9: Diagnostic Accuracy of Gonorrhea Tests**

<table>
<thead>
<tr>
<th>Author &amp; Title</th>
<th>Search Database / Method</th>
<th>Study Characteristics</th>
<th>Results</th>
<th>Conclusions/ Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass et al. (2005)</td>
<td>Databases: MEDLINE</td>
<td>N: 25 studies published since 1996 addressing one or more of the key questions about screening tests and their performance characteristics, of which eight studies met our inclusion criteria</td>
<td>No meta-analysis, see eight studies meeting our inclusion criteria listed in table below.</td>
<td>Screening tests and performance characteristics: NAATs and nucleic acid hybridization tests demonstrate high sensitivity and specificity, although studies are methodologically limited. Sensitivity is lower using urine specimens for some tests, and may vary by symptom status.</td>
</tr>
<tr>
<td><strong>Screening for</strong></td>
<td>Other sources: Hand searching of relevant medical journals and reference lists, and suggestions from experts</td>
<td>Setting: Prisons, STD and family planning clinics</td>
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<tr>
<td>Gonorrhea: update of the evidence.</td>
<td>Search period: January 1966 through July 2004</td>
<td>Inclusion criteria: Types of studies English- studies published in 1996 or later about screening strategies in the target populations; individual and population-level risk factors; characteristics and accuracy of tests used for screening; adverse effects of chemoprophylaxis treatment for newborns; as well as evidence on cost effectiveness for universal and targeted screening strategies conducted in the U.S., Australia, Canada, and Western Europe.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Funding: Agency for Healthcare Research and Quality.</td>
<td>Search terms: Not shown: search strategies for risk factors and cost</td>
<td>Exclusion criteria: Studies of non-human subjects and those without original data.</td>
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<tr>
<td></td>
<td>Screening 1. exp GONORRHEA/ 2. exp Neisseria gonorrhoeae/ 3. 1 or 2 4. exp Mass Screening/ 5. 3 and 4 6. limit 5 to (all adult &lt;19 plus years&gt; or adolescent &lt;13 to 18 years&gt;) 7. from 6 keep 1-138</td>
<td>Method: - No meta-analysis, narrative summaries - No formal testing of publication bias reported.</td>
<td></td>
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<td></td>
<td>Screening Tests 1. exp GONORRHEA/ 2. exp Neisseria gonorrhoeae/ 3. 1 or 2 4. exp Mass Screening/s, ma, mt, st [Instrumentation, Manpower, Methods, Standards] 5. 3 and 4 6. from 5 keep 1-54</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Test Performance 1. exp GONORRHEA/ 2. exp Neisseria gonorrhoeae/ 3. 1 or 2 4. exp &quot;Sensitivity and Specificity&quot;/ 5. exp Diagnostic Errors/ 6. 4 or 5 7. 3 and 6 8. from 7 keep 1-304</td>
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<td></td>
<td>Reported relevant outcomes/outcome measures: Sensitivity, specificity, positive predictive value, and negative predictive value of tests.</td>
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</tbody>
</table>
# Evidence Table 2.10: Effects of Antenatal Syphilis Screening

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion &amp; Exclusion Criteria</th>
<th>Age and Disease Incidence/Prevalence</th>
<th>Limitations / Biases</th>
<th>Intervention</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Munkhuu et al. (2009)</td>
<td><strong>Inclusion:</strong> New antenatal care attendees with single pregnancy. <strong>Excluded:</strong> Women known to be unable to attend the antenatal visit scheduled during the study period; living outside Ulaanbaatar; unwilling to give informed consent; absence of a willing guardian for under-aged women</td>
<td>Mean age 27 years; Syphilis incidence reported to have been increasing during the past decades; congenital syphilis rate increasing: 2 new cases reported in 1995 and 51 new cases in 2006 (based on clinical criteria only)</td>
<td>Follow up rate: 94.7%; final status of initially seronegative women and their newborns (false negative rate) unknown; syphilis tests supplied to the intervention arm only (but no supplier shortages reported during study period)</td>
<td>One-stop service with on-site syphilis testing with SD Bioline Syphilis 3.0 (Standard Diagnostics Inc., Kyunggi-do, Korea) and treatment at first antenatal visit and 3rd trimester antenatal visit vs. routine antenatal screening with off-site testing and case management</td>
<td>1 year (August 2007 to August 2008)</td>
<td><strong>Antenatal syphilis testing utilization:</strong> Significantly increased with intervention compared with control group (1st trimester: 3849/3850 [99.9%] vs. 3065/3650 [79.6%], p&lt;0.001; 3rd trimester: 3670/3756 [99.7%] vs. 2357/3823 [62.1%], p&lt;0.001) <strong>Detected syphilis cases:</strong> Significantly increased with intervention compared with control group (1st trimester: 73 [1.9%] vs. 27 [0.9%], p&lt;0.001; 3rd trimester: 20 [0.5%] vs. 2 [0.08%], p&lt;0.01) <strong>Adequate treatment:</strong> Significantly increased with intervention compared with control group (92/93 [98.9%] vs. 26/29 [89.6%], p&lt;0.02) <strong>Treatment of sexual partners:</strong> 94.6% vs. 55.2%, p&lt;0.001 <strong>Number of congenital syphilis cases:</strong> Reduced by 93.5% (95%CI 66% to 98.6%); 1/3632 vs. 15/3552 <strong>False positive rate of rapid testing (resulting in unnecessary first dose of antibiotic treatment):</strong> 13 women (10 of whom subsequently reported to have been diagnosed and treated for syphilis prior to testing)</td>
</tr>
</tbody>
</table>
### BMJ GRADE Evaluations

#### Evidence Table 2.11: GRADE Evaluation for Diagnostic Accuracy of HIV Testing

<table>
<thead>
<tr>
<th>Number of studies (participants)</th>
<th>Outcome</th>
<th>Comparison</th>
<th>Type of evidence</th>
<th>Quality</th>
<th>Consistency</th>
<th>Directness</th>
<th>Effect size</th>
<th>GRADE</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (14751) [Pascoe 2009][Stekler 2009][Zelin 2008][Debattista 2007]</td>
<td>Diagnostic accuracy</td>
<td>Oral or finger-prick rapid test vs. reference standard</td>
<td>2</td>
<td>-2</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>Very Low</td>
<td>Quality points deducted for unclear sample selection and high risk of bias; Consistency point deducted for heterogeneity.</td>
</tr>
<tr>
<td>3 (4559) [Fiscus 2007][Karim 2007][Klarovski 2009]</td>
<td>Diagnostic accuracy</td>
<td>WHO two-test diagnostic algorithm vs. reference standard</td>
<td>2</td>
<td>-2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Very Low</td>
<td>Quality points deducted for poor outcome reporting and high risk of bias.</td>
</tr>
<tr>
<td>1 (1450) [Fiscus 2007]</td>
<td>Diagnostic accuracy</td>
<td>Antigen p24 assay vs. reference standard</td>
<td>2</td>
<td>-2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Very low</td>
<td>Quality points deducted for incomplete outcome data and single study.</td>
</tr>
<tr>
<td>1 (unclear number of participants) [Teague 2009]</td>
<td>FPV</td>
<td>Blood-based rapid test vs. blood based rapid test</td>
<td>2</td>
<td>-2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Very Low</td>
<td>Quality points deducted for selective outcome reporting and single study.</td>
</tr>
<tr>
<td>1 (200) [Sarge-Njie 2006]</td>
<td>Diagnostic accuracy</td>
<td>5 HIV-testing strategies vs. reference standard</td>
<td>2</td>
<td>-2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Very low</td>
<td>Quality point deducted for unclear sample selection and single study.</td>
</tr>
<tr>
<td>2 (17212) [Priddy 2007][Truong 2009]</td>
<td>Chronic vs. acute HIV infection</td>
<td>Assays (BED-CEIA and Vironostika LS) vs. reference standard</td>
<td>2</td>
<td>-2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Very Low</td>
<td>Quality points deducted for unclear sample selection and poor outcome reporting</td>
</tr>
</tbody>
</table>
### Evidence Table 2.12: GRADE Evaluation for Downstream Effects of Blood and Oral Rapid HIV Testing

<table>
<thead>
<tr>
<th>Number of studies (participants)</th>
<th>Outcome</th>
<th>Comparison</th>
<th>Type of evidence</th>
<th>Quality</th>
<th>Consistency</th>
<th>Directness</th>
<th>Effect size</th>
<th>GRADE</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 (8765) [Metcalf 2005][Kendrick 2005][CDC 2001]</td>
<td>Receipt of HIV test result</td>
<td>Rapid testing (SUDS) vs. EIA</td>
<td>4</td>
<td>-2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td>Quality points deducted for inclusion of observational data and poor outcome reporting.</td>
</tr>
<tr>
<td>2 (5468) [Kendrick 2005][CDC 2001]</td>
<td>Entry into care/Access to therapy</td>
<td>Rapid vs. conventional testing</td>
<td>2</td>
<td>-1</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>Very Low</td>
<td>Quality point deducted for low number of events; Consistency point deducted for inconsistent result.</td>
</tr>
</tbody>
</table>

### Evidence Table 2.13: GRADE Evaluation for Antenatal STI Testing

<table>
<thead>
<tr>
<th>Number of studies (participants)</th>
<th>Outcome</th>
<th>Comparison</th>
<th>Type of evidence</th>
<th>Quality</th>
<th>Consistency</th>
<th>Directness</th>
<th>Effect size</th>
<th>GRADE</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (4155) [Kiss 2004]</td>
<td>Preterm delivery/low birth weight</td>
<td>Infection screening and treatment programme integrated into routine prenatal care versus usual care</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>

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For use within Kaiser Permanente only. 03/11  
care management institute  
National HIV/STI Clinical Practice Guideline  
54
### Evidence Table 2.14: GRADE Evaluation for Antenatal STI Testing

<table>
<thead>
<tr>
<th>Number of studies (participants)</th>
<th>Outcome</th>
<th>Comparison</th>
<th>Type of evidence</th>
<th>Quality</th>
<th>Consistency</th>
<th>Directness</th>
<th>Effect size</th>
<th>GRADE</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (187,135) [Patterson 2007]</td>
<td>Mother-to-child HIV transmission</td>
<td>Adding pooled NAAT to HIV antibody screening with EIA plus Western Blot, followed by HAART for all patients with acute HIV</td>
<td>2</td>
<td>-2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Very low</td>
<td>Quality points deducted due to sparse data and poor outcome reporting.</td>
</tr>
</tbody>
</table>

### Evidence Table 2.15: GRADE Evaluation for Downstream Effects of Blood and Oral Rapid HIV Testing in Pregnant Women

<table>
<thead>
<tr>
<th>Number of studies (participants)</th>
<th>Outcome</th>
<th>Comparison</th>
<th>Type of evidence</th>
<th>Quality</th>
<th>Consistency</th>
<th>Directness</th>
<th>Effect size</th>
<th>GRADE</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [Granade 2005]</td>
<td>Diagnostic accuracy</td>
<td>Serial vs. parallel triple rapid testing vs. reference standard</td>
<td>2</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td>Quality point deducted for poor allocation strategy.</td>
</tr>
<tr>
<td>3 [Rouet 2004][Black 2009][Tung 2010]</td>
<td>Diagnostic accuracy</td>
<td>Rapid tests vs. reference standard</td>
<td>2</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td>Quality point deducted for poor sampling.</td>
</tr>
<tr>
<td>1 [Bruzzone 2009]</td>
<td>Diagnostic accuracy</td>
<td>2nd-line testing with rapid test vs. EIA vs. reference standard</td>
<td>2</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td>Quality point deducted for poor recruitment strategy.</td>
</tr>
</tbody>
</table>
## Appendix D - HIV with Concomitant STIs

### 3. HIV with Concomitant STIs

#### Problem Formulation 3

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>Does the presence of other STIs (and by what mechanism, i.e., genital ulcers and other inflammatory STIs) increase the likelihood of transmitting and/or acquiring HIV?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>All persons aged ≥ 12 at risk for acquiring HIV/STI, including known high-risk groups (such as pregnant women, adolescents, men having sex with men).</td>
</tr>
<tr>
<td>Health Intervention</td>
<td>HIV Screening and appropriate treatment tests</td>
</tr>
</tbody>
</table>
| Important Health Outcomes | • Decrease in HIV/STI morbidity and mortality  
• Increased and earlier STI case identification  
• Increased HIV/STI case prevention  
• Benefits/harms of screening (including false negatives/positives)  
• Anxiety, labeling |
## Search Strategy 3

<table>
<thead>
<tr>
<th>Database</th>
<th>Terms</th>
<th>Article Type and Limits</th>
<th>Time Frame</th>
<th>No. Included/Total Retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVID</td>
<td>(exp HIV Infections/ep, tm or (HIV adj3 (transmission$ or acquisition$ or progress$ or mortality)).ti,ab. AND (exp Sexually Transmitted Diseases/ or Chlamydia trachomatis/ or Chlamydia Infections/ or Gonorrhea/ or Neisseria gonorrhoeae/ or exp Syphilis/ or Hepatitis B/ or Hepatitis C/ or Trichomonas vaginalis/ or Trichomonas Vaginitis or (STI or STIs or STD or STDs).ti. or (gonorrhea or gonorrhoea or chlamydia$ or syphilis or hepatitis b or hepatitis c or trichomonas vagin$).ti,ab AND exp Disease Susceptibility/ or (diathesis or comorbid$ or co-infection or susceptib$).ti,ab or (facilitat$ adj3 (transmission or acquisition)).ti,ab.</td>
<td>systematic reviews</td>
<td>5/2010</td>
<td>25/176</td>
</tr>
<tr>
<td>Medline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RCTs</td>
<td>7/2010</td>
<td>44/103</td>
</tr>
<tr>
<td></td>
<td></td>
<td>observational studies</td>
<td>5/2010</td>
<td>45/549</td>
</tr>
</tbody>
</table>

**Additional search (RCTs only):**

Acyclovir/
or (aciclovir or acyclovir).ti,ab.
or ((HSV or herpes simplex virus) adj2 suppressive therapy).ti,ab.
AND exp HIV Infections/
or HIV.ti,ab
<table>
<thead>
<tr>
<th>Database</th>
<th>Terms</th>
<th>Article Type and Limits</th>
<th>Time Frame</th>
<th>No. Included/Total Retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVID Embase</td>
<td>Human immunodeficiency virus infection/ep OR (HIV adj3 (transmission$ or acquisition$ or progress$ or mortality$)).ti,ab OR *Human immunodeficiency virus/ OR *Human immunodeficiency virus infection/ AND exp *sexually transmitted disease/ OR *Chlamydia trachomatis/ OR *chlamydia/ OR *gonorrhea/ OR *Neisseria gonorrhoeae/ OR *syphilis/ OR *hepatitis B/ OR *hepatitis C/ OR *trichomoniasis/ OR *Trichomonas vaginalis/ OR Trichomonas vagin$.ti,ab OR syphilis.ti,ab OR (Hepatitis adj c).ti,ab OR (Hepatitis adj B).ti,ab OR (gonorrhea or gonorrhoea).ti,ab OR chlamydia$.ti,ab AND (diathesis or comorbid$ or co-infection or susceptib$).ti,ab OR disease transmission/ OR risk factor/ OR infection sensitivity/ OR (facilitat$ adj3 (transmission or acquisition)).ti,ab</td>
<td>systematic reviews</td>
<td>5/2010</td>
<td>12/145</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RCTs</td>
<td>7/2010</td>
<td>0/18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>observational studies</td>
<td>5/2010</td>
<td>43/260</td>
</tr>
<tr>
<td>Database</td>
<td>Terms</td>
<td>Article Type and Limits</td>
<td>Time Frame</td>
<td>No. Included/Total Retrieved</td>
</tr>
<tr>
<td>----------</td>
<td>----------------------------------------------------------------------</td>
<td>-------------------------</td>
<td>------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>CENTRAL</td>
<td>HIV near (transmission or acquisition) or HIV Infections/ep, tm AND exp Sexually Transmitted Diseases/ or Chlamydia trachomatis/ or Chlamydia Infections/ or Gonorrhea/ or Neisseria gonorrhoeae/ or exp Syphilis/ or Hepatitis B/ or Hepatitis C/ or Trichomonas vaginalis/ or Trichomonas Vaginitis</td>
<td>RCTs</td>
<td>7/2010</td>
<td>0/2</td>
</tr>
<tr>
<td>CDSR</td>
<td>HIV near (transmission or acquisition) or HIV Infections/ep, tm AND exp Sexually Transmitted Diseases/ or Chlamydia trachomatis/ or Chlamydia Infections/ or Gonorrhea/ or Neisseria gonorrhoeae/ or exp Syphilis/ Hepatitis B/ or Hepatitis C/ or Trichomonas vaginalis/ or Trichomonas Vaginitis</td>
<td>systematic reviews</td>
<td>5/2010</td>
<td>0/0</td>
</tr>
<tr>
<td>Database</td>
<td>Terms</td>
<td>Article Type and Limits</td>
<td>Time Frame</td>
<td>No. Included/Total Retrieved</td>
</tr>
<tr>
<td>----------</td>
<td>-------</td>
<td>-------------------------</td>
<td>------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>DARE</td>
<td>HIV near (transmission or acquisition) or HIV Infections/ep, tm AND exp Sexually Transmitted Diseases/ or Chlamydia trachomatis/ or Chlamydia Infections/ or Gonorrhea/ or Neisseria gonorrhoeae/ or exp Syphilis/ or Hepatitis B/ or Hepatitis C/ or Trichomonas vaginalis/ or Trichomonas Vaginitis</td>
<td>systematic reviews</td>
<td>5/2010</td>
<td>0/0</td>
</tr>
<tr>
<td>HTA</td>
<td>HIV near (transmission or acquisition) or HIV Infections/ep, tm AND exp Sexually Transmitted Diseases/ or Chlamydia trachomatis/ or Chlamydia Infections/ or Gonorrhea/ or Neisseria gonorrhoeae/ or exp Syphilis/ or Hepatitis B/ or Hepatitis C/ or Trichomonas vaginalis/ or Trichomonas Vaginitis</td>
<td>systematic reviews</td>
<td>5/2010</td>
<td>0/0</td>
</tr>
<tr>
<td>TRIP</td>
<td>HIV acquisition AND STI or STD</td>
<td>systematic reviews</td>
<td>5/2010</td>
<td>0/0</td>
</tr>
</tbody>
</table>

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects online database; HTA: Health Technology Assessment online database; OVID Medline and OVID Embase: Medline and Embase via the Ovid platform; RCTs: randomized controlled trials; TRIP: TRIP online database.
**Search Strategy**

The literature review for this clinical question was completed through a collaborative effort with Kaiser Permanente’s Care Management Institute (CMI) and the British Medical Journal’s (BMJ) Evidence Center. The BMJ Evidence Center is world-renowned and responsible for supporting a wide range of evidence-based resources, including literature reviews, development of journal articles, and clinical reference tools.

The structure of this question was such that each study design required multiple database searches for each of the seven included pathogens - HIV, gonorrhea, chlamydia, syphilis, trichomonas, hepatitis B and C. These pathogens were selected based on many factors including incidence, prevalence, and increase in risk of HIV acquisition, transmission and impact on disease progression within the US population. In 2009, the Centers for Disease Control (CDC) and Prevention reported the following – a total of 1,244,180 cases of sexually transmitted Chlamydia trachomatis, the largest number of cases ever reported to CDC for any condition; a total of 301,174 cases of gonorrhea, which corresponds to a rate of 99.1 cases per 100,000 population; a total of 13,997 cases of syphilis, the highest number of cases reported since 1995 and corresponds to a rate of 4.6 cases per 100,000 population; and NHANES data from 2001 to 2004 indicated an overall prevalence of 3.1% of trichomonas cases. The CDC also reports that at the end of 2006, an estimated 1,106,400 persons in the US were living with HIV infection, with 21% undiagnosed, while figures for the number of persons living with hepatitis B and C are approximately 800,000 to1.4 million and 2.7 to 3.9 million for both pathogens, respectively.

The limited scope of this question meant that it was possible to use a single combined subject search strategy for all included pathogens, along with specific search strategies for each study design and relevant database. This resulted in a total of 11 separate searches.

To increase efficiency, BMJ performed searches for systematic reviews (SRs) and guidelines for all pathogens first and then appraised the results. Where an existing SR with suitable methodology and scope was found, it was used as a basis for limiting the search for primary studies to those published after the search date of the chosen SR. Where no suitable SR was identified, BMJ limited the primary study search to the agreed start date of 2000 and end date of May/June 2010.
Evidence Summary
For concomitant STI with HIV transmission, acquisition and progression.

STIs (In General)
There is limited evidence from one randomized controlled study (RCT) that monthly azithromycin added to intensive HIV-reduction strategies may reduce incidence of bacterial STIs but not of HIV in high-risk populations (moderate-quality evidence). Observational studies conducted in sub-Saharan countries found no association between STIs in general and HIV incidence, whereas one small US nested matched case-control study provided limited evidence that recent or concurrent STIs may increase the risk of HIV acquisition in homosexual men (very low-quality evidence).

Chlamydia Trachomatis
- Three cohort studies across a range of high-risk populations and from developed as well as developing countries provided limited evidence that *C. trachomatis* infection may be associated with increased risk of HIV seroconversion (very low-quality evidence).

Gonorrhea
- Six prospective cohort studies conducted mainly in men having sex with men (MSM) in developed countries found consistent evidence of a strong association between gonorrhea, in particular rectal/anal gonorrhea, and HIV seroconversion (low-quality evidence).

Hepatitis B
- One cross-sectional study provided limited evidence for an association between hepatitis B infection and HIV acquisition (low-quality evidence).
- One systematic review of 11 observational studies (including four US studies) found a 36% increase in all-cause mortality but no increase in progression to AIDS in people with concurrent hepatitis B.

Hepatitis C
- No studies that examined the association between hepatitis C infection and subsequent HIV transmission or acquisition were identified.
- In patients with HIV, nineteen observational studies including a total of nearly 43,000 HIV patients mainly in the USA and Europe found inconsistent results for the impact of hepatitis C coinfection on clinical HIV progression or immunological response to HIV treatment (very low-quality evidence). Eight studies with over 24,000 participants found no significant association between hepatitis C coinfection and virological response to HIV therapy (low-quality evidence).
Syphilis

- Four studies found a strong association between recent syphilis infection and newly acquired HIV, but no effect from long-standing (> 6 months) syphilis infection diagnosed prior to HIV seroconversion (low-quality evidence).
- One observational study provided limited evidence that syphilis coinfection may not adversely impact on survival time or time to progression to AIDS* (low-quality evidence).

Trichomoniasis

- One systematic review of seven observational studies conducted in sub-Saharan countries and populations mostly at high-risk of HIV found strong and consistent evidence for a 64% increase risk of acquiring HIV in women with trichomoniasis (low-quality evidence). No studies on men were found.

Evidence Review

One systematic review examined STI prevention randomized controlled studies (RCTs) and identified only one relevant RCT (moderate-quality evidence) (Padian 2010). A second systematic review with two observational studies in men and women respectively (Chen 2007) and one subsequent case control study (Zetola 2009) examined the association between STIs in general (as opposed to specific STIs that are dealt with in other sections) and HIV transmission/acquisition (very low-quality evidence). A third systematic review was found (Sexton 2005) with four studies reporting on HIV exposure, none of which met these inclusion criteria. Please refer to Evidence Tables 3.1 and 3.3 for details.

- The first review (Padian 2010) evaluated interventions aimed at preventing STIs and included one RCT of regular antibiotic therapy in female sex workers in Kenya (Kaul 2004). The RCT found that monthly azithromycin added to intensive HIV-reduction strategies did not significantly reduce HIV incidence despite decreasing incidence of bacterial STIs.

- The second review examined the association between STI history and HIV incidence in sub-Saharan countries, and found no significant difference in meta-analyses of high-risk population studies in women and men (two studies each) (Chen 2007).

- An observational study assessed the role of STIs diagnosed within the twelve and three months preceding HIV testing on HIV acquisition, by comparing their rate in patients with acute HIV versus matched controls without HIV (Zetola 2009). While this was a small US nested matched case-control study that provided very low-quality evidence, the authors found a significant and large difference between groups and concluded that acute HIV infection was associated with a recent or concurrent STI.

- A third review identified four studies reporting data on HIV exposure, none of which met the inclusion criteria (Sexton 2005).

---

* AIDS-defining opportunistic illness, as clinically defined by the Centers for Disease Control and Prevention classification, includes Pneumocystis jiroveci [formerly P. carinii] pneumonia, cytomegalovirus infection, candidiasis, Kaposi sarcoma, any lymphoma, toxoplasmosis, and AIDS-associated diarrheas.
**Chlamydia Trachomatis**

Three cohort studies across a range of high-risk populations and from developed as well as developing countries (Van de Wijgert 2009, Jin 2007, Sharghi 2005)\(^{(48-50)}\) provided limited evidence that Chlamydia trachomatis (infection may be associated with increased risk of HIV seroconversion (very low-quality evidence). Please refer to Evidence Table 3.4 for details.

- Van de Wijgert et al. followed a cohort of HIV-uninfected women attending family planning clinics in two African countries with high HIV prevalence, and reported significantly increased risk of HIV acquisition associated with *C. trachomatis* infection only if including the clinic visit prior to HIV detection in the analysis (HR = 2.65) (Van de Wijgert 2009).\(^{(48)}\)

- Sharghi et al. examined the impact of self-reported recent *C. trachomatis* infection, gonorrhea, or nonspecific urethritis in a cohort of US adults at high risk of HIV and found a significant association with HIV seroconversion at 18 months (adjusted OR = 3.91) (Sharghi 2005).\(^{(50)}\)

- Jin et al. compared HIV-positive versus HIV-negative cohorts of MSM in Australia and found higher prevalence of both urethral and anal *C. trachomatis* infection in men with HIV (age-adjusted OR 2.4 and 1.5 respectively), although the differences did not reach statistical significance.

**Gonorrhea**

Six prospective cohort studies conducted mainly in MSM in developed countries (Jin 2010, Zetola 2009, Jin 2007, Van de Wijgert 2009, Sharghi 2005, Van der Bij 2005)\(^{(45, 48-52)}\) examined the role of gonorrhea in HIV acquisition (low-quality evidence). They found consistent evidence of a strong association between gonorrhea, in particular rectal/anal gonorrhea, and HIV seroconversion. Please refer to Evidence Table 3.5 for details.

- Three studies in Australian and US MSM showed significant and consistent evidence that rectal/anal gonorrhea is associated with an increased risk of HIV acquisition by a factor of at least three but found no such effect from urethral or pharyngeal gonorrhea (Jin 2010, Zetola 2009, Jin 2007).\(^{(45, 49, 51)}\)

- Similarly, a fourth study in women attending family planning clinics in Zimbabwe and Uganda demonstrated that gonorrhea identified at the time of HIV detection and/or a prior visit was significantly associated with increased risk of HIV acquisition (Van de Wijgert 2009).\(^{(48)}\)

- Sharghi et al. showed that self-reported gonorrhea, chlamydia infection, and unspecific urethritis increased HIV seroconversion in US citizens at high risk of HIV at 18 months (Sharghi 2005).\(^{(50)}\)

- The sixth study in Dutch MSM found that having concurrent gonorrhea or syphilis was also associated with increased HIV incidence although the difference did not reach statistical significance (Van der Bij 2005).\(^{(52)}\)
Hepatitis B

One cross-sectional study (Jin 2007)\(^{(49)}\) provided limited evidence for an association between hepatitis B infection and HIV (low-quality evidence). Please refer to Evidence Table 3.6 for details.

- Jin et al. compared cohorts of HIV-positive versus HIV-negative homosexual men in Australia and found significantly increased prevalence of current and previous hepatitis B infection in HIV patients. (Jin 2007)\(^{(49)}\) They also demonstrated that HIV was associated with significantly lower rates of hepatitis B vaccination.

Regarding HIV progression, one systematic review of 11 observational studies (including four US studies) found a 36% increase in all-cause mortality but no increase in progression to AIDS in people with concurrent hepatitis B.

One systematic review (Nikolopoulos 2009)\(^{(53)}\) assessed the impact of hepatitis B on all-cause mortality and HIV progression to AIDS-defining events, and four additional or subsequent studies (Hoffmann 2009, Law 2004, Lincoln 2003, De Luca 2002)\(^{(54-57)}\) also examined the association between hepatitis B and immunological and virological progression. Please refer to Evidence Tables 3.6 and 3.9 for details.


- Hoffmann et al. evaluated AIDS- and non-AIDS-related mortality, progression to AIDS-defining events, and virological and immunological progression in 816 US homosexual HIV patients. They found no association between HIV-related outcomes and hepatitis B coinfection, although one analysis showed a significant increase in non-AIDS-related death in co-infected people, mainly due to liver disease.

- None of the other three observational studies conducted in Thailand, Australia and Italy, and including a total of nearly 5,000 men and women with HIV found significant association between hepatitis B coinfection and clinical, immunological or virological HIV-related progression (Law 2004, Lincoln 2003, De Luca 2002).\(^{(55-57)}\)

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\* AIDS-defining opportunistic illness, as clinically defined by the Centers for Disease Control and Prevention classification, includes Pneumocystis jiroveci [formerly P. carinii] pneumonia, cytomegalovirus infection, candidiasis, Kaposi sarcoma, any lymphoma, toxoplasmosis, and AIDS-associated diarrheas.
Hepatitis C

No studies that examined the association between hepatitis B infection and subsequent HIV transmission or acquisition were identified. However, several observational studies were found regarding hepatitis C and HIV coinfection.


- Of these, five prospective studies assessed all-cause mortality. (Sulkowski 2002, Hung 2005, Rockstroh 2005, Voirin 2004, Tedaldi 2003) (71, 76, 77, 80, 82) Rockstroh et al. found a significant increase in all-cause mortality (adjusted incidence rate ratio [IRR] 1.8) but found a much stronger association with liver disease-related death (adjusted IRR 12.31). Only one other study showed a significant association in the subgroup of intravenous drug users during the HAART era (adjusted hazard ratio [HR] 2.9) (Voirin 2004). (80)

- However, in a prospective study, Kovacs et al. reported a significantly higher incidence of AIDS-related death in hepatitis C-positive viremic women compared with hepatitis C-negative women (p-value < 0.03).

- One prospective (Macias 2002)(83) and two retrospective studies (Anderson 2005, Sullivan 2006) (13, 75) examined the impact of hepatitis C coinfection on survival time, with only Anderson et al. reporting significant shortening both from time of HIV (HR = 2.47) and AIDS diagnosis (HR = 1.84).
Progression to AIDS-defining events* was evaluated in six prospective studies showing conflicting results (Sulkowski 2002, Kovacs 2010, Hung 2005, Rockstroh 2005, Stebbing 2005, Mayer 2003). Two studies reported significantly higher rates (HR = 1.52, OR in women with baseline DS4 counts > 500 cells/mm² 3.22) (Stebbing 2005, Mayer 2003) whereas one study demonstrated a significantly lower incidence of progression to AIDS-defining illness in hepatitis C coinfected patients (adjusted IRR 0.78) (Rockstroh 2005).

One prospective (Lincoln 2003) and two retrospective studies (Sullivan 2006, Anderson 2005) examined time to progression to AIDS, none of which reported significant results.

Two of four prospective studies found significant results for composite outcomes of all-cause mortality and progression to AIDS* (HR = 1.7 and 2.4) (Greub 2000, Jaen 2004, Law 2004, Rockstroh 2005). Two prospective studies evaluating time to any death or AIDS reported accelerated clinical progression in hepatitis C coinfection (HR 1.55 and 1.63) (De Luca 2002, Piroth 2000). On the other hand, one retrospective analysis found no significant impact from hepatitis C on progression to AIDS-related death or AIDS-related event* (Carmo 2008).


Five prospective (Greub 2000, Law 2004, Lincoln 2003, De Luca 2002, Rockstroh 2005) and three retrospective studies (Chung 2002, Carmo 2008, Sullivan 2006) examined the impact of hepatitis C coinfection on virological response to HIV therapy with a small retrospective analysis with short follow-up (16 weeks) reporting a significantly higher rate of HIV RNA suppression to < 500 copies/mL in hepatitis C-positive vs. negative HIV patients (p-value = 0.04) (Chung 2002).

*AIDS-defining opportunistic illness, as clinically defined by the Centers for Disease Control and Prevention classification, includes Pneumocystis jiroveci [formerly P. carinii] pneumonia, cytomegalovirus infection, candidiasis, Kaposi sarcoma, any lymphoma, toxoplasmosis, and AIDS-associated diarrohas.
Syphilis
Four observational studies mainly in high-risk homosexual men (MSM, men having sex with men) examined the association between syphilis and HIV acquisition (low-quality evidence) (Sanchez 2009, Reynolds 2006, Jin 2007, Zetola 2009). They found a strong association between recent syphilis infection and newly acquired HIV (odds ratios ranging from 3.7 to 5.9) but no effect from long-standing (> six months) syphilis infection diagnosed prior to HIV seroconversion (Sanchez 2009, Reynolds 2006, Jin 2007, Zetola 2009). Please refer to Evidence Table 3.7 for details.

- Despite limited methodological quality, there was consistent and strong evidence from five studies pointing towards an independent association between recent syphilis infection and newly acquired HIV infection (Sanchez 2009, Reynolds 2006, Jin 2007, Zetola 2009).

- One study evaluated HIV incidence following a cohort of high-risk HIV-negative MSM in Peru, and found a significant association between HIV seroconversion and recently acquired syphilis or HSV-2 infection (adjusted odds ratio 5.9) (Sanchez 2009).

- Reynolds et al. also followed a cohort of both HIV and syphilis-negative adults attending an STI clinic in India, and found a strong association between newly acquired HIV and syphilis co-infection (adjusted hazard ratio 4.4) but no significant effects in the group with syphilis infection diagnosed > six months prior to HIV seroconversion and analyzing the data of HIV-negative but syphilis-positive participants clinic attendants (Reynolds 2006).

- Two studies measured the prevalence of concurrent syphilis comparing patient groups with and without HIV infection, and also found statistically significant adjusted odds ratios of 3.7 and 5.8 (Jin 2007, Zetola 2009).

- One observational study assessed the impact of syphilis on HIV progression, and found that syphilis co-infection did not adversely impact survival time or time to progression to AIDS (Weintrob 2010). Please refer to Evidence Table 3.7 for details.

- Weintrob et al. followed a cohort of mainly male HIV seroconverters and found no significant difference in HIV progression (defined as time to AIDS* or death) in people with or without confirmed syphilis (Weintrob 2010).

Trichomoniasis
One systematic review (Hilber 2010) identified seven observational studies conducted in sub-Saharan countries and populations mostly at high-risk of HIV (McClelland 2007, Myer 2006, Ghys 2001, Hester 2003, Kapiga 2007, Kleinschmidt 2007) that examined the role of trichomoniasis as risk factor for HIV transmission or acquisition in women (very low-quality evidence). Please refer to Evidence Table 3.2 for details.

- The review found strong and consistent evidence from seven observational studies that trichomoniasis increases women’s risk of acquiring HIV (adjusted effect 1.64, 95% CI: 1.28 to 2.09) (Hilber 2010).

* AIDS-defining opportunistic illness, as clinically defined by the Centers for Disease Control and Prevention classification, includes Pneumocystis jiroveci [formerly P. carinii] pneumonia, cytomegalovirus infection, candidiasis, Kaposi sarcoma, any lymphoma, toxoplasmosis, and AIDS-associated diarrheas.
### Evidence Tables 3

#### Systematic Reviews

**Evidence Table 3.1: HIV Transmission/Acquisition in STIs**

<table>
<thead>
<tr>
<th>Author &amp; Title</th>
<th>Search Database / Method</th>
<th>Study Characteristics</th>
<th>Results</th>
<th>Conclusions/ Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Padian et al. (2010)</strong>&lt;br&gt;Weighing the gold in the gold standard: Challenges in HIV prevention research.</td>
<td><strong>Databases:</strong>&lt;br&gt;Medline, Embase, Cochrane Library, Web of Science.&lt;br&gt;<strong>Other sources:</strong>&lt;br&gt;Not reported.</td>
<td><strong>N:</strong>&lt;br&gt;9 RCTs (59,200 non-pregnant people with STIs) on STI prevention and treatment, of which 1 RCT (Kaul 2004) met our inclusion criteria: 466 FSWs randomized to monthly azithromycin prophylaxis vs. control.</td>
<td><strong>Kaul 2004:</strong>&lt;br&gt;HIV incidence: No significant difference between groups: IRR at 2 years 1.2, 95%CI 0.6 to 2.5, p-value</td>
<td><strong>Kaul 2004:</strong>&lt;br&gt;&quot;Addition of monthly azithromycin prophylaxis to established HIV-1 risk reduction strategies substantially reduced the incidence of bacterial STIs but did not reduce the incidence of HIV-1.&quot;</td>
</tr>
<tr>
<td><strong>Funding:</strong>&lt;br&gt;SR: Bill and Melinda Gates Foundation.&lt;br&gt;National Institute of Allergy and Infectious Diseases.</td>
<td><strong>Search period:</strong>&lt;br&gt;Until December 2009</td>
<td><strong>Age:</strong>&lt;br&gt;Not reported;&lt;br&gt;Kaul 2004: &gt;18 years, mean age 29 years</td>
<td><strong>Incidence of bacterial STIs:</strong>&lt;br&gt;Significant reduction with treatment vs. control in some STIs: Gonorrhea RR, 0.46; 95% CI 0.31-0.68&lt;br&gt;C. trachomatis RR, 0.38; 95% CI 0.26-0.57&lt;br&gt;T. vaginalis RR, 0.56; 95% CI, 0.40-0.78 No difference between groups in bacterial vaginosis (RR 0.91, 96% CI 0.77-1.10) or syphilis (RR 1.02, 96% CI 0.54-1.95)</td>
<td>Level of care provided was higher than usual care in both groups (free condom provision, prompt STI treatment, regular 6-monthly STI screening; together with an observed decline in client rates in both groups, this may have contributed to the lower than expected HIV incidence (only 35 new cases instead of expected 54) Retention rate 73.1%</td>
</tr>
<tr>
<td><strong>Kaul 2004:</strong> Rockefeller Foundation (2000 HE 025), European Commission (DG VIII/8, contract No. 7-RPR-28), Canadian Research Chair Programme, Ontario HIV Treatment Network, Canadian Institutes of Health Research, and the Canadian Infectious Disease Society; study drug and placebo provided by Pfizer Inc.</td>
<td><strong>Search terms:</strong>&lt;br&gt;Not provided in paper, but available from authors; incl HIV infection terms, incidence or hazard, prevention, and a study design filter.</td>
<td><strong>Setting:</strong>&lt;br&gt;Range of settings for interventions;&lt;br&gt;Kaul 2004: STI clinic in Nairobi, Kenya</td>
<td><strong>Incidence of bacterial STIs:</strong>&lt;br&gt;Significant reduction with treatment vs. control in some STIs: Gonorrhea RR, 0.46; 95% CI 0.31-0.68&lt;br&gt;C. trachomatis RR, 0.38; 95% CI 0.26-0.57&lt;br&gt;T. vaginalis RR, 0.56; 95% CI, 0.40-0.78 No difference between groups in bacterial vaginosis (RR 0.91, 96% CI 0.77-1.10) or syphilis (RR 1.02, 96% CI 0.54-1.95)</td>
<td>Level of care provided was higher than usual care in both groups (free condom provision, prompt STI treatment, regular 6-monthly STI screening; together with an observed decline in client rates in both groups, this may have contributed to the lower than expected HIV incidence (only 35 new cases instead of expected 54) Retention rate 73.1%</td>
</tr>
<tr>
<td><strong>Reported relevant outcomes/outcome measures:</strong>&lt;br&gt;HIV incidence with STI treatment</td>
<td><strong>Method:</strong>&lt;br&gt;No meta-analysis&lt;br&gt;- No formal testing of publication bias reported.</td>
<td><strong>Inclusion criteria:</strong>&lt;br&gt;Types of studies&lt;br&gt;RCTs which evaluated interventions focusing on HIV transmission in nonpregnant populations, reporting HIV incidence</td>
<td><strong>Incidence of bacterial STIs:</strong>&lt;br&gt;Significant reduction with treatment vs. control in some STIs: Gonorrhea RR, 0.46; 95% CI 0.31-0.68&lt;br&gt;C. trachomatis RR, 0.38; 95% CI 0.26-0.57&lt;br&gt;T. vaginalis RR, 0.56; 95% CI, 0.40-0.78 No difference between groups in bacterial vaginosis (RR 0.91, 96% CI 0.77-1.10) or syphilis (RR 1.02, 96% CI 0.54-1.95)</td>
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<td><strong>Exclusion criteria:</strong>&lt;br&gt;Non-RCTs, not reporting HIV incidence.</td>
<td><strong>Incidence of bacterial STIs:</strong>&lt;br&gt;Significant reduction with treatment vs. control in some STIs: Gonorrhea RR, 0.46; 95% CI 0.31-0.68&lt;br&gt;C. trachomatis RR, 0.38; 95% CI 0.26-0.57&lt;br&gt;T. vaginalis RR, 0.56; 95% CI, 0.40-0.78 No difference between groups in bacterial vaginosis (RR 0.91, 96% CI 0.77-1.10) or syphilis (RR 1.02, 96% CI 0.54-1.95)</td>
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<td>Level of care provided was higher than usual care in both groups (free condom provision, prompt STI treatment, regular 6-monthly STI screening; together with an observed decline in client rates in both groups, this may have contributed to the lower than expected HIV incidence (only 35 new cases instead of expected 54) Retention rate 73.1%</td>
</tr>
<tr>
<td>Author &amp; Title</td>
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<tr>
<td>Chen et al. (2007)</td>
<td>Databases: Embase, Medline, PreMed, Web of Science. Other sources: None reported</td>
<td>N: Overall 68 epidemiological studies (17,000 HIV-positive adults and 73,000 controls) incl 18 high-risk studies and 4 general population studies recategorised as high-risk. High-risk population reporting history of STI as risk factor: 2 studies in women and 2 studies in men (no references or study sizes given). Age: Not reported. Setting: High-risk population studies: truck drivers, FSWs, hotel and bar workers and STI clinics attendees in sub-Saharan Africa. Inclusion criteria: Types of studies: Studies reporting details on demographic data, HIV-seropositive participants and controls, methods of diagnosing STI, other study and population characteristics (not reported). Exclusion criteria: Studies looking at male circumcision, unpublished, or in language other than French or English. Poor quality, insufficient size, non-pertinent population (details of these not given).</td>
<td>HIV incidence in high-risk population studies: Women with vs. women without history of STI (2 studies): Summary OR 1.05, 95%CI 0.68 to 1.63 Men with vs. men without history of STI (2 studies): Summary OR 2.22, 95%CI 0.95 to 5.16</td>
<td>Meta-analyses showed no significant difference in HIV incidence between people with and without history of STIs. Review included very few longitudinal studies (668); no causality mechanisms; small number of relevant studies. STI history defined as a clinical history of chancroid, herpes, syphilis, genital warts, chlamydia, gonorrhea or trichomoniasis confirmed by laboratory testing or clinical examination.</td>
</tr>
<tr>
<td>Author &amp; Title</td>
<td>Search Database / Method</td>
<td>Study Characteristics</td>
<td>Results</td>
<td>Conclusions/ Limitations</td>
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<tr>
<td>Sexton et al. (2005)</td>
<td><strong>Databases:</strong> Medline, PreMedline. <strong>Other sources:</strong> None reported.</td>
<td><strong>N:</strong> 31 studies identified, 4/31 reporting data on HIV exposure, none of which met our inclusion criteria (published prior to 2000).</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td><strong>Search period:</strong> 2000-2003</td>
<td><strong>Age:</strong> Not reported.</td>
<td></td>
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<tr>
<td></td>
<td><strong>Search terms:</strong> HIV infections OR HIV AND Sexually Transmitted Diseases[Text word] OR STDs[Text word] OR Sexually Transmitted Diseases, Bacterial OR Herpes genitalis OR Herpes Simplex OR Herpesvirus 1, Human OR Herpesvirus 2, Human OR Syphilis OR Chancroid OR Treponema pallidum OR Chancroid OR Haemophilus ducreyi OR Gonorrhea OR Neisseria gonorrhoeae OR Chlamydia infections OR Lymphogranuloma venereum OR Chlamydia trachomatis OR Trichomonas vaginalis OR Trichomonas vaginalis OR Vaginosis, bacterial OR Cervicitis OR Urethritis.</td>
<td><strong>Setting:</strong> Range of settings including STI clinics and workplace.</td>
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<tr>
<td></td>
<td><strong>Reported relevant outcomes/outcome measures:</strong> Effects of other STIs on HIV-1 susceptibility, HIV transmission risk with any STD</td>
<td><strong>Inclusion criteria:</strong> Types of studies No criteria reported.</td>
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<tr>
<td></td>
<td><strong>Method:</strong> Meta-analysis: Mixed-effects metaregression model and random-effects model.</td>
<td><strong>Exclusion criteria:</strong> No criteria reported.</td>
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<td></td>
<td></td>
<td><strong>No formal testing of publication bias reported.</strong></td>
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</tbody>
</table>

FSWs: Female sex workers; IRR: Incidence rate reduction; OR: Odds ratio; RCT: Randomized controlled trial; RR: Relative risk
### Evidence Table 3.2: HIV Transmission/Acquisition in Trichomoniasis

<table>
<thead>
<tr>
<th>Author &amp; Title</th>
<th>Search database / Method</th>
<th>Study characteristics</th>
<th>Results</th>
<th>Conclusions/ Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hilber et al. (2010)</td>
<td>Databases: EMBASE, MEDLINE, CINAHL, Cochrane Library, ERIC databases; ten other databases including GHL, Popline and WHO regional indexes</td>
<td>Overall: 15 prospective studies</td>
<td>HIV incidence with trichomoniasis: Unadjusted effect (7 studies): 1.78, 95%CI 1.42–2.23, p-value not reported; no between study heterogeneity</td>
<td>“This study showed strong and consistent evidence that trichomoniasis increases women’s risk of acquiring HIV.”</td>
</tr>
<tr>
<td></td>
<td>Other sources: Handsearch of conference abstracts from the International AIDS Society Conferences, the Conference on Retroviruses and Opportunistic Infections, the International Society for STD Research, and Microbicides conferences since 1990; reference lists of included papers, systematic reviews, letters and commentaries; contact with experts</td>
<td>Association between trichomoniasis and HIV infection: 7 prospective cohort studies (7715 women, mostly high risk population)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Search period: Earliest dates up to 31st January 2008</td>
<td>Age: Not reported</td>
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</tr>
<tr>
<td></td>
<td>Search terms: Subject headings/thesaurus terms: HIV, bacterial vaginosis, trichomoniasis, candidiasis</td>
<td>Location: Overall: 13/15 studies in sub-Saharan Africa; 2/15 in USA</td>
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<tr>
<td></td>
<td>Free text terms and wildcard characters related to intravaginal practices incl vagina, vulva, intravaginal, dry sex, cleansing, cleaning, washing, cutting, douching, insertion, practice, lubrication, microbicide and genital lesions</td>
<td>Association between trichomoniasis and HIV infection: Kenya (x2), South Africa (x3), Côte d’Ivoire, Zambia, Tanzania, Malawi</td>
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<tr>
<td></td>
<td>Reported relevant outcomes/outcome measures: HIV-1 incidence.</td>
<td>Setting: Association between trichomoniasis and HIV infection: STI clinic (x3), cervical cancer screening (x2), living with HIV partner, women working in bars, family planning clinic, antenatal clinic (incl postnatal follow-up)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Method: Random-effects meta-analyses presented as Forest plots of adjusted and unadjusted effect sizes.</td>
<td>Inclusion criteria: Types of studies</td>
<td></td>
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<tr>
<td></td>
<td>- Testing of publication bias with funnel plots.</td>
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<td></td>
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<td>Exclusion criteria: Cross-sectional studies, editorials, commentaries, letters without original data and case reports.</td>
<td></td>
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</tbody>
</table>
### Individual Studies

#### Evidence Table 3.3: HIV Transmission/Acquisition in STIs in General

<table>
<thead>
<tr>
<th>Name</th>
<th>Design</th>
<th>N</th>
<th>Sample ages</th>
<th>% Female</th>
<th>Follow-up Rate</th>
<th>Follow-up Time</th>
<th>Risk Factor</th>
<th>Adjusted OR</th>
<th>95% CI, p-Value</th>
<th>Data Analysis</th>
<th>Comment/ Study Quality/ Biases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zetola 2009</td>
<td>1. Matched case-control study between October 2003 and March 2007 in San Francisco, USA</td>
<td>13,662 MSM attending an STI clinic for HIV testing in Rotterdam, the Netherlands; 350/13,662 [2.56%] testing positive for HIV compared vs. 144/13,312 HIV-negative participants randomly selected as controls for matched case-control analyses</td>
<td>33 yrs (mean)</td>
<td>0%</td>
<td>None</td>
<td>n/a</td>
<td>Concurrent STIs in acute HIV diagnosed in previous 12 months compared without HIV</td>
<td>5.2</td>
<td>2.2 to 12.6, p=0.000</td>
<td>Conditional logistic regression</td>
<td>Small sample size; cases and controls may have differed in unmeasured characteristics; results not generalizable to other MSM or non-MSM populations; study conducted as part of routine HIV testing potentially leading to selection and referral bias; temporality of HIV not possible to determine</td>
</tr>
<tr>
<td>Zetola 2009</td>
<td>2. Infected analysis</td>
<td>36/350 [10.3%] diagnosed as having acute HIV (positive HIV RNA result in HIV antibody-negative specimen) compared vs. 314/350 [89.7%] chronic HIV infection</td>
<td>33 yrs (mean)</td>
<td>0%</td>
<td>None</td>
<td>n/a</td>
<td>Concurrent STIs in acute HIV diagnosed in previous 3 months compared with chronic HIV</td>
<td>1.4</td>
<td>1.0 to 2.0, p=0.060</td>
<td></td>
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</tr>
<tr>
<td>Zetola 2009</td>
<td>3. Case-crossover analysis</td>
<td>25/36 [70%] acute HIV cases providing data on 54 prior clinic visits</td>
<td>33 yrs (mean)</td>
<td>0%</td>
<td>None</td>
<td>n/a</td>
<td>Concurrent STIs in acute HIV cases diagnosed in previous 12 months compared with themselves at a prior visit</td>
<td>1.3</td>
<td>0.5 to 3.1, p=0.560</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 3.4: HIV Transmission/Acquisition in C. Trachomatis Infection

<table>
<thead>
<tr>
<th>Name</th>
<th>Design</th>
<th>N</th>
<th>Sample Ages</th>
<th>% Female</th>
<th>Follow-up Rate</th>
<th>Follow-up Time</th>
<th>Add'l Variable</th>
<th>Risk Factor on Outcome</th>
<th>Adjusted OR unless otherwise specified</th>
<th>95% CI</th>
<th>Data Analysis Comments/ Study Quality/ Biases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van de Wijgert 2009 Prospective cohort study between November 1999 and January 2004</td>
<td>4,439 HIV-uninfected women attending family planning clinics in Zimbabwe &amp; Uganda; HIV prevalence at screening: 39% in Zimbabwe and 17% in Uganda; HIV incidence: in Zimbabwe 4.1/100 women-years of follow-up (138 new cases) and in Uganda; HIV incidence was 1.3/100 women-years of follow-up (general population) and 2.6/100 woman-years of follow-up (high risk population), (51 new cases); overall HIV incidence 1.5/100 woman-years of follow-up (189 new cases); C. trachomatis prevalence at enrolment: in Zimbabwe 3%, in Uganda 2.9%, overall 3%; C. trachomatis incidence: in Zimbabwe 3.7/100 woman-years of follow-up, in Uganda 4.1/100 woman-years of follow-up</td>
<td>18 to 35 years, mean age 25 years</td>
<td>100%</td>
<td>7776 person-years of follow-up over 31,197 follow-up visits; median time between study visits 3 months</td>
<td>Mean follow-up 23.3 months</td>
<td>Country</td>
<td>Chlamydia identified at same visit with HIV detection on risk of HIV acquisition in Zimbabwe</td>
<td>HR 1.95</td>
<td>1.0 to 3.8 (p-value=0.05)</td>
<td>Multivariable Cox proportional hazards model Incidents of C. trachomatis were defined as a positive PCR test after a negative test at the previous visit. Temporal relationships between chlamydia and HIV acquisition remain uncertain because of infection detection delays, STI persistence in the genital tracts, and the fact that some STI episodes may have gone unnoticed because the interval between study visits was approximately 3 months. To minimize uncertainty, authors used HIV DNA PCR to better time the HIV transmission event, encouraged women to visit the study clinic in case of symptoms; did statistical analyses for various observation periods before HIV detection. High 24 months retention rates: 92% in Zimbabwe and 97% in Uganda Not possible to differentiate between persistent and recurrent infections.</td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td>Design</td>
<td>Sample Size</td>
<td>Sample Ages</td>
<td>% Female</td>
<td>Follow-up Rate</td>
<td>Follow-up Time</td>
<td>Add'l Variable</td>
<td>Risk Factor on Outcome</td>
<td>Adjusted OR unless otherwise specified</td>
<td>95% CI</td>
<td>Data Analysis</td>
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<tr>
<td>Sharghi 2005</td>
<td>Prospective cohort study (1995 to 1997) USA</td>
<td>4,652 high-risk participants in the HIV Network for Prevention Trials (HIVNET) Vaccine Preparedness Study; HIV incidence: 86/4652 (2004/4652 HIV seroconverters incl 13 women); overall annual seroconversion rate 1.3/100 person-years</td>
<td>&gt;18 years; percentages given for 3 age groups</td>
<td>17.4%</td>
<td>6-monthly</td>
<td>18 months</td>
<td>Self-reported recent Chlamydia, nonspecific urethritis or gonorrhea infection on HIV seroconversion by 18 months</td>
<td>3.91</td>
<td>1.93 to 7.91, <em>p</em> value&lt;0.0001</td>
<td>Multi variate models</td>
<td>High-risk defined as: In men - Reported anal sex with ≥2 men in the past year or injected drugs at least once in the previous 6 months. In women - Reported injecting drugs within the previous 6 months; reported current relationship with a man who was HIV-1 positive, who had sex with other men, who reported injection drug use in the past 5 years, or who was diagnosed with syphilis, gonorrhea, or Chlamydia infection; or reported one of the following behaviors within the past year: exchanging sex for money or drugs, “crack” cocaine use, having ≥ 10 male partners, or had a diagnosis of syphilis, gonorrhea, chancroid, pelvic inflammatory disease, trichomoniasis, or an initial episode of genital herpes. HIV-1 seroconversion diagnosed using HIV enzyme-linked immunosorbent assay (ELISA) and confirmed by Western Blot; Clinical symptoms assessed by providing a list of symptoms and asking participants if they had experienced any of them since their prior study visit; STIs assessed by providing a list of common infections and asking the participants whether a medical provider had diagnosed or treated them for any of the infections since their last interview; Retention rate 88%; Potential recall bias due to self-reporting of STIs; appropriate laboratory tests for acute HIV-1 infection not conducted; scoring system not validated in a separate validation population; no subgroup analysis by risk possible due to limited sample size; composite risk factor assessment (Chlamydia, nonspecific urethritis, gonorrhea).</td>
</tr>
<tr>
<td>Name Design</td>
<td>N</td>
<td>Sample Ages</td>
<td>% Female</td>
<td>Follow-up Rate</td>
<td>Follow-up Time</td>
<td>Add'l Variable</td>
<td>Risk Factor on Outcome</td>
<td>Adjusted OR unless otherwise specified</td>
<td>95% CI</td>
<td>Data Analysis</td>
<td>Comments/Study Quality/ Biases</td>
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<tr>
<td>Jin 2007 Comparison of a HIV-positive (enrolled 2001 to 2006) and HIV-negative (enrolled 2001 to 2004) cohorts in Sydney, Australia</td>
<td>1,622 MSM; 226/1622 [13.9%] HIV-positive and 1396/1622 [86.1%] HIV-negative</td>
<td>Median age in HIV-positive cohort: 45 years; median age in HIV-negative cohort: 35 years</td>
<td>0%</td>
<td>Annual</td>
<td>Not reported.</td>
<td>Concurrent urethral chlamydia</td>
<td>2.4</td>
<td>0.8 to 7.2, p-value = 0.10</td>
<td>Age-adjustment</td>
<td>Comparison of C. trachomatis infection prevalence in HIV-positive vs. negative cohorts rather than HIV incidence</td>
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<td></td>
<td>Concurrent anal chlamydia</td>
<td>1.5</td>
<td>0.8 to 2.8, p-value = 0.25</td>
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</tr>
</tbody>
</table>

*C. trachomatis*: Chlamydia trachomatis; HR: Hazard ratio; OR: Odds ratio; MSM: Men who have sex with men; PCR: Polymerase chain reaction
### Evidence Table 3.5: HIV Transmission/Acquisition in Gonorrhea

<table>
<thead>
<tr>
<th>Design</th>
<th>Name</th>
<th>N</th>
<th>Sample Ages</th>
<th>% Female</th>
<th>Follow-up Rate</th>
<th>Follow-up Time</th>
<th>Add’l Variable 1</th>
<th>Add’l Variable 2</th>
<th>Risk Factor on Outcome</th>
<th>OR</th>
<th>95% CI, p-value</th>
<th>Data Analysis</th>
<th>Comment/ Study Quality/ Biases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community-based</td>
<td>Jin 2010 Community-</td>
<td>About 1427 MSM in the Health in Men (HIM) study, followed up to the end of June 2007</td>
<td>Median age 35 years; ranging from 18 to 75 years</td>
<td>0%</td>
<td>annual</td>
<td>2 years, 516 person-years, median 3.9 years per participant</td>
<td>Urethral gonorrhea</td>
<td>Interval diagnosis</td>
<td>Study visit diagnosis</td>
<td>HR: 1.37</td>
<td>0.33 to 5.66, p-value=0.665</td>
<td>Multivariate Cox regression models</td>
<td>Interval diagnoses: Self-reported diagnoses between study visits; Study visit diagnoses: Diagnosis made at study visits through screening tests; Retention at 1 and 2 years 87% and 81% respectively</td>
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<tr>
<td>prospective cohort study</td>
<td>based on June 2001 to December 2004</td>
<td>Sydney, Australia</td>
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<td></td>
<td>Zetola 2009</td>
<td>13,662 MSM attending an STI clinic for HIV testing; 350/13,662 [2.56%] testing positive for HIV compared vs. 144/13,312 HIV-negative participants randomly selected as controls for matched case-control analyses</td>
<td>33 years</td>
<td>0%</td>
<td>None</td>
<td>n/a</td>
<td>Rectal</td>
<td>Concurrent gonorrhea in acute HIV compared without HIV</td>
<td>17.0</td>
<td>2.6 to 111.4, p-value=0.003</td>
<td>Conditional logistic regression</td>
<td>Small sample size; cases and controls may have differed in unmeasured characteristics; results not generalizable to other MSM or non-MSM populations; study conducted as part of routine HIV testing potentially leading to selection and referral bias; temporality of HIV and gonorrhea infections not possible to determine; comparing gonorrhea prevalence in patients with positive HIV RNA result vs. matched controls rather than HIV incidence</td>
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<tr>
<td></td>
<td>1. Matched case-control study between October 2003 and March 2007 in San Francisco, USA</td>
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<td>Zetola 2009</td>
<td>13,662 MSM attending an STI clinic for HIV testing; 350/13,662 [2.56%] testing positive for HIV compared vs. 144/13,312 HIV-negative participants randomly selected as controls for matched case-control analyses</td>
<td>33 years</td>
<td>0%</td>
<td>None</td>
<td>n/a</td>
<td>Rectal</td>
<td>Concurrent gonorrhea in acute HIV compared without HIV</td>
<td>17.0</td>
<td>2.6 to 111.4, p-value=0.003</td>
<td>Conditional logistic regression</td>
<td>Small sample size; cases and controls may have differed in unmeasured characteristics; results not generalizable to other MSM or non-MSM populations; study conducted as part of routine HIV testing potentially leading to selection and referral bias; temporality of HIV and gonorrhea infections not possible to determine; comparing gonorrhea prevalence in patients with positive HIV RNA result vs. matched controls rather than HIV incidence</td>
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<td>2. Infected analysis</td>
<td>36/350 [10.3%] diagnosed as having acute HIV (positive HIV RNA result in HIV antibody-negative specimen) compared vs. 314/350 [89.7%] chronic HIV infection</td>
<td>33 years</td>
<td>0%</td>
<td>None</td>
<td>n/a</td>
<td>Rectal</td>
<td>Concurrent gonorrhea in acute HIV compared with chronic HIV</td>
<td>2.7</td>
<td>(0.8 to 8.8, p-value=0.111</td>
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<td>3. Case-crossover</td>
<td>25/36 [70%] acute HIV cases providing data on 54 prior clinic visits</td>
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<td>Name</td>
<td>Design</td>
<td>N</td>
<td>Sample Ages</td>
<td>% Female</td>
<td>Follow-up Rate</td>
<td>Follow-up Time</td>
<td>Add'l Variable 1</td>
<td>Risk Factor on Outcome</td>
<td>OR</td>
<td>95% CI, p-value</td>
<td>Data Analysis</td>
<td>Comment/Study Quality/ Biases</td>
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<tr>
<td>Jin 2007</td>
<td>Comparison of a HIV-positive (enrolled 2001 to 2006) and HIV-negative (enrolled 2001 to 2004) cohorts in Sydney, Australia</td>
<td>1,622 MSM, 226/1622 [13.9%] HIV-positive and 1396/1622 [86.1%] HIV-negative; 226/9 [7.2%] HIV-positive people were positive for urethral and anal gonorrhea respectively, and 7/222 [3.2%] of HIV-positive people were positive for urethral and anal gonorrhea respectively</td>
<td>Median age in HIV-positive cohort: 45 years; median age in HIV-negative cohort: 35 years</td>
<td>0%</td>
<td>Annual</td>
<td>Not reported.</td>
<td>Concurrent urethral gonorrhea</td>
<td>No cases</td>
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<td>Comparison of gonorrhea prevalence in HIV-positive vs. negative cohorts rather than HIV incidence</td>
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<td></td>
<td>Concurrent anal gonorrhea</td>
<td>6.0</td>
<td>2.0 to 17.4, p-value&lt;0.01</td>
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<td>Van de Wijger 2009</td>
<td>Prospective cohort study between November 1999 and January 2004 Zimbabwe and Uganda</td>
<td>4,439 HIV-uninfected women attending family planning clinics in Zimbabwe and Uganda; HIV prevalence at screening: 39% in Zimbabwe and 17% in Uganda; HIV incidence in Zimbabwe 4.1/100 woman-years of follow-up (p 138 new cases) and in Uganda, HIV incidence was 1.3/100 woman-years of follow-up (general population) and 2.6/100 woman-years of follow-up (high risk population), (51 new cases); overall HIV incidence 1.5/100 woman-years of follow-up (189 new cases); Gonorrhea prevalence at enrollment: in Zimbabwe 22%, in Uganda 18%, overall 2.0%; Gonorrhea incidence: in 18 to 35 years, mean age 25 years</td>
<td>100%</td>
<td>7,776 person-years of follow-up over 31,197 follow-up visits; median time between study visits 3 months</td>
<td>Country</td>
<td>Gonorrhea identified at same visit with HIV detection on risk of HIV acquisition in Zimbabwe</td>
<td>HR: 5.66</td>
<td>3.22-9.95, p-value&lt;0.001</td>
<td>Multivariable Cox proportional hazards model</td>
<td>Incidents of gonorrhea were defined as. Temporal relationships between gonorrhea and HIV acquisition remain uncertain because of infection detection delays, STI persistence in the genital tracts, and the fact that some STI episodes may have gone unnoticed because the interval between study visits was approximately 3 months. To minimize uncertainty, authors used HIV DNA PCR to better time the HIV transmission event; encouraged women to visit the study clinic in case of symptoms; did statistical analyses for various observation periods before HIV detection. High 24 months retention rates: 92% in Zimbabwe and 97% in Uganda. Not possible to differentiate between persistent and</td>
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<tr>
<td>Name Design</td>
<td>N</td>
<td>Sample Ages</td>
<td>% Female</td>
<td>Follow-up Rate</td>
<td>Follow-up Time</td>
<td>Add'l Variable 1</td>
<td>Add'l variable 2</td>
<td>Risk Factor on Outcome</td>
<td>OR</td>
<td>95% CI, p-value</td>
<td>Data Analysis</td>
<td>Comment/ Study Quality/ Biases</td>
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<td>Zimbabwe 3.7/100 woman-years of follow-up, in Uganda 5.2/100 woman-years of follow-up</td>
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<td>Gonorrhea identified at either same visit with or visit prior to HIV detection on risk of HIV acquisition overall</td>
<td>HR: 3.42</td>
<td>2.10-5.66</td>
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<td></td>
<td>Gonorrhea identified at both same visit with or visit prior to HIV detection on risk of HIV acquisition overall</td>
<td>HR: 7.09</td>
<td>3.13-16.08</td>
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<tr>
<td>Sharghi 2005 Prospective cohort study (1995 to 1997) USA</td>
<td>4,652 high-risk participants in the HIV Network for Prevention Trials (HIVNET) Vaccine Preparedness Study; High-risk defined as: In men - Reported anal sex with ≥1 men in the past year or injected drugs at least once in the previous 6 months In women - Reported injecting drugs within the previous 6 months; reported current relationship with a man who was HIV-1 positive, who had sex with other men, who reported injection drug use in the past 5 years, or</td>
<td>&gt;18 years; percentages given for 3 age groups</td>
<td>17.4%</td>
<td>6-monthly</td>
<td>18 months</td>
<td>Self-reported recent gonorrhea, Chlamydia infection or nonspecific urethritis on HIV seroconversion since last</td>
<td>3.91</td>
<td>1.93 to 7.91, p-value=0.0001</td>
<td>Multivariate models</td>
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<td>Self-reported recent gonorrhea, Chlamydia infection or nonspecific urethritis on HIV seroconversion by 18 months</td>
<td>3.13</td>
<td>1.53 to 6.41, p-value=0.0018</td>
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</table>

Sharghi 2005 Prospective cohort study (1995 to 1997) USA

4,652 high-risk participants in the HIV Network for Prevention Trials (HIVNET) Vaccine Preparedness Study; High-risk defined as: In men - Reported anal sex with ≥1 men in the past year or injected drugs at least once in the previous 6 months In women - Reported injecting drugs within the previous 6 months; reported current relationship with a man who was HIV-1 positive, who had sex with other men, who reported injection drug use in the past 5 years, or >18 years; percentages given for 3 age groups.

17.4% 6-monthly 18 months

Self-reported recent gonorrhea, Chlamydia infection or nonspecific urethritis on HIV seroconversion since last

3.91 1.93 to 7.91, p-value=0.0001 Multivariate models

HIV-1 seroconversion diagnosed using HIV enzyme-linked immunosorbent assay (ELISA) and confirmed by Western Blot; Clinical symptoms assessed by providing a list of symptoms and asking participants if they had experienced any of them since their prior study visit; STIs assessed by providing a list of common infections and asking the participants whether a medical provider had diagnosed or treated them for any of the infections since their last interview; Retention rate 88%; Potential recall bias due to self-reporting of STIs; appropriate recurrent infections.
<table>
<thead>
<tr>
<th>Name Design</th>
<th>N</th>
<th>Sample Ages</th>
<th>% Female</th>
<th>Follow-up Rate</th>
<th>Follow-up Time</th>
<th>Add'l Variable 1</th>
<th>Add'l Variable 2</th>
<th>Risk Factor on Outcome</th>
<th>OR</th>
<th>95% CI, p-value</th>
<th>Data Analysis</th>
<th>Comment/ Study Quality/ Biases</th>
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<tr>
<td>who was diagnosed with syphilis, gonorrhea, or Chlamydia infection; or reported one of the following behaviors within the past year: exchanging sex for money or drugs, &quot;crack&quot; cocaine use, having ≥ male partners, or had a diagnosis of syphilis, gonorrhea, chancroid, pelvic inflammatory disease, trichomoniasis, or an initial episode of genital herpes</td>
<td>Age at enrollment ≤ 30 years; mean age 25 years</td>
<td>0%</td>
<td>9488 visits</td>
<td>Median follow-up time 4.0 years</td>
<td>Concurrent gonorrhea or syphilis on HIV incidence</td>
<td>RR: 3.5</td>
<td>0.8 to 15.1, p-value=0.085</td>
<td>Multivariate regression</td>
<td>New case of gonorrhea was defined as a self reported new episode in the past 6 months</td>
<td>Date of HIV seroconversion estimated as the midpoint between last HIV-negative and first HIV-positive test</td>
<td>ACS: Amsterdam Cohort Studies; HR: hazard ratio; MSM: Men who have sex with men; OR: Odds ratio; RR: Relative risk</td>
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</table>
### Evidence Table 3.6: HIV Transmission/Acquisition in Hepatitis B

<table>
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<tr>
<th>Name</th>
<th>Design</th>
<th>N</th>
<th>Sample Ages</th>
<th>% Female</th>
<th>Follow-up Rate</th>
<th>Follow-up Time</th>
<th>Risk Factor</th>
<th>OR</th>
<th>95% CI, p-value</th>
<th>Data Analysis</th>
<th>Comment/ Study Quality/ Biases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jin 2007</td>
<td>Cross-sectional comparison of a HIV-positive (enrolled 2001 to 2006) and HIV-negative (enrolled 2001 to 2004) cohorts in Sydney, Australia</td>
<td>1,622 MSM, 226/1622 [13.9%] HIV-positive and 1396/1622 [86.1%] HIV-negative [86.1%] HIV-negative; 121/216 [56%] of HIV-positive and 260/1397 [18.60%] HIV-negative people ever infected with hepatitis B; 8/216 [3.7%] of HIV-positive and 7/1397 [0.5%] HIV-negative people currently infected with hepatitis B; 51/216 [23.6%] of HIV-positive and 737/1397 [52.8%] HIV-negative people vaccinated against hepatitis B</td>
<td>Median age in HIV-positive cohort: 45 years; median age in HIV-negative cohort: 35 years</td>
<td>0%</td>
<td>Annual</td>
<td>Not reported.</td>
<td>Ever infected with hepatitis B</td>
<td>3.4</td>
<td>2.4 to 4.7, p&lt;0.01</td>
<td>Cox regression analysis</td>
<td>Ever infected = hepatitis B virus core antibody positive; Currently infected = hepatitis B virus core antibody positive and hepatitis B virus surface antigen positive; Vaccinated = hepatitis B surface antibody positive only. Comparison of syphilis prevalence in HIV-positive vs. negative cohorts rather than HIV incidence</td>
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</tbody>
</table>

*Note: Follow-up rate and time are not reported.*
### Evidence Table 3.7: HIV Transmission/Acquisition in Syphilis

<table>
<thead>
<tr>
<th>Name</th>
<th>Design</th>
<th>N</th>
<th>Sample Ages</th>
<th>% Female</th>
<th>Follow-up Rate</th>
<th>Follow-up Time</th>
<th>Risk Factor</th>
<th>Adjusted OR unless otherwise specified</th>
<th>95% CI</th>
<th>Study Quality</th>
<th>Biases</th>
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</thead>
<tbody>
<tr>
<td>Sanchez 2009</td>
<td>Case-control nested in prospective cohort study in Lima, Peru</td>
<td>1,056</td>
<td>18 years</td>
<td>0%</td>
<td>Initially 6-monthly, then 3-monthly</td>
<td>Average 335 days</td>
<td>Recently acquired syphilis or HSV-2 infection</td>
<td>5.9</td>
<td>1.5 to 22.7 (p&lt;0.01)</td>
<td>Multivariate stepwise backward enter logistic regression model</td>
<td>Relatively small sample size; not generalizable population; composite risk factor syphilis and HSV-2</td>
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<td>Reynolds 2006</td>
<td>Cohort study in Pune, India from May 1993 to April 2000</td>
<td>2324/2729 [14.8%]</td>
<td>HIV negative at baseline, 172 participants with clinical or laboratory evidence of syphilis during follow up = syphilis incidence of 5.4 per 100 person years, 96% CI 4.8 to 6.5 per 100 person years; incidence of HIV-1 was 5.8 per 100 person years (95% CI 5.0 to 6.6 per 100 person years)</td>
<td>16.7%</td>
<td>3-monthly, median number 3</td>
<td>Median 10.7 months, ranging from 45 days to 60 months</td>
<td>HIV infection in people with incident syphilis (within 6 months of infection) compared without syphilis</td>
<td>Adjusted HR 4.44</td>
<td>2.99 to 6.65 (p&lt;0.001)</td>
<td>Cox proportional hazards model</td>
<td>Mostly high-risk STI patients; temporality of HIV-1 vs. syphilis infection difficult to establish as measuring both HIV and syphilis incidence simultaneously</td>
</tr>
<tr>
<td>Name Design</td>
<td>N</td>
<td>Sample Ages</td>
<td>% Female</td>
<td>Follow-up Rate</td>
<td>Follow-up Time</td>
<td>Risk Factor</td>
<td>Adjusted OR unless otherwise specified</td>
<td>95% CI</td>
<td>Study Quality</td>
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<tr>
<td>Jin 2007 Comparison of a HIV-positive (enrolled 2001 to 2006) and HIV-negative (enrolled 2001 to 2004) cohorts in Sydney, Australia</td>
<td>1,622 MSM, 226/1622 [13.9%] HIV-positive and 1396/1622 [86.1%] HIV-negative; 42/226 [18.6%] of HIV-positive and 42/1396 [3.0%] HIV-negative people co-infected with syphilis</td>
<td>Median age in HIV-positive cohort: 45 years; median age in HIV-negative cohort: 35 years</td>
<td>0%</td>
<td>Annual</td>
<td>Not reported.</td>
<td>Concurrent syphilis</td>
<td>3.7</td>
<td>2.3 to 5.8</td>
<td>(p=0.01)</td>
<td>Comparison of syphilis prevalence in HIV-positive vs. negative cohorts rather than HIV incidence</td>
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<tr>
<td>Zetola 2009 1. Matched case-control study between October 2003 and March 2007 in San Francisco, USA</td>
<td>13,662 MSM attending an STI clinic for HIV testing; 350/13,662 [2.56%] testing positive for HIV compared vs. 144/13,312 HIV-negative participants randomly selected as controls for matched case-control analyses</td>
<td>Median age in HIV-positive cohort: 45 years; median age in HIV-negative cohort: 35 years</td>
<td>0%</td>
<td>None</td>
<td>n/a</td>
<td>Concurrent syphilis in acute HIV compared without HIV</td>
<td>5.8</td>
<td>1.1 to 32.3</td>
<td>(p=0.04)</td>
<td>Small sample size; cases and controls may have differed in unmeasured characteristics; results not generalizable to other MSM or non-MSM populations; study conducted as part of routine HIV testing potentially leading to selection and referral bias; temporality of HIV and syphilis infections not possible to determine; comparing syphilis prevalence in patients with positive HIV RNA result vs. matched controls result vs. matched controls rather than HIV incidence</td>
<td></td>
</tr>
<tr>
<td>2. Infected analysis</td>
<td>36/350 [10.3%] diagnosed as having acute HIV (positive HIV RNA result in HIV antibody-negative specimen) compared vs. 314/350 [89.7%] chronic HIV infection</td>
<td>None</td>
<td>33 years</td>
<td>None</td>
<td>n/a</td>
<td>Concurrent syphilis in acute HIV compared with chronic HIV</td>
<td>0.4</td>
<td>0.1 to 2.4</td>
<td>(p=0.331)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Case-crossover analysis</td>
<td>25/36 [70%] acute HIV cases providing data on 54 prior clinic visits</td>
<td>None</td>
<td></td>
<td>None</td>
<td>n/a</td>
<td>Concurrent syphilis in acute HIV cases compared with themselves at a prior visit</td>
<td>1.3</td>
<td>0.3 to 5.9</td>
<td>(p=0.779)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR: hazard ratio; HSV-2: Herpes simplex virus type 2; IDU: Intravenous drug user; MSM: Men who have sex with men; OR: Odds ratio
HIV Progression in Concurrent STIs

**Systematic Reviews**

**Evidence Table 3.8: HIV Progression in Coinfection with Hepatitis B**

<table>
<thead>
<tr>
<th>Author &amp; Title</th>
<th>Search Database / Method</th>
<th>Study Characteristics</th>
<th>Results</th>
<th>Conclusions/ Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nikolopoulos et al. (2009) Impact of Hepatitis B virus infection on the progression of AIDS and mortality in HIV-infected individuals: A cohort study and meta-analysis.</td>
<td>Databases: Pubmed, Scopus, Google Scholar</td>
<td>N: 11 studies (12,382 participants)</td>
<td>All-cause mortality (11 studies, 12,382 participants): Significantly increased among hepatitis B-infected participants; combined effect estimate 1.36, 95%CI 1.12 to 1.64; significant result sustained in subgroup analyses pre- and post-HAART; no evidence of heterogeneity.</td>
<td>Hepatitis B is associated with increased all-cause mortality but not with progression to AIDS in HIV-1 positive patients.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: Not reported</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>Setting: Not reported</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Inclusion criteria: Cohort or case-control studies with HIV-positive patients and examining effect of hepatitis B on AIDS progression or mortality</td>
<td></td>
<td>Search of dubious exhaustiveness; data about HBV-DNA levels not always available.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Types of studies</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Reported relevant outcomes/outcome measures: Progression to AIDS; mortality</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Method: Meta-analysis: fixed and random effects models</td>
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<tr>
<td></td>
<td></td>
<td>- Formal testing of publication bias by Egger regression method.</td>
<td></td>
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</tr>
</tbody>
</table>

- Setting:
- Inclusion criteria:
- Exclusion criteria:
- Funding:
- Other sources:
<table>
<thead>
<tr>
<th>Author &amp; Title</th>
<th>Search Database / Method</th>
<th>Study Characteristics</th>
<th>Results</th>
<th>Conclusions/ Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulkowski et al. (2003)</td>
<td>Databases: Medline</td>
<td>N: 7 relevant studies, of which 4 met our inclusion criteria (Greub 2000, Sulkowski 2000, Sulkowski 2002, Chung 2002).</td>
<td>Conflicting results for HIV progression (see data tables for included studies); no meta-analysis.</td>
<td>Search strategy of questionable quality; poor data reporting.</td>
</tr>
<tr>
<td></td>
<td>Other sources: Bibliographies of selected articles.</td>
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<td></td>
<td>Search period: 1966 to 2002</td>
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<tr>
<td></td>
<td>Search terms: HIV, AIDS, human immunodeficiency virus OR acquired immunodeficiency syndrome AND HCV or hepatitis C or Non-A, non-B</td>
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<tr>
<td></td>
<td><strong>Reported relevant outcomes/outcome measures:</strong></td>
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<tr>
<td></td>
<td>None reported</td>
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<td></td>
<td><strong>Method:</strong></td>
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</tr>
<tr>
<td></td>
<td>No meta-analysis. No formal testing of publication bias.</td>
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<tr>
<td>Funding: National Institute on Injection Drug Abuse.</td>
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</tbody>
</table>
### Individual Studies

#### Evidence Table 3.9: HIV Progression in Coinfection with Hepatitis B

<table>
<thead>
<tr>
<th>Name</th>
<th>Design</th>
<th>N</th>
<th>Sample Aages</th>
<th>% Female</th>
<th>Follow-up Rate</th>
<th>Follow-up Time</th>
<th>Risk Factor on Outcome</th>
<th>OR unless Otherwise Specified</th>
<th>95% CI, p-value</th>
<th>Data Analysis</th>
<th>Comment/ Study Quality/ Biases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoffmann 2009</td>
<td>Prospective cohort study April 1984- March 1985, 1987-1991, 2001-2003 USA</td>
<td>816 HIV-infected MSM who are part of MACS study. 350/816 never infected with hepatitis B; 357/816 with previous infection; 458/816 with chronic hepatitis B; 648/816 with isolated core; 87/816 patients died during study (17 per 1000 person-years); 43/87 due to AIDS; 30/87 non-AIDS-related deaths of which 66.7% was due to liver disease; 14/87 unknown causes</td>
<td>Median age at HAART initiation 40 years</td>
<td>%</td>
<td>6-monthly until time of death, date of last visit or 31 March 2006</td>
<td>Median follow up 7 years</td>
<td>Hepatitis B coinfection on AIDS-related death vs. never-infected patients</td>
<td>Adjusted IRR 2.7</td>
<td>0.90 to 8.2, p-value=0.08</td>
<td>Poisson regression</td>
<td>Small number of patients; late introduction of tenofovir disoproxil fumarate; hepatotoxicity risk is usually a transient event that may have been missed due to infrequent transaminase; underlying liver disease may have been underreported on death certificates.</td>
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<td></td>
<td>Hepatitis B coinfection on non AIDS-related death vs. never-infected patients</td>
<td>Adjusted IRR 4.1</td>
<td>1.0 to 16, p-value=0.04</td>
<td>Logistic regression with robust variance estimates using generalized estimating equations with unstructured correlation matrices</td>
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<td></td>
<td>Hepatitis B coinfection on AIDS-defining events vs. never-infected patients</td>
<td>Adjusted IRR 1.1</td>
<td>0.49 to 2.5</td>
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<td></td>
<td>Hepatitis B coinfection on HIV RNA suppression vs. never-infected patients</td>
<td>RR 1.6</td>
<td>0.55 to 4.5</td>
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<td></td>
<td>Hepatitis B coinfection on CD4 cell count vs. never-infected patients</td>
<td>Not reported</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td>Design</td>
<td>N</td>
<td>Sample Ages</td>
<td>% Female</td>
<td>Follow-up Rate</td>
<td>Follow-up Time</td>
<td>Risk Factor on Outcome</td>
<td>OR unless Otherwise Specified</td>
<td>95% CI, p-value</td>
<td>Data Analysis</td>
<td>Comment/ Study Quality/ Biases</td>
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</tr>
<tr>
<td>Law 2004</td>
<td>Observational study</td>
<td>Thailand December 1996 and March 2001</td>
<td>692</td>
<td>48%</td>
<td>At weeks 4, 8, 12, 24, 36 and 48</td>
<td>48 weeks</td>
<td>Concurrent HBV infection on achieving undetectable HIV viral load following initiation of antiretroviral therapy</td>
<td>Not reported (data given as median HIV RNA reductions [log10 copies/ml]; around 1.5 in all groups from week 4 to week 48)</td>
<td>Not reported, p-value=0.73</td>
<td>Cox regression analysis</td>
<td>Prevalence of HBV was 8.7% at baseline, defined as HBsAg presence at baseline.</td>
</tr>
</tbody>
</table>

- **Follow-up Rate:** At weeks 4, 8, 12, 24, 36 and 48
- **Follow-up Time:** 48 weeks
- **Risk Factor on Outcome:** Concurrent HBV infection on achieving undetectable HIV viral load following initiation of antiretroviral therapy
- **Follow-up Rate:** Not reported (data given as median HIV RNA reductions [log10 copies/ml]; around 1.5 in all groups from week 4 to week 48)
- **OR unless Otherwise Specified:** Not reported, p-value=0.73
- **Data Analysis:** Cox regression analysis
- **Comment/ Study Quality/ Biases:** Prevalence of HBV was 8.7% at baseline, defined as HBsAg presence at baseline.
<table>
<thead>
<tr>
<th>Name Design</th>
<th>N</th>
<th>Sample Ages</th>
<th>% Female</th>
<th>Follow-up Rate</th>
<th>Follow-up Time</th>
<th>Risk Factor on Outcome</th>
<th>OR unless Otherwise Specified</th>
<th>95% CI, p-value</th>
<th>Data Analysis</th>
<th>Comment/Study Quality/Biases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lincoln 2003</td>
<td>2086 HIV-infected patients; 1605/2086 (77%) tested for HBV surface antigen; 101/1605 (6.3%) with positive HBV surface antigen test result; 38/1465 [2.6%] with positive HBV surface antigen and anti-HCV antibody</td>
<td>Not reported (data given as percentages in 3 age groups)</td>
<td>6.3%</td>
<td>Not reported</td>
<td>Not reported</td>
<td>HBV coinfection on time to first AIDS defining illness or death</td>
<td>HR 1.27</td>
<td>0.71 - 2.29 (p = 0.423)</td>
<td>Cox proportional hazards model of trend, but retained when calculating and reporting odds ratios for HBV and HCV status were based on clinician reporting to the AHOD database rather than through a standardized serological survey; HBV and HCV status was not available for all patients in AHOD; HCV coinfection status was based on antibody rather than HCV RNA detection; no assessment of liver disease outcomes conducted</td>
<td></td>
</tr>
</tbody>
</table>

**Data Analysis:**
- Missing values of the nominal covariates were dropped for the tests of trend, but retained when calculating and reporting odds ratios.

**Comment/Study Quality/Biases:**
- HBV and HCV status were based on clinician reporting to the AHOD database rather than through a standardized serological survey; HBV and HCV status was not available for all patients in AHOD; HCV coinfection status was based on antibody rather than HCV RNA detection; no assessment of liver disease outcomes conducted.

**Lincoln 2003**
- Longitudinal cohort study of patients recruited to the Australian HIV Observational Database (data from hospitals, sexual health clinics and GPs) between September 1999 and September 2002.

**Follow-up Rate:**
- Not reported

**Follow-up Time:**
- Not reported

**Risk Factor on Outcome:**
- HBV coinfection on time to first AIDS defining illness or death
- Cox proportional hazards model of trend, but retained when calculating and reporting odds ratios

**HBV coinfection on virological response following HAART (viremia at 12 months):**
- HR 1.04
- 0.54 to 2.01, p-value=0.903

**HBV coinfection on immunological response (change in CD4 count during 24 months following commencement of HAART):**
- Change from baseline -12.39
- -60.85 to 36.07, p-value=0.616
<table>
<thead>
<tr>
<th>Name Design</th>
<th>Sample</th>
<th>% Female</th>
<th>Follow-up</th>
<th>Follow-up Rate</th>
<th>Risk Factor on Outcome</th>
<th>OR unless Otherwise Specified</th>
<th>95% CI, p-value</th>
<th>Data Analysis</th>
<th>Comment/Study Quality/Biases</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Luca 2002 Multicenter prospective cohort study in Italy (Italian Cohort Naive Antiretrovirals, started April 1, 1997)</td>
<td>1320 HIV-1 positive patients, antiretroviral-drug-naïve at the time of enrolment; 90/1320 (6.8%) with HBV surface antibody; 335/1320 patients changed initial regimen because of toxicity or intolerance (6 for hepatotoxicity); 56/1320 developed a new AIDS-defining event (pulmonary or extrapulmonary tuberculosis (n=9), Kaposis sarcoma (n=8), disseminated Mycobacterium avium complex infection (n=7), Pneumocystis carinii pneumonia (n=7), toxoplasmic encephalitis (n=6), AIDS dementia (n=4), recurrent bacterial pneumonia (n=4), Candida esophagitis (n=4), progressive multifocal leukoencephalopathy (n=3), wasting syndrome (n=3), cytomegalovirus retinitis (n=2), cervical cancer (n=2), disseminated lymphoma (n=1), brain lymphoma (n=1), herpes simplex perianal ulcerations (n=1), and intestinal cryptosporidiosis (n=1); 7/56 patients showed 2 events at the same time; 7/56 patients died subsequently but were analyzed as new AIDS event cases; 43/1320 patients died due to end-stage liver disease (n=3); HIV-related diseases (n=24); non-HIV, non-liver-related diseases (n=12); and unknown (n=4)</td>
<td>Median age 33 years, ranging from 14 to 79 years</td>
<td>Not reported.</td>
<td>Median follow-up 36.8 months, ranging from 1 to 48 months</td>
<td>HBV coinfection on time to new AIDS-defining opportunistic disorder or death</td>
<td>Adjusted HR 1.83</td>
<td>0.72 to 4.65, p-value=0.2</td>
<td>Cox proportional hazards regression</td>
<td>Inclusion criteria: (1) started a potent antiretroviral regimen, defined as the combination of at least 3 antiretroviral agents, without previous treatment for HIV-1 infection; (2) been tested for HCV antibodies and hepatitis B surface antigen (HBsAg); (3) have at least 2 measurements of CD4+ cell counts and HIV RNA levels after treatment start; and (4) had no treatment with interferon or other immunomodulating agents before baseline or during follow-up. HBV evaluated using serum surface only; this might lead to occult HBV infection (i.e., presence of HBV DNA in serum or liver tissue in the absence of serum HBsAg positivity.</td>
</tr>
</tbody>
</table>

HBV: Hepatitis B virus; MACS: Multicenter AIDS Cohort Study; MSM: Men who have sex with men; OR: Odds ratio; RR: Relative risk
### Evidence Table 3.10: HIV Progression in Coinfection With Hepatitis C

<table>
<thead>
<tr>
<th>Name</th>
<th>Design</th>
<th>N</th>
<th>Sample Ages</th>
<th>% Female</th>
<th>Follow-up Rate</th>
<th>Follow-up Time</th>
<th>Risk Factor on Outcome</th>
<th>OR unless Otherwise Specified</th>
<th>95% CI</th>
<th>Data Analysis</th>
<th>Comments/Study Quality/ Biases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulkowski 2002</td>
<td>Prospective cohort study (January 1995-January 2001) Baltimore, USA</td>
<td>1955 HIV positive patients who had at least 1 return visit to the HIV clinic and who had not developed an AIDS-defining illness prior to enrolment</td>
<td>Median age 37 years</td>
<td>30%</td>
<td>4 weeks after initiation of treatment, then 3-monthly</td>
<td>Median 2.19 years (HIV-infected people) and 2 years (HIV-uninfected people)</td>
<td>Concurrent hepatitis C on acquiring AIDS-defining illness</td>
<td>HR 1.03</td>
<td>0.86-1.23</td>
<td>Cox proportional hazards regression</td>
<td>The authors did not differentiate between the causes of death, i.e. the risk of death due to AIDS or liver disease. Potential for misclassifications as some patients with HCV antibodies might have been cleared and some HIV-infected patients may have HCV infection in the absence of a reactive antibody test. Relatively short period of follow-up; findings of this study may not be generalizable to HIV-infected patients receiving care outside of urban settings in which HCV infection and injection drug use may be less prevalent; no evaluation of the effect of other potential cofactors such as GB virus C and TT virus infections.</td>
</tr>
<tr>
<td>Greub 2000</td>
<td>Prospective cohort study (June 1, 1996-May 31, 1999) Switzerland</td>
<td>3111 patients with HIV infection enrolled in Swiss HIV Cohort study, 1157/3111 [37.2%] HCV seropositive; of these 1015/1157 [87.7%] with a history of intravenous drug use</td>
<td>16 years or older</td>
<td></td>
<td></td>
<td></td>
<td>Concurrent hepatitis C on an AIDS-defining event or death</td>
<td>HR 1.7</td>
<td>1.26 - 2.30</td>
<td>Cox regression analysis</td>
<td>HCV seropositivity could be a marker for accelerated HIV-1 disease progression, rather than representing a causal pathogenic factor in the evolution of HCV-HIV-1 coinfection. Inclusion criteria: all participants who started potent antiretroviral therapy between June 1, 1996 and May 31, 1999, who had a CD4-cell count and viral-load measurement not more than 6 months before starting potent antiretroviral therapy, and who had at least one follow-up visit more than 1 month after the start of treatment.</td>
</tr>
<tr>
<td>Name</td>
<td>Design</td>
<td>Sample</td>
<td>% Female</td>
<td>Follow-up</td>
<td>Risk Factor on Outcome</td>
<td>OR unless Otherwise Specified</td>
<td>95% CI</td>
<td>Data Analysis</td>
<td>Comments/ Study Quality/ Biases</td>
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</tr>
<tr>
<td>Chung 2002</td>
<td>Retrospective analysis USA</td>
<td>169</td>
<td>20%</td>
<td>16 weeks</td>
<td>Concurrent hepatitis C on immunological response (overall mean CD4 cell change)</td>
<td>Not reported (data given as mean change: +133 cells/mm³ in HCV-positive patients vs. +100 cells/mm³ in HCV-negative patients)</td>
<td>Not given; p-value=0.1513</td>
<td>Kruskal-Wallis test</td>
<td>The analysis of this retrospective cohort was confined to week 16, because the treatments from months 7-24 were randomly divided to one of three arms of the clinical trial (indinavir, zidovudine-lamivudine, zidovudine-lamivudine-indinavir maintenance for month 6 HIV-1-RNA responders)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Law 2004</td>
<td>Prospective cohort study Thailand</td>
<td>992</td>
<td>48%</td>
<td>48 weeks</td>
<td>Concurrent HCV infection on achieving undetectable HIV viral load following initiation of antiretroviral therapy</td>
<td>Not reported (data given as median HIV RNA reductions [log10 copies/mL]: around 1.5 in all groups from week 4 to week 48)</td>
<td>Not reported, p-value=0.73</td>
<td>Cox regression analysis</td>
<td>Co-infection with HCV defined as the detection of anti-HCV antibody at baseline, rather than HCV RNA; no systematic assessment of liver disease outcomes conducted</td>
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<tr>
<td>Name Design</td>
<td>N</td>
<td>Sample Ages</td>
<td>% Female</td>
<td>Follow-up Rate</td>
<td>Follow-up Time</td>
<td>Risk Factor on Outcome</td>
<td>OR unless Otherwise Specified</td>
<td>95% CI</td>
<td>Data Analysis</td>
<td>Comments/ Study Quality/ Biases</td>
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<tr>
<td>Lincoln 2003 Longitudinal cohort study of patients recruited to the Australian HIV Observational Database (data from hospitals, sexual health clinics and GPs between September 1999 and September 2002)</td>
<td>2086 HIV-infected patients; 1704/2086 [82%] tested for anti-HCV antibody; 223/1704 [13.1%] with positive HCV antibody test result; 219/1704 tested also for HCV-RNA; 5/111 [4.5%] with positive HCV-RNA but negative HCV antibody results; prevalence of HCV coinfection similar for MSM (90%), IDUs (63.9%) and recipients of blood products (57.1%), and considerably higher than MSM (8.7%) and heterosexuals (9.9%); 1271/2086 [60.9%] commenced HAART; 181/2086 progressed to an AIDS event</td>
<td>Not reported (data given for as percentages in 3 age groups)</td>
<td></td>
<td>Not reported.</td>
<td>Not reported.</td>
<td>HCV coinfection on time to first AIDS defining illness or death</td>
<td>HR 0.99</td>
<td>0.63 to 1.56; P=0.985</td>
<td>Cox proportional hazard model</td>
<td>Missing values of the nominal covariates were dropped for the tests of trend, but retained when calculating and reporting odds ratios</td>
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<td></td>
<td>HBV and HCV status were based on clinician reporting to the AHOD database rather than through a standardized serological survey; HBV and HCV status was not available for all patients in AHOD; HCV coinfection status was based on antibody rather than HCV RNA detection; no assessment of liver disease outcomes conducted</td>
<td></td>
</tr>
</tbody>
</table>
**Evidence Table 3.10: HIV Progression in Coinfection With Hepatitis C continued**

<table>
<thead>
<tr>
<th>Name Design</th>
<th>Sample</th>
<th>N</th>
<th>Ages</th>
<th>% Female</th>
<th>Follow-up Rate</th>
<th>Follow-up Time</th>
<th>Risk Factor on Outcome</th>
<th>OR unless Otherwise Specified</th>
<th>95% CI</th>
<th>Data Analysis</th>
<th>Comments/Study Quality/ Biases</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Luca 2002 Multicenter prospective cohort study in Italy (Italian Cohort Naive Antiretrovirals, started April 1, 1997)</td>
<td>1320 HIV-1 positive patients, antiretroviral drug-naive at the time of enrollment; 600/1320 [45.5%] with HCV antibodies; prevalence significantly higher in IDUs (93.3%) and lower in MSM and people infected through heterosexual contact or other routes (11.7% and 16.4%, respectively, P=0.001); 335/1320 patients changed initial regimen because of toxicity or intolerance (6 for hepatotoxicity); 56/1320 developed a new AIDS-defining event (pulmonary or extrapulmonary tuberculosis (n=9), Kaposi sarcoma (n=8), disseminated Mycobacterium avium complex infection (n=7), Pneumocystis carinii pneumonia (n=7), toxoplasmic encephalitis (n=6), AIDS dementia (n=4), recurrent bacterial pneumonia (n=4), Candida esophagitis (n=4), progressive multifocal leukoencephalopathy (n=3), wasting syndrome (n=3), cytomegalovirus retinitis (n=2), cervical cancer (n=2), disseminated lymphoma (n=1), brain lymphoma (n=1), herpes simplex perianal ulcerations (n=1), and intestinal cryptosporidiosis (n=1); 7/56 patients showed 2 events at the same time; 7/56 patients died subsequently but were analyzed as new AIDS event cases; 43/1320 patients died due to end-stage liver disease (n=3); HIV-related diseases (n=54); non-HIV, non-liver-related diseases (n=12); and unknown (n=4)</td>
<td>Median age 33 years, ranging from 14 to 79 years</td>
<td>25%</td>
<td>Not reported.</td>
<td>Median follow-up 36.8 months, ranging from 1 to 48 months</td>
<td>HCV coinfection on time to new AIDS-defining opportunistic disorder or all-cause death</td>
<td>Adjusted HR 1.55</td>
<td>1.00 to 2.41, p-value=0.05</td>
<td>Cox proportional hazards regression</td>
<td>Inclusion criteria: (1) started a potent antiretroviral regimen, defined as the combination of at least 3 antiretroviral agents, without previous treatment for HIV-1 infection; (2) been tested for HCV antibodies and hepatitis B surface antigen (HBsAg); (3) have at least 2 measurements of CD4+ cell counts and HIV RNA levels after treatment start; and (4) had no treatment with interferon or other immunomodulating agents before baseline or during follow-up. HCV infection analyzed by serologic examination only, possibly leading to underestimate of HCV incidence and diluted effect of HCV on CD+ recovery and clinical progression</td>
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<td>HCV coinfection on immunologic response (CD4 cell count increase of at least 100 CD4+ cells/μL or achievement of 500 cells/μL)</td>
<td>Adjusted HR 0.72</td>
<td>0.62 to 0.89, p-value=0.008</td>
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<td>HCV coinfection on virologic response (HIV RNA level &lt;500 copies/mL)</td>
<td>Adjusted HR 0.98</td>
<td>0.88 to 1.17, p-value&gt;0.05</td>
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<td>Name Design</td>
<td>N</td>
<td>Sample Ages</td>
<td>% Female</td>
<td>Follow-up Rate</td>
<td>Follow-up Time</td>
<td>Risk Factor on Outcome</td>
<td>OR unless Otherwise Specified</td>
<td>95% CI</td>
<td>Data Analysis</td>
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<td>Kovacs 2010 Prospective Cohort study (1994-1995, 2001-2002) USA</td>
<td>1307 (813 HCV-negative women and 87 HCV-positive nonviremic women, and 407 HCV-positive viremic women) who were enrolled in The Women Interagency HIV Study (WIHS)</td>
<td>17-67</td>
<td>100%</td>
<td>6-monthly</td>
<td>Total 14,420 person-years; median 5.2 years, ranging from 0.35 to 9.9 years</td>
<td>Concurrent hepatitis C on incidence of AIDS-related event</td>
<td>Not reported; data displayed graphically</td>
<td>p-value&lt;0.001</td>
<td>Kaplan-Meier test</td>
<td>No information given on timing of HCV infection; immune activation markers measured for a subset only; HCV RNA levels measured only at baseline.</td>
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<td>Concurrent hepatitis C on incidence AIDS-related death</td>
<td>Not reported; data displayed graphically</td>
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<td>Concurrent hepatitis C on immunological response (CD4 cell increase, overall mean value)</td>
<td>Not reported; data given as mean changes for 4 RNA levels</td>
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<td>Multivariate analysis</td>
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<td>Name Design</td>
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<td>Carmo 2008 Retrospective cohort follow-up (January 1, 1996-June 30, 2001) Brazil</td>
<td>824 HIV patients</td>
<td>Overall: 824 HIV patients; 151/824 [18.3%] had a new AIDS event; 72/824 [8.7%] died; 65/72 [90.3%] died due to AIDS; 272 died due to end-stage liver disease; overall cumulative incidence of AIDS event or death 22.2%; incidence rate 0.27/1000 person-days</td>
<td>&gt;12 years</td>
<td>36%</td>
<td>2 to 3 times per year</td>
<td>Median 776 days, ranging from 7 to 2,057 days</td>
<td>Concurrent hepatitis C on progression to new AIDS-defining opportunistic illness or AIDS-related death</td>
<td>HR 1.08</td>
<td>0.66 to 1.77, p-value=0.767</td>
<td>Multivariate Cox regression model</td>
<td>HIV-1 infected women who received HAART during pregnancy were excluded. Analysis only based on chart data collection; HCV antibody positivity was the only marker used for HCV infection, and HIV and HCV seroconversions dates were unknown, with possible systematic differences in the duration of both infections.</td>
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<td>For this analysis: 797 HIV patients; 486/797 [61%] achieved viral load&lt;400 copies/mL after the start of HAART; incidence rate 1.19/1000 person-days</td>
<td>For this analysis: 753 HIV patients; 611/753 [81.1%] achieved increase in CD4 cell count &gt;50 cells/mL after the start of HAART; incidence rate 2.91/1000 person-days</td>
<td>Median 155 days, ranging from 12 to 1960 days</td>
<td>Concurrent hepatitis C on virological response (viral load&lt;400 copies/mL after the start of HAART)</td>
<td>HR 0.81</td>
<td>0.56 to 1.17, p-value=0.236</td>
<td>For this analysis: 824 HIV patients; 151/824 [18.3%] had a new AIDS event; 72/824 [8.7%] died; 65/72 [90.3%] died due to AIDS; 272 died due to end-stage liver disease; overall cumulative incidence of AIDS event or death 22.2%; incidence rate 0.27/1000 person-days</td>
<td>Concurrent hepatitis C on immunological response (increase in CD4 cell count &gt;50 cells/mL after the start of HAART)</td>
<td>HR 0.68</td>
<td>0.49 to 0.92, p-value=0.015</td>
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<td>Jaén 2008</td>
<td>Prospective cohort study Spain</td>
<td>2035 asymptomatic naïve patients on HAART enrolled in PISCIS cohort; 148/2035 (7.3%) progressed to AIDS or death; 642/2035 (36.1%) positive for hepatitis C</td>
<td>35.5 years</td>
<td>24.6%</td>
<td>Not reported.</td>
<td>Median 34.3 months</td>
<td>Concurrent hepatitis C on risk progression to AIDS or all-cause death</td>
<td>HR 2.4</td>
<td>1.65 - 3.49</td>
<td>p = 0.001</td>
<td>Cox proportional hazards model</td>
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<td>Sullivan 2006 Longitudinal retrospective medical records review (1998-2004) USA</td>
<td>13 years and older; 28 years; data reported across subgroups.</td>
<td>Not reported.</td>
<td>10,481 HIV-infected individuals enrolled in the Adult and Adolescent Spectrum of HIV Disease project (ASD); 19% recorded hepatitis C infection; 59% with history of intravenous drug use; 1107/10,481 [11%] died; 609/7521 [8%] developed an AIDS-defining opportunistic illness</td>
<td>22,430 person-years of follow-up; median 1.9 years</td>
<td>Concurrent hepatitis C on time to death</td>
<td>HR 1.1</td>
<td>0.9 to 1.2, p=0.38</td>
<td>Proportional hazards regression</td>
<td>Sample not representative of all individuals in care for HIV infection. Information on HCV viral load and genotype was not collected; this might lead to modifying the effect of HCV infection on HIV disease. This prevalence of HCV might be underestimated as not all patients were screened for HCV, which might lead to bias the association between HCV and progression to AIDS.</td>
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<td>Concurred hepatitis C on time to AIDS-defining opportunistic illness diagnosis</td>
<td>HR 1.2</td>
<td>0.9 to 1.5, p-value=0.07</td>
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<td>Concurrent hepatitis C on immunological response (CD4 cell count after HAART initiation)</td>
<td>Not reported; data given as CD4 cell count change per month during the initial year on therapy</td>
<td>Not reported, p-value=0.09</td>
<td>Linear regression, with robust variances estimated from generalized estimating equations</td>
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<td>Concurrent hepatitis C on virological response (change in viral load after HAART initiation)</td>
<td>Not reported; data given as change in estimated number of log10 copies/ml during the initial 30 days on therapy</td>
<td>Not reported, p-value = 0.22</td>
<td>Random intercept model with an exchangeable covariance structure</td>
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<td>Hung 2005</td>
<td>36 years, ranging from 15-74</td>
<td>89%</td>
<td>Every 3 to 4 months</td>
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<td>Concurrent hepatitis C on immunological response (increase in &gt;100 x 10 to the 6/L CD4 cell count by the end of the study)</td>
<td>1.0</td>
<td>0.509 to 1.965, p-value=1.00</td>
<td>Logistic regression analysis</td>
<td>Small sample size, small case number with coinfection and short observation duration.</td>
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<td>Prospective observational study, Taiwan June 1994 - Dec 2002</td>
<td>440 non-hemophiliac, HIV-positive and HBV-negative patients; 53/440 with hepatitis C co-infection; 108/440 patients died, mainly due to AIDS-related causes, only 2/108 due to hepatic complications; 103/440 patients developed AIDS-defining illness</td>
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<td>Concurrent hepatitis C on immunological response (increase in &gt;200 x 10 to the 6/L CD4 cell count by the end of the study)</td>
<td>0.957</td>
<td>0.487 to 1.881, p-value=0.9</td>
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<td>Concurrent hepatitis C on AIDS-defining illness per 100 PY</td>
<td>1.826</td>
<td>0.738 to 4.522</td>
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<td>Concurrent hepatitis C on mortality rate</td>
<td>Adjusted HR 0.781</td>
<td>0.426 to 1.423, p-value=0.42</td>
<td>Cox proportional hazards model</td>
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<td>Rockstroh 2005 Prospective observational study (1994-2004) Europe</td>
<td>5957 patients enrolled in EuroSIDA; 917 AIDS-defining illnesses; 819 any deaths; 109 liver-disease related deaths; 462 non-HIV-related deaths</td>
<td>Median 36 years</td>
<td>31%</td>
<td>Not reported.</td>
<td>Not reported.</td>
<td>Concurrent hepatitis C on new AIDS-defining illness or any death</td>
<td>Adjusted IRR 1.05</td>
<td>0.89 - 1.28, p-value=0.5</td>
<td>Poisson regression</td>
<td>&lt;10% of the HCV-seropositive patients had had HCV RNA loads measured (data not shown), preventing a direct comparison between patients with viremia and those with self-limited HCV infection.</td>
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<td>Concurrent hepatitis C on new AIDS-defining illness</td>
<td>Adjusted IRR 0.78</td>
<td>0.62 to 0.98, p-value=0.03</td>
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<td>Concurrent hepatitis C on any death</td>
<td>Adjusted IRR 1.8</td>
<td>1.44 to 2.25, p-value&lt;0.0001</td>
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<td>Concurrent hepatitis C on liver disease-related deaths</td>
<td>Adjusted IRR 12.31</td>
<td>6.77 - 22.41, p-value&lt;0.0001</td>
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<td>Concurrent hepatitis C on virological response after initiating HAART (HIV-1 viral load &lt;500 copies/mL)</td>
<td>HR 1.13</td>
<td>0.84 to 1.51, p-value=0.42</td>
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<td>Concurrent hepatitis C on immunological response after initiating HAART (&gt;50 CD4 cells/ul)</td>
<td>HR 0.92</td>
<td>0.77 to 1.11, p-value=0.4</td>
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<td>Concurrent hepatitis C on immunological response after initiating HAART (&gt;50% increase in CD4 count)</td>
<td>HR 0.94</td>
<td>0.77 to 1.16, p-value=0.58</td>
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<td>Stebbing 2005</td>
<td>Prospective cohort study, UK</td>
<td>5,832 patients followed up during the HAART era; 1467/5,832 tested for HCV; 1382/1467 HCV-negative; 85/1467 (5.8%) with HIV-1-HCV coinfection</td>
<td>34.2</td>
<td>13.4%</td>
<td>34,133 patient-years of follow-up</td>
<td>34,133 patient-years of follow-up</td>
<td>Concurrent hepatitis C on HIV progression (CD4+ cell count of &lt;200 cells/mm³ or onset of the patient's first AIDS-defining illness)</td>
<td>HR 1.52</td>
<td>1.07 to 2.17, p-value=0.019</td>
<td>Multivariable Cox proportional hazards regression method</td>
<td>Individuals who had a baseline CD4+ cell count of &lt;200 cells/mm³, or onset of an AIDS-defining opportunistic illness, as clinically defined by the Centre for Disease Control and Prevention classification (including Pneumocystis jiroveci [formerly P. carinii] pneumonia, cytomegalovirus infection, candidiasis, Kaposi sarcoma, any lymphoma, toxoplasmosis, and AIDS-associated diarrhea) were excluded from this study.</td>
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<td>Anderson 2004</td>
<td>Retrospective, clinic-based cohort study (January 1982-October 2001), USA</td>
<td>970 patients who were seen during the period of January 1997 through May 2001 in the HIV Atlanta VA Cohort Study (HAVACS) and who had been tested for HCV antibody since 1982; prevalence of HCV infection 31.6%</td>
<td>41.7</td>
<td>Not reported.</td>
<td>Not reported.</td>
<td>Not reported.</td>
<td>Concurrent hepatitis C on time to death from date of diagnosis of HIV infection</td>
<td>HR 2.47</td>
<td>1.26 to 4.82, p-value=0.0085</td>
<td>Kaplan-Meier curves and multivariate survival models</td>
<td>Unavailability of important data regarding liver disease, including HCV genotype, alcohol use, and clinical data, such as aspartate aminotransferase and alanine aminotransferase levels, which were not routinely and reliably available for most patients</td>
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<td>Voirin 2004 Prospective cohort study (1992-2002) Lyon, France</td>
<td>2761 HIV-positive patients who enrolled in the French Hospital Database (FHD), Lyon section; Pre-HAART: 264/1271 patients HCV-positive; 170/1271 IDUs; HAART: 205/1490 HCV-positive; 110/1490 IDUs</td>
<td>Median 34 years</td>
<td>20%</td>
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<td>Concurrent hepatitis C on progression to death in the pre-HAART era for HCV+ Non IDUs</td>
<td>Adjusted HR 1.05</td>
<td>0.75 to 1.47, p-value=0.75</td>
<td>Cox regression model</td>
<td>Patients were stratified into 4 groups, (G1) HCV-/IDU-, (G2) HCV+/IDU-, (G3) HCV-/IDU+, (G4) HCV+/IDU+. Lack of data to calculate the mortality attributable to HCV-liver damage; use of years of inclusion as a proxy of the use of HAART; duration of exposure for both IDU and HCV infection unknown.</td>
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<td>Concurrent hepatitis C on progression to death in the pre-HAART era for HCV+ IDUs</td>
<td>Adjusted HR 0.90</td>
<td>0.65 to 1.24, p-value=0.51</td>
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<td>Concurrent hepatitis C on progression to death in the HAART era HCV+ Non IDUs</td>
<td>Adjusted HR 0.76</td>
<td>0.28 to 2.08, p-value =0.59</td>
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<td>Concurrent hepatitis C on progression to death in the HAART era HCV+ IDUs</td>
<td>Adjusted HR 2.90</td>
<td>1.62 to 5.20, p-value &lt;0.001</td>
<td></td>
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</tr>
<tr>
<td>Name</td>
<td>Design</td>
<td>Sample</td>
<td>% Female</td>
<td>Follow-up Rate</td>
<td>Follow-up Time</td>
<td>Risk Factor on Outcome</td>
<td>OR unless Otherwise Specified</td>
<td>95% CI</td>
<td>Data Analysis</td>
<td>Comments/Study Quality/Biases</td>
<td></td>
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</tr>
<tr>
<td>Mayer 2003</td>
<td>Prospective, longitudinal, case-control study (April 1993-January 1995) USA</td>
<td>871 HIV-infected women were enrolled in the HIV Epidemiology Research Study (HERS); 233/871 had a CD4 lymphocyte count of ≤200 cells/mm^3 at baseline and were not included in the progression analyses in this paper; 46.1% developed AIDS, but only 20 [1.6%] of these developed opportunistic infection; by the end of the study 52% were on HAART</td>
<td>52% ≤45 years, ranging from 16-55 yrs</td>
<td>100%</td>
<td>6-monthly</td>
<td>7 years; 2304 women-years of follow-up</td>
<td>Concurrent hepatitis C on progression to AIDS for women with baseline CD4 counts &gt; 500 cells/mm^3</td>
<td>3.22</td>
<td>1.24 to 8.35</td>
<td>Logistic regression model Progression to AIDS at a specific study site visits defined as having developed a documented AIDS-defining clinical condition since the prior visit, if the CD4 lymphocyte count decreased to &lt;200 cells/mm^3, or if the CD4% was &lt;14. CD4 counts were categorized based on clinically relevant criteria: &lt;200, 200-349, 350-499, 500/cells/mm^3. Categories were collapsed for regression models. Specially trained clinical chart abstractors documented all deaths and assessed, in conjunction with the study investigators, whether the cause of death was related to HIV</td>
<td></td>
</tr>
<tr>
<td>Tedaldi 2003</td>
<td>Prospective cohort study HOPS (HIV Outpatient Study) (January 1996- June 2001) at 8 clinics in 7 cities in the USA</td>
<td>823 HIV-infected patients with and without HCV coinfection 32.4% (267/823) were infected with both HIV and HCV, and 556 (67.6%) were seropositive only for HIV. Compared with the 556 patients in the HIV-only group, HIV-HCV-coinfected patients were more likely to have injection drug use as their HIV transmission risk (69.7% vs. 5.4%; P&lt;0.001), to be non-white (68.9% vs. 62.0%; were African American or Hispanic, P&lt;0.001), to have received &lt;12 years of education (26.6% vs. 17.8%; P&lt;.001), and to have undergone care with the use of public funds, such as Medicaid, Medicare, and Ryan White funding (75.7% vs. 57.7%; P&lt;0.001).</td>
<td>40.5 in co-infected group, 35 in HIV-only group</td>
<td>Not reported</td>
<td>Not reported.</td>
<td>6 months observation; median around 3 years</td>
<td>Concurrent hepatitis C on survival in patients with coinfection compared with those without</td>
<td>HR 0.91</td>
<td>0.55 to 1.51, p-value=0.7129</td>
<td>Cox proportional survival model, controlling for CD4+ cell count, number of weeks receiving HAART, and patient age Persons (especially injection drug users who continue to use drugs) may have seroconversions to HCV antibody positivity after they test negative and may have been placed in the HIV-only comparison group erroneously. Misclassifications of patients in the HIV-only patients group. These patients had ≥1 negative result of an HCV test, but these tests were not performed at the same time that persons were assigned into the patients groups. This misclassification was avoided by excluding the 269 patients who did not undergo serological testing for hepatitis C. Another source of misclassification might be result from using quantitative and not qualitative HCV testing was used by the clinicians who tested patients receiving ambulatory care, resulting in false-negative virological results among HCV-infected patients.</td>
<td></td>
</tr>
<tr>
<td>Name Design</td>
<td>Sample</td>
<td>N</td>
<td>% Female</td>
<td>Follow-up Rate</td>
<td>Follow-up Time</td>
<td>Risk Factor on Outcome</td>
<td>OR unless Otherwise Specified</td>
<td>95% CI</td>
<td>Data Analysis</td>
<td>Comments/ Study Quality/ Biases</td>
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</tr>
<tr>
<td>Macias 2002 Prospective cohort study (April 1989-September 2000) Spain</td>
<td>492 patients who were prescribed antiretroviral drugs between April 1989 and September 2000, and who were seen at least two scheduled visits were enrolled in this study. HCV infection was present in 66% (323/492) patients. - The duration of HCV infection could be estimated in 255 (79%) of 323 HCV-coinfected patients. - The median (Q1-Q3) duration of HCV infection in those patients was 12.7 years @range, 10.7-14.6 years</td>
<td>31.5; ranging from 28.6 to 36 years</td>
<td>12.8%</td>
<td>3-monthly</td>
<td>Concurrent hepatitis C on time to death from any cause</td>
<td>Not reported</td>
<td>P-value=0.4</td>
<td>Cox model controlling for age, sex, risk group, AIDS at baseline, CD4 count at baseline</td>
<td>Death certificates were used as the source of data on the cause of death when the patient was lost to follow-up. The causes of death were classified into three groups: death due to AIDS, death due to a complication of liver failure; and death due to other causes. Duration of hepatitis C virus infection was estimated as the difference in years between the end of the follow-up in the study cohort and the first years in which the patients shared the equipment for intravenous drug use. It is thought that the change in the case definition of HCV infection, during the study period, between periods could be a source of bias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Design</td>
<td>Name</td>
<td>Sample</td>
<td>N</td>
<td>% Female</td>
<td>Follow-up Rate</td>
<td>Follow-up Time</td>
<td>Risk Factor on Outcome</td>
<td>OR unless Otherwise Specified</td>
<td>95% CI</td>
<td>Data Analysis</td>
<td>Comments/Study Quality/BIases</td>
</tr>
<tr>
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</tr>
<tr>
<td>Prospective cohort study France</td>
<td>Piroth 2000</td>
<td>812 HIV-infected patients with known HIV acquisition date, 89/812 [11%] co-infected with HCV; 150 patients showed clinical progression; 3 deaths occurred, none of which was related to hepatic disease; 254 patients had CD4 cell counts that fell below 200 mm-3</td>
<td>Median age at HIV acquisition 31 years, ranging from 16 to 73 years</td>
<td>29%</td>
<td>Every 3 months</td>
<td>Mean 30 months, ranging from 1 month to 6.5 years</td>
<td>Concurrent hepatitis C on shortened time to clinical progression (incl AIDS or any-cause death)</td>
<td>HR 1.63</td>
<td>1.06 to 2.49, p-value=0.003</td>
<td>Multivariate Cox model</td>
<td>- The major inclusion criterion was a known HIV-acquisition date, assessed by one or more of the following: 1. Symptomatic HIV primary infection 2. HIV contamination risk period shorter than 2 years, and/or 3. Documented HIV seroconversions, with time between last negative and first positive HIV-1 enzyme-linked immunosorbent assay (ELISA) serology shorter than 2 years. Clinical progression defined as one or more of the following: 1. 20% decrease in initial weight; and/or 2. 30% decrease in initial Karnofsky's index; and/or 3. AIDS-defining illness (according to the 1993 Centre for Disease Control [CDC, Atlanta, GA] classification); and/or 4. Death (except by accident, suicide or drug overdose). Immunological progression defined as a decrease in the CD4 T-cell count to below 200 mm-3. Time to progression defined as the interval between acquisition date and time when clinical or immunological progression criteria was met. Uncertainties about hepatitis C infection in the studies population as exact duration of HCV infection could not be definitely established, and HCV viremia and liver history were not available for HCV-infected patients.</td>
</tr>
</tbody>
</table>

GPs: general practitioners; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HR: Hazard ratio; IDU: Injecting drug user; IRR: Incidence Rate Ratio; MSM: Men who have sex with men; PY: Person-years; RR: Relative risk
### Evidence Table 3.11: HIV Progression in Syphilis Coinfection

<table>
<thead>
<tr>
<th>Name Design</th>
<th>N</th>
<th>SAMPLE AGES</th>
<th>% Female</th>
<th>Follow-up Rate</th>
<th>Follow-up Time</th>
<th>Risk Factor</th>
<th>HR</th>
<th>95% CI</th>
<th>Comment/Study Quality/ Biases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weintrob et al. (2010) Cohort study (US Military HIV Natural History Study) between 1985 and 2006 in USA</td>
<td>2239 HIV seroconverters; 205 [9.2%] with confirmed syphilis (concurrently positive non-treponemal and treponemal assays), 66 [2.9%] with probable syphilis (treated for clinical diagnosis of syphilis or inconsistent assay results)</td>
<td>Mean age 28 years</td>
<td>6%</td>
<td>Approximately 6-monthly</td>
<td>Mean follow-up from HIV diagnosis: 3.5 years; 7827 person-years in total</td>
<td>HIV progression (time to death or AIDS) in those with confirmed syphilis</td>
<td>0.99 (p = 0.90)</td>
<td>0.73 to 1.33</td>
<td>Stage of syphilis at diagnosis not always known, response to syphilis treatment not considered.</td>
</tr>
</tbody>
</table>

HR: Hazard ratio
### Evidence Table 3.12: STIs in General

<table>
<thead>
<tr>
<th>Number of Studies (Participants)</th>
<th>Outcome</th>
<th>Intervention/ Risk Factor</th>
<th>Type of Evidence</th>
<th>Quality</th>
<th>Consistency</th>
<th>Directness</th>
<th>Effect Size</th>
<th>Grade</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (466) [Kaul 2004]</td>
<td>HIV incidence</td>
<td>Regular antibiotic prophylaxis of bacterial STIs in addition to intensive HIV risk reduction strategies vs. intensive HIV risk reduction strategies alone</td>
<td>4</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Moderate</td>
<td>Quality point deducted for single study with low HIV incidence rate.</td>
</tr>
<tr>
<td>At least 3 (at least 466)</td>
<td>HIV incidence</td>
<td>STIs in general</td>
<td>2</td>
<td>0</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>Very low</td>
<td>Consistency point deducted for large difference between results</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chlamydia trachomatis</td>
<td>2</td>
<td>-1</td>
<td>0</td>
<td>-2</td>
<td>+1</td>
<td>Very low</td>
<td>Quality point deducted for self-reported data in one study; Directness points deducted for composite risk factor in one study and significant difference between analyzed cohorts in another; Point added for large effect size found in one study</td>
</tr>
<tr>
<td>3 (10,713) [Van de Wijgert 2009] [Jin 2007] [Sharghi 2005]</td>
<td>HIV incidence</td>
<td>Chlamydia trachomatis infection</td>
<td>2</td>
<td>-1</td>
<td>0</td>
<td>-2</td>
<td>+1</td>
<td>Very low</td>
<td>Quality point deducted for self-reported data in one study; Directness points deducted for composite risk factor in one study and significant difference between analyzed cohorts in another; Point added for large effect size found in one study</td>
</tr>
<tr>
<td>6 (26,665) [Jin 2010] [Zetola 2009] [Jin 2007] [Van de Wijgert 2009] [Sharghi 2005] [Van der Bij 2005]</td>
<td>HIV incidence</td>
<td>Gonorrhea</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>+1</td>
<td>Low</td>
<td>Directness point deducted for composite risk factor in 2 studies; point added for large effect size (ranging from 3.03 to 17)</td>
</tr>
<tr>
<td>Number of Studies (Participants)</td>
<td>Outcome</td>
<td>Intervention/ Risk Factor</td>
<td>Type of Evidence</td>
<td>Quality</td>
<td>Consistency</td>
<td>Directness</td>
<td>Effect Size</td>
<td>Grade</td>
<td>Comment</td>
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<tr>
<td>Hepatitis B</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 (1,622) Jin 2007</td>
<td>HIV incidence</td>
<td>Hepatitis B infection</td>
<td>2</td>
<td>-2</td>
<td>+1</td>
<td>-1</td>
<td>+2</td>
<td>Low</td>
<td>Quality points deducted for cross-sectional study design and single study; consistency point added for risk increase with hepatitis B coinfection and protective effect from hepatitis B vaccination; directness point deducted for including homosexual men only; two points added for very large effect size</td>
</tr>
<tr>
<td>4 (4,914) Hoffmann 2009</td>
<td>HIV virological or immunological progression</td>
<td>Concurrent hepatitis B</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Low</td>
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<tr>
<td>Law 2004</td>
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<tr>
<td>Lincoln 2003</td>
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<tr>
<td>De Luca 2002</td>
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</tr>
<tr>
<td>At least 11,935 (at least 11,935) Nikolopoulos 2009</td>
<td>HIV progression to AIDS-defining event or AIDS-related mortality</td>
<td>Concurrent hepatitis B</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td></td>
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<tr>
<td>Hoffmann 2009</td>
<td></td>
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<td>Law 2004</td>
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<tr>
<td>Lincoln 2003</td>
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<tr>
<td>De Luca 2002</td>
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</table>
### STIs in General

<table>
<thead>
<tr>
<th>Number of Studies (Participants)</th>
<th>Outcome</th>
<th>Intervention/ Risk Factor</th>
<th>Type of Evidence</th>
<th>Quality</th>
<th>Consistency</th>
<th>Directness</th>
<th>Effect Size</th>
<th>Grade</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis C</strong></td>
<td></td>
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</tr>
<tr>
<td>19 (42,938)</td>
<td>Clinical progression or immunological response to HIV therapy</td>
<td>Concurrent hepatitis C</td>
<td>2</td>
<td>0</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>Very low</td>
<td>Consistency point deducted for conflicting results</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>8 (24,640)</td>
<td>Virolgical response to HIV therapy</td>
<td>Concurrent hepatitis C</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td></td>
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</tr>
<tr>
<td><strong>Syphilis</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4(19,069)</td>
<td>HIV incidence</td>
<td>Recent syphilis</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>+1</td>
<td>Low</td>
<td>Directness point deducted for composite risk factor in one study and HIV estimated from HIV RNA prevalence results in another study; point added for large effect size</td>
</tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 (2239)</td>
<td>HIV progression</td>
<td>Concurrent syphilis</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td></td>
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</table>
### STIs in General

<table>
<thead>
<tr>
<th>Number of Studies (Participants)</th>
<th>Outcome</th>
<th>Intervention/ Risk Factor</th>
<th>Type of Evidence</th>
<th>Quality</th>
<th>Consistency</th>
<th>Directness</th>
<th>Effect Size</th>
<th>Grade</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 (7,715) [Hilber 2010]</td>
<td>HIV incidence</td>
<td>Trichomoniasis</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>0</td>
<td>Very low</td>
<td>Directness point deducted for studies conducted in women only</td>
</tr>
</tbody>
</table>

*Trichomoniasis*
### Appendix E – Patient Counseling

#### 4. Patient Counseling

##### Problem Formulation 4

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>Does patient counseling reduce STI transmission and risk behavior?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>All persons aged $\geq 12$ at risk for acquiring HIV/STI</td>
</tr>
</tbody>
</table>
| Health Intervention | • One-on-one counseling  
                    |   • Group counseling                                      |
| Important Health Outcomes | • Decrease in HIV/STI mortality  
                                    |   • Decrease in HIV/STI morbidity  
                                    |   • Increased and earlier HIV/STI case identification  
                                    |   • Increased HIV/STI case prevention  
                                    |   • Benefits, harms of counseling  |
Search Strategy 4

The search strategy was to update the searches conducted previously. Selected evidence was restricted to systematic reviews, meta-analyses, and RCTs in populations at risk of STI and/or HIV.

<table>
<thead>
<tr>
<th>Database</th>
<th>Terms</th>
<th>Article Type and Limits</th>
<th>Time Frame</th>
<th>No. Included / Total Retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Randomized Controlled Trial, English, Human</td>
<td>1996 to 10/2010</td>
<td>4/4</td>
</tr>
<tr>
<td>Cochrane</td>
<td>STI OR HIV AND patient counseling</td>
<td>Systematic Reviews, Clinical Trials</td>
<td>Accessed 10/2010</td>
<td>0/0</td>
</tr>
<tr>
<td>Clinical Evidence</td>
<td>STI OR HIV AND patient counseling</td>
<td>Patient counseling for STIs and/or HIV</td>
<td>Accessed 10/2010</td>
<td>1/1</td>
</tr>
</tbody>
</table>

**Search Strategy**

A comprehensive search was conducted in September 2010 (and refreshed in November 2010) to identify RCTs relevant to this problem formulation.

RCTs were evaluated for inclusion if they compared patient counseling techniques to usual treatment (other counseling modalities or no counseling) in adolescents and adults at risk for STI. A total of four studies and one set of recommendations from the US Preventive Services Task Force (USPSTF) were identified. Upon additional review of the USPSTF recommendations, all four studies were included in the evidence synthesis prepared for the USPSTF’s October 2008 recommendations on Behavioral Counseling to Prevent Sexually Transmitted Infections (Lin et al., 2008). Therefore, the evidence synthesis prepared for the USPSTF serves as the systematic review of the literature relevant to the clinical question on the effect of behavioral counseling on STI transmission and risk behavior. As the USPSTF is a nationally-renowned and respected source of evidence-based material, the GDT agreed to use its systematic reviews and recommendations as the foundation for its own recommendations. See Appendix G for information on USPSTF inclusion and exclusion criteria.
Evidence Summary
Using the USPSTF’s established methodology, five key questions were used to update and guide the literature search and systematic review (See Summary of Results section).

Overall, the USPSTF found fair to good evidence that moderate to high intensity behavioral counseling conducted in STI clinics effectively reduced STI incidence in at risk populations. Among sexually active adolescents, there is fair to good evidence that high intensity behavioral counseling effectively reduced STI incidence in primary care settings. There is a need for additional evidence for both lower-intensity behavioral counseling interventions and studies in lower-risk populations. See Appendix G for summary evaluation.

USPSTF Recommendations Summary
- The USPSTF recommends high-intensity behavioral counseling for all sexually active adolescents and for adults at increased risk for STIs. (B recommendation*)
- Current evidence is insufficient to assess the balance of benefits and harms of behavioral counseling to prevent STIs in non-sexually active adolescents and in adults not at increased risk for STIs. (I statement†)

Effective Behavioral Counseling Interventions
- Among the studies reviewed, successful high-intensity interventions were delivered through multiple sessions, most often in groups, with total durations from three to nine hours. Little evidence suggests that single-session interventions or interventions lasting less than 30 minutes were effective in reducing STIs (Lin et al., 2008).(3)
- Although two studies of moderate-intensity interventions did demonstrate effect (Danielson et al., 1990; Wenger et al, 1992),(95, 96) a third study (Kamb et al., 1998)(97) demonstrated that two 20-minute counseling sessions before and after HIV testing resulted in a clinically and statistically significant reduction in STIs.
- The USPSTF found no studies of abstinence-only counseling programs delivered in the clinical setting (Lin 2008).(3)
- There is convincing evidence that high-intensity behavioral counseling interventions targeted to sexually active adolescents and adults at increased risk for STIs reduce the incidence of STIs. These results were found six and twelve months after counseling took place.

Implementation Considerations
- High-intensity behavioral counseling may be delivered in primary care settings or in other sectors of the health system after referral from the primary care clinician or system. In addition, risk-reduction counseling may be offered by community organizations. Strong linkages between the primary care setting and the community may greatly improve the delivery of this service.

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* The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.

† The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.
Effectiveness of Counseling to Change Behavior

- Most of the evidence found by the review concerns high-intensity interventions given to sexually active adolescents and adults who were at increased risk for STIs.
- Five of six trials demonstrated statistically significant reductions in biologically confirmed STIs at six and twelve months after the interventions.
- The absolute risk reduction rate ranged from 2.6% to 11.1%, with generally higher rates of reduction among adolescents.
- As noted, the interventions in this group were considered “high-intensity”; they included a single 4-hour session, three 1-hour sessions over three consecutive weeks, four 4-hour sessions, and a 10-session intervention.
- One fair-quality study found that HIV testing in combination with two 20-minute individual counseling sessions (a less intensive intervention than the others reviewed) led to a significant reduction in new STIs, including chlamydia, gonorrhea, syphilis, and HIV, at both six and twelve months after the intervention.
- Another study found that a single, 20-minute, one-to-one skills counseling session delivered in a primary care office may reduce STIs 12 months thereafter among women who are at increased risk for STIs (Jemmott et al., 2005). Because the reported results combined women who received this low-intensity intervention with a group of women who received 200 minutes of group counseling, additional research is needed to determine whether lower-intensity interventions can be effective.
- The review did not identify any trials evaluating behavioral counseling interventions directed at adults or adolescents who are not at increased risk for STIs.

Potential Harms of Counseling

- No evidence of significant behavioral or biological harms resulting from behavioral counseling about risk reduction has been found. The USPSTF concluded that the potential harms of counseling are no greater than small.

Summary of Results

Key Question 1 - Is there direct evidence that behavioral counseling interventions to reduce risky sexual behaviors and increase protective sexual behaviors reduce STI incidence and/or related morbidity and mortality?

Adults

- The majority of evidence (four RCTs, n = 7,558) suggests a modest reduction in STI at six or twelve months among “at-risk” adults receiving multiple intervention sessions (Carey et al., 2004; Kamb et al., 1998; Shain et al, 1999; Shain et al., 2004). Three of the four trials conducted in STI clinics (three RCTs, n = 7,150) showed a moderate decrease in bacterial STI incidence at 12 months, compared to usual care that included only minimal counseling (Kamb et al., 1998; Shain et al, 1999; Shain et al., 2004). One of these trials, Project SAFE 2, reported a similar magnitude of reduction in STI incidence at two years. One trial, Project RESPECT, combined HIV counseling with testing (Kamb et al., 1998).
In contrast, one fair-quality trial conducted in an STI clinic (n = 393) did not show an effect on STI incidence at six months. In a fair-quality RCT (n = 408), psychiatric clinic outpatients with a history of alcohol or other substance abuse who received ten sessions of group counseling on sexual risk reduction had a lower incidence of self-reported STI at six months, compared to those receiving similarly formatted substance abuse counseling (Carey et al., 2004). In the single fair-quality RCT conducted in an HMO primary care setting (n = 210), young nonmonogamous women receiving two rounds of tailored printed materials did not show a significant difference in self-reported STIs at six months, compared with usual care (Scholes et al, 2003). In general, all trials were well conducted RCTs. Project RESPECT, however, had only 70 percent follow-up at six months, and 66 percent follow-up at 12 months. Similarly, an RCT by Boyer et al. with non-significant intervention effects had approximately 70 percent follow-up at six months. Two trials, one by Carey et al. (2004) and one by Scholes et al. (2003) used self-reported measures of STI incidence.

Adolescents

- The majority of evidence (three RCTs, n = 1,998) showed a modest reduction in STI incidence at 12 months in sexually active adolescents.
- All three RCTs in sexually active adolescents, who had much higher baseline risks for STIs, showed a decrease in laboratory positive STIs at 12 months.
- One of these trials, Project RESPECT, combined HIV counseling with testing.
- One fair-quality RCT that included pre-sexually active adolescents (n = 219) found that in those who received a low-intensity counseling intervention (15 minute standardized risk assessment and discussion of risk with pediatrician) did not have a significant difference in self-reported STIs at three or nine months (Boekeloo et al, 1999).
- The RCT by Boekeloo et al. (1999) with non-significant intervention effects was likely not powered to show a difference in STI incidence, given the small sample size and low percentages of incident STI. In addition, this RCT used self-reported measures of STI incidence.

Pregnant Women

- No studies were identified that met the inclusion criteria specifically addressing pregnant women.
- One study by Shain et al. (2004) included about 30% pregnant women. Their results, however, were not reported separately for this subgroup.
**Key Question 2 - Do behavioral counseling interventions to prevent STIs in primary care reduce risky sexual behaviors or increase protective sexual behaviors?**

**Adults**

- Of the three trials only one showed a reduction in risk sexual behaviors (unprotected sexual intercourse, multiple sex partners) or an increase in consistent condom use. This trial by Ehrhardt et al. (2002)\(^{(103)}\) was conducted in a family planning clinic. The trial showed a decrease at 12 months in self-reported unprotected sexual intercourse and an increase in (male and female) condom use in the extremely intensive counseling intervention arm. The intervention consisted of nine 2-hour group sessions, but not using a less-intensive intervention consisting of five 2-hour group sessions. Measures of self-reported behavioral outcomes (e.g., unprotected sexual intercourse, condom use, and number of sexual partners) and methods of data collection (e.g., interview or questionnaire) varied amongst trials.

**Adolescents**

- One fair-quality trial that examined the impact of primary care feasible behavioral counseling interventions on reducing self-reported risky sexual behaviors or increasing protective sexual behaviors in adolescents was identified (Danielson et al, 1990).\(^{(95)}\) This fair-quality RCT was conducted in an HMO, which included both sexually and presexually active adolescents.
- This RCT did not show an increase in condom use or abstinence at 12 months in male adolescents who received a single 1-hour counseling intervention, compared with those who did not.

**Pregnant Women**

- No studies that met the inclusion criteria were found that specifically addressed pregnant women.
- One study by Hobfoll et al. (1994)\(^{(104)}\) was excluded for poor quality.
Key Question 3 - Are there other positive outcomes besides sexual behavioral changes and reduced incidence of STI resulting from behavioral counseling interventions to prevent STIs in primary care?

- Within the body of literature examined for Key Question 1 and Key Question 2, evidence of other positive outcomes obtained from behavioral counseling interventions was examined.

- The USPSTF did not discuss outcomes that were primarily psychosocial mediators of behavior (e.g., knowledge, attitude and self-esteem, and ability changes), although these measures were reported in many of the included studies (Boyer et al., 1997; Carey et al., 2004; Kamb et al., 1998; Scholes et al., 2003; Boekeloo et al., 1999; DiClemente et al., 2004; Jemmott et al., 2005; Proude et al., 2004; Wenger et al., 1992; Danielson et al., 1990; Korte, et al., 2004). (95-98, 100-102, 105-108)

- In general, few studies reported on other behavioral or biological outcomes.

- Adults – evidence suggests that behavioral counseling increases compliance with treatment recommendations for women in an STI clinic setting (Shain et al., 1999; Shain et al, 2004; Ehrhardt et al., 2002). (99, 100, 103)

- Adolescents - evidence suggests that behavioral counseling may decrease other risky behavior and pregnancy in sexually active female adolescents, and increase general contraception use in male adolescents (Boekeloo et al., 1999; DiClemente et al., 2004; Jemmott et al., 2005; Danielson et al., 1990). (95, 102, 106, 107)

Key Question 4 - What are the adverse effects associated with behavioral counseling interventions to prevent STIs in primary care to reduce risky sexual behaviors and increase protective sexual behaviors?

**Adults**

- Overall, the nine trials evaluating risk reduction counseling in adult populations showed no evidence of increased incidence of STIs or self-reported risky behaviors, including increased unprotected sex or increased number of sexual partners (Boyer et al., 1997; Carey et al., 2004; Kamb et al., 1998; Scholes et al., 2003; Shain et al., 1999 and 2004; Ehrhardt et al., 2002; Proude et al., 2004; Wenger et al., 1992). (96-101, 103, 105, 108)

- The six trials that reported on biological outcomes showed no evidence of increased incidence of STIs, either by self report or laboratory testing (Boyer et al., 1997; Carey et al., 2004; Kamb et al., 1998; Scholes et al., 2003; Shain et al., 1999 and 2004). (97-101, 105) Eight trials showed no evidence of self-reported increased unprotected sex (or decreased use of condoms) (Boyer et al., 1997; Carey et al., 2004; Kamb et al., 1998; Scholes et al., 2003; Shain et al., 1999; Ehrhardt et al., 2002; Proude et al., 2004; Wenger et al., 1992). (96-99, 101, 103, 105, 108) Six trials showed no evidence of self-reported increase in the number of sexual partners.
Adolescents

- Overall, the five trials evaluating risk-reduction counseling in adolescents showed no evidence of increased incidence of STIs or self-reported risk behaviors including increased unprotected sex, increased number of sexual partners, or earlier onset of sexual debut (Boekeloo et al., 1999; DiClemente et al., 2004; Jemmott et al., 2005; Danielson et al., 1990). No trials evaluating abstinence-only counseling interventions met inclusion criteria. Therefore, potential harms or benefits could not be assessed.

- The four trials that reported on biological outcomes showed no evidence of increased incidence of STIs, either by self-report or laboratory testing (Boekeloo et al., 1999; DiClemente et al., 2004; Jemmott et al., 2005; Danielson et al., 1990).

- Five trials showed no evidence of an increase in self-reported unprotected sex (or decreased use of condoms) (Boekeloo et al., 1999; DiClemente et al., 2004; Jemmott et al., 2005; Danielson et al., 1990).

- Two trials showed no evidence of an increase in the participants’ self-reported number of sexual partners (Kamb et al., 1998; Jemmott et al., 2005).

- One trial by (Boekeloo, 1999) showed a transient increase in self-reported vaginal sex at three months, but not at nine months, in adolescents aged 12 to 15 years.

- There was no increase, however, in self-reported overall sexual intercourse (vaginal, oral, or anal sex).

**Key Question 5 - Do sexual behavioral changes, including reducing risky sexual behaviors and increasing protective sexual behaviors, lead to a reduced incidence of STIs and/or related morbidity and mortality?**

- As the effectiveness of male condoms for the prevention of STIs has already been established, the literature on female condom use was evaluated.

- Four trials examining the effectiveness of female condoms in reducing the incidence of STIs were identified.

- One study was excluded for poor quality (Soper et al., 1993).

- The remaining three studies were RCTs comparing the effectiveness of female plus male condom use compared to male condom use alone (Feldblum et al., 2001; Fontanet et al., 1998; French et al., 2003).

- Only one study was conducted in the US, the other two were conducted in Kenya and Thailand.

- All three studies suggest that counseling women to use female condoms and providing female condoms offers similar protection against bacterial STIs as counseling women to use male condoms.

- Although none of these trials were powered as non-inferiority studies, there were no statistical differences in the incidences of bacterial STIs between the women using female and male condoms versus the women only using male condoms. The percentages of women using female condoms were consistently low in the two trials that report on female condom use.
**Professional Society Recommendations**

- The American Academy of Family Physicians recommends counseling adolescents and adults on the risks for sexually transmitted diseases and how to prevent them (2008).

- The American Academy of Pediatrics does not have a specific recommendation regarding behavioral counseling to prevent STIs; however, in related recommendation statements, they recommend counseling for adolescents regarding abstinence and the importance of barrier contraceptives (2006).

- The American College of Obstetricians and Gynecologists recommends counseling all women regarding partner selection and use of barrier contraception to prevent STIs. In addition, they recommend counseling female adolescents about what constitutes responsible, consensual sexual behavior and that abstinence from sexual intercourse is the only definitive way to prevent pregnancy and STIs (2004).

- The American Medical Association encourages all physicians to educate their patients about sexually transmitted diseases and proper condom use (2008).
Appendix F - Population Risk and Intervention Intensity Terminology

The USPSTF did not identify any trials evaluating primary care feasible behavioral counseling interventions to prevent STIs in general-risk (i.e., “average”) populations.

All the populations assessed in the review were “at risk”, typically reporting higher than average STI incidence (e.g., adolescents and young adults, black/African-American, Hispanics, mentally ill and disturbed persons, those living in low-income urban areas or persons with a previous or present history of an STI). Consequently, the term “low-risk” is used to describe the general primary care population while “high-risk” is used to describe “at-risk” groups.

Given the large variation in intensity of behavioral counseling interventions studied, the term “low intensity” describes single-visit counseling interventions lasting less than 30 minutes, or any intervention that could be added to usual primary care without significant additional time visit. Moderate intensity is used to describe interventions lasting longer than 30 minutes, but less than two hours in total while high intensity describes multiple-visit interventions requiring longer than two hours.

Inclusion and Exclusion Criteria

Included studies -

- A primary care feasible behavioral counseling intervention addressing sexual behavior change (e.g., sexual risk reduction or sexual risk avoidance) with the primary intention of preventing STI transmission,
- Behavioral counseling interventions conducted in primary care settings, or judged to be feasible for delivery in primary care based,
- Counseling interventions with individual-level participant identification; a primary care practitioner or related clinical staff; and individual or small-group format, with a limited number of sessions, or at a minimum be viewed as connected to the health care system,
- Behavioral counseling interventions that included an active component of community outreach, use of community members (e.g., opinion leaders, peer facilitators), use of community programs (e.g., worksite programs, school programs), use of social marketing, or use of public policy changes were not considered primary care feasible and
- Studies that reported either biological (e.g., STI incidence) or behavioral outcomes at three months post counseling or later.

Excluded studies -

- School- and university-based trials unless conducted in a school- or university-based health clinic. Studies that exclusively enrolled participants from correctional facilities, substance abuse- treatment facilities, HIV clinics, and inpatient hospital units were also excluded, and
- Studies that reported outcomes on knowledge, attitudes, self-esteem, and ability changes (skills).
**Appendix G - USPSTF –**  
Patient Counseling: Evidence Summary and Evaluation\(^{(3),*}\)  

### Question 1 - Is there direct evidence that behavioral counseling interventions to reduce risky sexual behaviors and increase protective sexual behaviors reduce STI incidence and/or related morbidity and mortality? (Biological Outcomes)

<table>
<thead>
<tr>
<th># of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Applicability</th>
<th>Overall Quality</th>
<th>Summary of Findings</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>6(^{(02, 00, 101, 113)})</td>
<td>RCT</td>
<td>Limited number of trials with significant heterogeneity in populations and interventions.</td>
<td>Inconsistency between STI clinic and non-STI clinic setting and intensity of intervention.</td>
<td>Trials conducted in urban areas; 4 trials in predominantly African American (AA) and/or Hispanic adults; 4 trials in STI clinics; 1 trial in a psychiatric clinic</td>
<td>Fair-Good</td>
<td>Three of the six trials (n = 7150) showed a moderate reduction in STI incidence at 12 months among adults in STI clinics receiving moderate to high-intensity counseling interventions. One trial (n=393) did not show a reduction in STI incidence at 6 months in adults attending an STI clinic receiving a high-intensity counseling intervention. One trial in a psychiatric clinic (n = 408) showed a moderate reduction in self-reported STI incidence using a high-intensity counseling intervention. One trial (n = 1210) did not show a reduction in self-reported STIs in adults receiving a low-intensity counseling intervention.</td>
<td>Self-reported measures of STI outcomes should be interpreted cautiously.</td>
</tr>
</tbody>
</table>

* Behavioral Counseling to Prevent Sexually Transmitted Infections, prepared for AHRQ (October 2008); AHRQ Publication No. 08-05123-EF-1
<table>
<thead>
<tr>
<th># of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Applicability</th>
<th>Overall Quality</th>
<th>Summary of Findings</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>4[97, 102, 114]</td>
<td>RCT</td>
<td>Limited number of trials with significant heterogeneity in populations and interventions.</td>
<td>Inconsistency between sexually active adolescents and general adolescent population and intensity of intervention.</td>
<td>Trials conducted in urban areas in predominantly AA and/or Hispanic adolescents</td>
<td>Fair-Good</td>
<td>Sexually active adolescents: All three trials (n = 1998) showed a modest reduction in laboratory diagnosed STI incidence at 12 months in sexually active adolescents receiving moderate to high-intensity counseling interventions. Pre-sexually and sexually active adolescents: One trial (n = 219) did not show a reduction in self-reported STI incidence at 3 or 9 months in young adolescents receiving a low-intensity counseling intervention.</td>
<td>One of the 4 trials is a subgroup analysis by age group of Project RESPECT</td>
</tr>
</tbody>
</table>
Question 2 – Do behavioral counseling interventions to prevent STIs in primary care reduce risky sexual behaviors or increase protective sexual behaviors? (Behavioral Outcomes)

<table>
<thead>
<tr>
<th># of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Applicability</th>
<th>Overall Quality</th>
<th>Summary of Findings</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>RCT</td>
<td>Limited number of trials with significant heterogeneity in populations, interventions, and measurement of outcomes.</td>
<td>Inconsistency by intervention intensity and population risk.</td>
<td>Trials conducted in urban areas; 1 trials in predominantly AA and/or Hispanic adults; 1 trial in a university health clinic; 1 trial in Australia</td>
<td>Fair</td>
<td>Two of the three trials did not show a decrease in self reported risky sexual behavior (i.e. unprotected sexual intercourse or multiple sex partners or increase in self reported male condom use) in adults receiving low to high-intensity counseling interventions. Only one trial showed a decrease in self-reported unprotected sexual intercourse and increase in self reported (male and female) condom use at 12 months in women with a high percentage of previous STI, receiving a very high-intensity counseling intervention (18 hours), but not a high-intensity counseling intervention (10 hours).</td>
<td></td>
</tr>
<tr>
<td>Adolescents</td>
<td>RCT</td>
<td>Only one study, N/A</td>
<td>N/A</td>
<td>High school boys in urban HMO setting</td>
<td>Fair</td>
<td>Pre-sexuality and sexually active adolescents: This study did not show an increase in condom use or abstinence at 12 months in male adolescents receiving a moderate intensity counseling intervention.</td>
<td></td>
</tr>
</tbody>
</table>
### Question 3 - Are there other positive outcomes besides sexual behavioral changes and reduced incidence of STI resulting from behavioral counseling interventions to prevent STIs in primary care? (Other Positive Outcomes)

<table>
<thead>
<tr>
<th># of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Overall Quality</th>
<th>Summary of Findings</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>RCT</td>
<td>Limited number of trials with significant heterogeneity in populations and interventions</td>
<td>No inconsistencies</td>
<td>Trials conducted in urban areas in predominantly AA and/or Hispanic adults</td>
<td>Fair</td>
<td>Two trials conducted in STI clinics found that women receiving high-intensity group counseling also had increased STI treatment compliance, as measured by self-reported unprotected intercourse with untreated or incompletely treated sex partner. Another trial did not show an increase in self-reported 'alternative risk reduction' strategies with high-intensity group counseling at 12 months.</td>
</tr>
<tr>
<td>Adolescents</td>
<td>RCT</td>
<td>Limited number of trials with significant heterogeneity in populations and interventions</td>
<td>No serious inconsistencies</td>
<td>Trials conducted in urban areas; 3 trials in predominantly AA and/or Hispanic adolescents</td>
<td>Fair</td>
<td>Sexually active adolescents: One trial showed a decrease in self-reported sex while intoxicated at 3 and 6 months, but not at 12 months in female adolescents receiving high-intensity group counseling. Another trial showed a decrease in self-reported pregnancy at 6 months, but not at 12 months, in female adolescents receiving high intensity group counseling. Pre-sexually and sexually active adolescents: One trial did not show a statistically significant decrease in self-reported pregnancy in adolescents receiving a low intensity counseling intervention, which also had a smaller sample size and fewer reported pregnancies. Another trial showed an increase in general contraception use in male adolescents receiving a moderate-intensity counseling intervention.</td>
</tr>
</tbody>
</table>
**Question 4 – What are the adverse effects associated with behavioral counseling interventions to prevent STIs in primary care to reduce risky sexual behaviors and increase protective sexual behaviors? (Adverse Effects)**

<table>
<thead>
<tr>
<th># of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Applicability</th>
<th>Overall Quality</th>
<th>Summary of Findings</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>RCT</td>
<td>Limited number of trials with significant heterogeneity in populations, interventions, and measurement of outcomes.</td>
<td>No inconsistencies</td>
<td>Trials conducted in urban areas; 6 trials in predominantly AA and/or Hispanic adults; 4 trials in STI clinics; 1 trial in a psychiatric clinic, 1 trial in a university health clinic; 1 trial in Australia</td>
<td>Fair-Good</td>
<td>Overall, no increase in number of sexual partners, unprotected sexual intercourse or STI incidence by testing or self-report with low- to high-intensity counseling interventions.</td>
<td></td>
</tr>
<tr>
<td>Adolescents</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>RCT</td>
<td>Limited number of trials with significant heterogeneity in populations, interventions, and measurement of outcomes.</td>
<td>No serious inconsistencies</td>
<td>Trials conducted in urban areas; 3 trials in predominantly AA and/or Hispanic adolescents</td>
<td>Fair-Good</td>
<td>Sexually active adolescents: Overall, no increase in number of sexual partners, unprotected sexual intercourse, or STI incidence by testing or self-report with high-intensity counseling interventions. Pre-sexually and sexually active adolescents: One study showed a transient increase of vaginal sex in young adolescents receiving a low-intensity counseling intervention at 3 months, OR 2.46, 95%CI (1.04-5.84); but NOT at 9 months, and no increase in overall sexual activity at either follow-up. Another study in an HMO setting showed no evidence of earlier sexual debut in male adolescents receiving a moderate-intensity counseling intervention.</td>
<td>Risk reduction counseling only.</td>
</tr>
</tbody>
</table>
**Question 5 – Do sexual behavioral changes, including reducing risky sexual behaviors and increasing protective sexual behaviors, lead to a reduced incidence of STIs and/or related morbidity and mortality? (Female Condoms)**

<table>
<thead>
<tr>
<th># of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Applicability</th>
<th>Overall Quality</th>
<th>Summary of Findings</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>3(10-11)</td>
<td>1 RCT, 2 cluster RCT</td>
<td>Limited number of trials with significant heterogeneity in populations and interventions.</td>
<td>No inconsistencies</td>
<td>One in US STI clinic; one in Thai sex workers in Thailand; and one in rural Kenya</td>
<td>Fair</td>
<td>All three studies suggest that counseling women to use female condoms and providing female condoms in addition to male condoms offers similar protection against bacterial STIs as counseling women to use male condoms and providing male condoms.</td>
<td></td>
</tr>
</tbody>
</table>

Overall use of female condoms was low-about 7 percent of women in the Kenyan RCT and 12% of sex acts in the Thai RCT.
Appendix H – Screening in Pregnancy

5. Screening in Pregnancy

Problem Formulation 5

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>Should all pregnant women be screened for STI for each pregnancy and if so, when should pregnant women at increased risk be rescreened?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>All pregnant women aged $\geq 12$ at risk for acquiring HIV/STI</td>
</tr>
<tr>
<td>Intervention</td>
<td>STI screening</td>
</tr>
</tbody>
</table>
| Important Health Outcomes | Maternal and fetus/infant -  
  • Infection, morbidity and mortality  
  • Benefits/harms of routine screening  
  • Anxiety, labeling (maternal)  
  • Increased and earlier STI case identification  
  • Increased HIV/STI case prevention |
**Search Strategy 5**

The search strategy was restricted to systematic reviews, meta-analyses, and RCTs in pregnant women at risk for STI and/or HIV.

<table>
<thead>
<tr>
<th>Database</th>
<th>Terms</th>
<th>Article Type and Limits</th>
<th>Time Frame</th>
<th>No. Included/Total Retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Randomized Controlled Trial, English, Human</td>
<td>1996 to 11/2010</td>
<td>0/5</td>
</tr>
<tr>
<td>Cochrane</td>
<td>STI and/or HIV screening AND pregnancy</td>
<td>Systematic Reviews, Clinical Trials</td>
<td>Last Accessed 11/2010</td>
<td>0/0</td>
</tr>
<tr>
<td>Clinical Evidence</td>
<td>STI and/or HIV screening AND pregnancy</td>
<td>Systematic Reviews, Clinical Trials, Guidelines</td>
<td>Last Accessed 11/2010</td>
<td>7/7</td>
</tr>
</tbody>
</table>
**Search Strategy**

A comprehensive search was conducted in September 2010 (and refreshed in November 2010) to identify RCTs relevant to this problem formulation.

The GDT elected to evaluate HIV, Chlamydia, gonorrhea, syphilis, Hepatitis B and C and genital herpes based on incidence, prevalence, increased risk of HIV acquisition and transmission, and impact on disease progression within the US population. In 2009, the Centers for Disease Control (CDC) and Prevention reported the following – a total of 1,244,180 cases of sexually transmitted Chlamydia trachomatis, the largest number of cases ever reported to CDC for any condition; a total of 301,174 cases of gonorrhea, which corresponds to a rate of 99.1 cases per 100,000 population; a total of 13,997 cases of syphilis, the highest number of cases reported since 1995 and corresponds to a rate of 4.6 cases per 100,000 population; and NHANES data from 2001 to 2004 indicated an overall prevalence of 3.1% of trichomonas cases. The CDC also reports that at the end of 2006, an estimated 1,106,400 persons in the US were living with HIV infection, with 21% undiagnosed, while figures for the number of persons living with hepatitis B and C are approximately 800,000 to 1.4 million and 2.7 to 3.9 million for both pathogens, respectively.

RCTs were included in this review if they evaluated screening tools used in pregnant women at risk for HIV/STI. A total of five studies and seven recommendation statements from the US Preventative Services Task Force (USPSTF) were identified. After further examination, the five studies were assessed in the USPSTS systematic reviews and were not included in this problem formulation.

Furthermore, one Cochrane systematic review was identified on the effects of antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery. Other studies included in the review (one systematic review and three additional observational) examined the diagnostic accuracy of different HIV rapid testing strategies in pregnant women and one observational study that evaluated the effects of antenatal screening for acute HIV on transmission to infants. These additional studies were included in this review to examine the diagnostic accuracy and effects of antenatal testing in pregnant women.
Evidence Summary

Using the USPSTF’s established methodology, key questions were used to update and guide the literature searches and systematic reviews for the USPSTF documents (See Summary of Results section).

- The USPSTF recommends all pregnant women be screened for HIV. (A recommendation)*
- The USPSTF recommends that all pregnant women should be screened for syphilis infection, HIV, and Hepatitis B. (A recommendation).
- The USPSTF recommends that clinicians should screen all sexually active women, including those who are pregnant, for gonorrhea and chlamydial infection if they are at increased risk for infection (that is, if they are young or have other individual or population risk factors). (B recommendation†)
- The U.S. Preventive Services Task Force (USPSTF) recommends against routine serological screening for herpes simplex virus (HSV) in asymptomatic pregnant women at any time during pregnancy to prevent neonatal HSV infection as well as screening for bacterial vaginosis in asymptomatic pregnant women at low risk for preterm delivery. (D recommendation‡)
- The Centers for Disease Control (CDC) and Prevention (2010) suggest that pregnant women be screened for HCV risk factors. Those with HCV risk factors should be screened for anti-HCV. However, they do not recommend that pregnant women be routinely screened for anti-HCV.

* A recommendation - the USPSTF recommends the service. There is high certainty that the net benefit is substantial.
† B recommendation - the USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.
‡ D recommendation - the USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.
Summary of Results
Screening for Syphilis Infection

The USPSTF recommends that clinicians should screen all pregnant women for syphilis infection. (A recommendation)

Screening Tests
1. Nontreponemal tests commonly used for initial screening include
   - Venereal Disease Research Laboratory (VDRL)
   - Rapid Plasma Reagin (RPR)
2. Confirmatory tests include
   - Fluorescent treponemal antibody absorbed (FTA-ABS)
   - Treponema pallidum particle agglutination (TPPA)

Other Clinical Considerations
- Most organizations recommend testing high-risk women again during the third trimester and at delivery. Groups at increased risk include -
  - Uninsured women
  - Women living in poverty
  - Sex workers
  - Illicit drug users
  - Those diagnosed with other sexually transmitted diseases (STDs)
  - Other women living in communities with high syphilis morbidity
  - Prevalence is higher in southern U.S. and in metropolitan areas and in Hispanic and black/African-American populations.

Screening Intervals
- All pregnant women should be tested at their first prenatal visit. For women in high-risk groups, many organizations recommend repeat serologic testing in the third trimester and at delivery. Most states mandate that all pregnant women be screened at some point during pregnancy, and many mandate screening at the time of delivery. Follow-up serologic tests should be obtained after treatment to document decline in titers. To ensure that results are comparable, follow-up tests should be performed by using the same nontreponemal test that was used initially to document the infection (for example, VDRL or RPR).

Interventions
- The Centers for Disease Control and Prevention (CDC) recommends treatment with parenteral benzathine penicillin G. Women with penicillin allergies should be desensitized and treated with penicillin.

[Excerpt ends here.]
External Organizations

- The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists recommend that all pregnant women be screened for syphilis with serologic testing at the first prenatal visit, after exposure to an infected partner, and at the time of delivery. They recommend that pregnant women who are considered at high risk for acquiring syphilis should also be tested at the beginning of the third trimester.

- The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists advise using a nontreponemal screening test initially (RPR or VDRL), followed by a confirmatory treponemal antibody test.

- The CDC recommends that all pregnant women be screened for syphilis with serologic testing at the first prenatal visit. Pregnant women who are at high risk, live in areas with a high prevalence of syphilis, have not been previously tested, or have had a positive serology test for syphilis during the first trimester should be screened again early in the third trimester (28 weeks) and at the time of delivery.

- The American Academy of Family Physicians strongly recommends that all pregnant women be screened for syphilis. It advises screening with serologic testing at the first prenatal visit, with repeat serologic testing at 28 weeks and at the time of delivery for pregnant women who are at high risk.

Screening for HIV

The USPSTF recommends that clinicians should screen all pregnant women for HIV.

(A Recommendation)

[Excerpt begins here.]

There are no published trials directly linking screening for HIV in pregnant women with clinical outcomes. In developed countries, the rate of mother-to-child transmission from untreated HIV-infected women ranges from 14% to 25%. Targeted screening of pregnant women with risk factor assessment would miss a significant proportion of infected persons. Standard office-based testing is highly (> 99%) sensitive and specific, and initial studies of rapid HIV tests in labor and delivery settings found similar diagnostic accuracy. Rapid testing may facilitate timely interventions in those testing positive. HIV testing rates during pregnancy continue to vary widely in the U.S. and appear to be higher in states using ‘opt-out’ testing policies. Recommended interventions (combination antiretrovirals, elective cesarean section in selected patients, and avoidance of breastfeeding) are associated with transmission rates of 1% to 2% in clinical trials and large observational studies. Shorter regimens are less effective, but also decrease the rate of transmission. Currently recommended combination antiretroviral regimens appear safe, but long-term follow-up is not yet available. Elective cesarean section is associated with an increased risk of mostly short-term adverse events. There are insufficient data to estimate the effects of interventions during pregnancy on long-term maternal outcomes.

[Excerpt ends here.]
Screening for Gonorrhea
The USPSTF recommends that clinicians should screen all sexually active women, including those who are pregnant, for gonorrhea infection if they are at increased risk for infection (that is, if they are young or have other individual or population risk factors) (B recommendation).

[Excerpt begins here.]

The USPSTF found insufficient evidence to recommend for or against routine screenings for gonorrhea infection in pregnant women who are not at increased risk for infection. [I statement]

Key Question 1A - Does screening reduce adverse maternal/pregnancy outcomes (septic abortion, stillbirth, preterm delivery/low birth weight)?
- No studies meeting inclusion criteria addressed this question.
- Several professional groups, including the American College of Obstetricians and Gynecologists (ACOG) and the CDC, recommend repeat screening for gonorrhea during the third trimester for at-risk patients.

Key Question 1B - Does screening reduce adverse neonatal outcomes (gonococcal conjunctivitis, blindness)?
- No studies meeting inclusion criteria addressed this question.

Key Question 2A - Does screening reduce maternal complications (chorioamnionitis, premature rupture of membranes, preterm labor)?
- No studies meeting inclusion criteria addressed this question.

Key Question 2B - Does screening reduce transmission to the newborn?
- No studies meeting inclusion criteria addressed this question.

Key Question 3. What is the evidence on cost effectiveness for universal vs. targeted strategies?
- No studies meeting inclusion criteria addressed this question.

[Excerpt ends here.]
Screening for Chlamydial Infections
The USPSTF recommends screening for chlamydial infection for all pregnant women aged 24 and younger and for older pregnant women who are at increased risk. (B recommendation).

[Excerpt begins here.]

The USPSTF recommends against routinely providing screening for chlamydial infection for women aged 25 and older, whether or not they are pregnant, if they are not at increased risk. (C recommendation)

Detection
- The USPSTF found fair evidence that nucleic acid amplification tests (NAATs) can identify chlamydial infection in asymptomatic men and women, including asymptomatic pregnant women, with high test specificity.
- In low prevalence populations, however, a positive test is more likely to be a false positive than a true positive, even with the most accurate tests available.

Benefits of detection and early intervention
- There is good evidence that screening for chlamydial infection in women who are at increased risk can reduce the incidence of PID.
- The USPSTF concluded that the benefits of screening women at increased risk are substantial.

Pregnant women at increased risk
- There are no studies evaluating the effectiveness of screening for chlamydial infection in pregnant women who are at increased risk. The USPSTF, however, found the following:
  - Screening identifies infection in asymptomatic pregnant women.
  - There is a relatively high prevalence of infection among pregnant women who are at increased risk.
  - There is fair evidence of improved pregnancy and birth outcomes for women who are treated for chlamydial infection.

Women not at increased risk
- The USPSTF identified no studies documenting the benefits of screening women, including pregnant women, who are not at increased risk for chlamydial infection.
- While recognizing the potential benefit to women identified through screening, the USPSTF concluded the overall benefit of screening would be small, given the low prevalence of infection among women not at increased risk.
**Harms of detection and early treatment**
- The USPSTF concluded that the harms of screening for chlamydial infection are no greater than small, although few studies have been published on this subject.
- Potential harms include anxiety and relationship problems arising from false positive results and over-treatment.
- The USPSTF identified the lack of evidence related to potential harms of screening as a gap in the evidence.

**Assessment of Risk**
- All sexually active women 24 years of age or younger, including adolescents, are at increased risk for Chlamydial infection. In addition to sexual activity and age, other risk factors for chlamydial infection include history of chlamydial or other STI, new or multiple sexual partners, inconsistent condom use, and exchanging sex for money or drugs. Risk factors for pregnant women are the same for non pregnant women.

**Screening Tests**
- Nucleic acid amplification tests have high specificity and sensitivity when used as screening tests for chlamydial infection. Nucleic acid amplification tests can be used with urine and vaginal swabs, enabling screening when a pelvic examination is not performed.

**Screening Intervals**
- Screening for pregnant women who are at increased risk for chlamydial infection is recommended at the first prenatal visit.
- For pregnant women who remain at increased risk and for those who acquire a new risk factor, such as a new sexual partner, a screening should be conducted during the third trimester.
- The optimal interval for screening for nonpregnant women is unknown. The CDC recommends at least annual screening for women at increased risk.

[Excerpt ends here.]
Screening for Hepatitis B Virus Infection
The USPSTF recommends screening for hepatitis B virus (HBV) infection in pregnant women at their first prenatal visit (A Recommendation)

Detection
- The principal screening test for detecting maternal HBV infection is the serologic identification of hepatitis B surface antigen (HBsAg).
- Immunoassays for detecting HBsAg have a reported sensitivity and specificity greater than 98%.

Benefits of Detection and Early Intervention
- The USPSTF found convincing evidence that universal prenatal screening for HBV infection substantially reduces perinatal transmission of HBV and the subsequent development of chronic HBV infection.
- The current practice of vaccinating all infants against HBV infection and providing postexposure prophylaxis with hepatitis B immune globulin administered at birth to infants of mothers infected with HBV substantially reduces the risk for acquiring HBV infection.

Harms of Detection and Early Intervention
- The USPSTF found no published studies that describe harms of screening for HBV infection in pregnant women.
- The USPSTF concluded that the potential harms of screening are no greater than small.

Screening Tests
- Screening for HBV infection by testing for HBsAg should be performed in each pregnancy, regardless of previous hepatitis B vaccination or previous negative HBsAg test results.

Timing of Screening
- A test for HBsAg should be ordered at the first prenatal visit with other recommended screening tests.
- At the time of admission to a hospital, birth center, or other delivery setting, women with unknown HBsAg status or with new or continuing risk factors for HBV infection (such as injection drug use or evaluation or treatment for a sexually transmitted disease) should receive screening.

[Excerpt ends here.]
Screening for Genital Herpes
The U.S. Preventive Services Task Force (USPSTF) recommends against routine serological screening for herpes simplex virus (HSV) in asymptomatic pregnant women at any time during pregnancy to prevent neonatal HSV infection.  

[D Recommendation]

[Excerpt begins here.]

- The USPSTF found fair evidence that screening asymptomatic pregnant women using serological screening tests for HSV antibody does not reduce transmission of HSV to newborn infants. Women who develop primary HSV infection during pregnancy have the highest risk for transmitting HSV infection to their infants. Because these women are initially seronegative, serological screening tests for HSV (enzyme-linked immunosorbent assay [ELISA], immunoblot, and western blot assay [WBA]) do not accurately detect those at highest risk. There is no evidence that treating seronegative women decreases risk for neonatal infection. There is limited evidence that the use of antiviral therapy in women with a history of recurrent HSV, or performance of cesarean section in women with active HSV lesions at the time of delivery, decreases neonatal herpes infection. There also is limited evidence of the safety of antiviral therapy in pregnant women and neonates.

- The potential harms of screening include false-positive test results, labeling, and anxiety, as well as false negative tests and false reassurance, although these potential harms are not well studied. The USPSTF determined there are no benefits associated with screening, and therefore the potential harms outweigh the benefits.

- Serological screening tests for genital herpes can detect prior infection with HSV in asymptomatic persons, and new type-specific serological tests can differentiate between HSV-1 and HSV-2 exposure (these tests cannot differentiate between oral vs. genital herpes exposure); however, given the natural history of genital herpes, there is limited evidence to guide clinical intervention in those asymptomatic persons who have positive serological test results. False-positive test results may lead to labeling and psychological stress without any potential benefit to patients. Negative test results (both false-negative and true-negative results) may provide false reassurance to continue high-risk sexual behaviors.

- There is new, good-quality evidence demonstrating that systemic antiviral therapy effectively reduces viral shedding and recurrences of genital herpes in adolescents and adults with a history of recurrent genital herpes. There are multiple efficacious regimens that may be used to prevent the recurrence of clinical genital herpes.

- The USPSTF did not examine the evidence for the effectiveness of counseling to avoid high-risk sexual behavior in persons with a history of genital herpes to prevent transmission to discordant partners, or for the primary prevention of genital herpes in persons not infected with HSV. There are known health benefits of avoiding high-risk sexual behavior, including prevention of sexually transmitted infections (STIs) and HIV infection.
Primary HSV infection during pregnancy presents the greatest risk for transmitting infection to the newborn. The fact that women with primary HSV infection are initially seronegative limits the usefulness of screening with antibody tests. The USPSTF did not find any studies testing the use of antibody screening to find and treat seronegative pregnant women (i.e., those at risk for primary HSV infection) prophylactically. However, the number of seronegative pregnant women one would need to treat to theoretically avoid one primary infection would be very high, making the potential benefit small. At the same time, the potential harm to many low-risk women and fetuses from the side effects of antiviral therapy may be great.

There is fair evidence that antiviral therapy in late pregnancy can reduce HSV recurrence and viral shedding at delivery in women with recurrent HSV infection; however, there is currently no evidence that antiviral use in women with a history of HSV leads to reduced neonatal infection. Likewise, there is limited information on the benefits of screening women in labor for signs of active genital HSV lesions, and for the performance of cesarean delivery on those with lesions.

**Potential harms**

- Include labeling, anxiety, and disrupting partner relationships.
- A qualitative assessment of the psychosocial impact of a serological diagnosis of HSV-2 concluded that patients may experience strong psychological responses to their diagnoses.
- False-positive test results may lead to needless work-up and anxiety. Negative test results may potentially provide false reassurance to continue high-risk sexual behavior.
- Potential harms of antiviral treatment may include drug hypersensitivity and renal impairment; however, antiviral treatments are generally well tolerated with mild harms.
- There is limited evidence on the safety of antiviral treatments during pregnancy.

[Excerpt ends here.]

**Recommendations of Other Groups**

The American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP) guidelines are available in print form. ACOG recommends that all women and their partners be asked about a history of HSV infection; women with a history of genital HSV infection should be questioned about recent symptoms and should undergo careful examination of the perineum before delivery. ACOG recommends cesarean delivery for all women with active primary and recurrent lesions at the time of delivery. ACOG does not recommend screening nonpregnant women for HSV; ACOG makes treatment recommendations, including methods to reduce the risk for transmission among discordant couples.
Screening for Bacterial Vaginosis

The USPSTF recommends against screening for bacterial vaginosis in *asymptomatic pregnant women* at low risk for preterm delivery. (D recommendation)

- The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for bacterial vaginosis in asymptomatic pregnant women at high risk for preterm delivery. (I statement)

[Excerpt begins here.]

**Detection**

- Good-quality evidence indicates that screening tests (the Amsel clinical criteria or Gram stain) can detect bacterial vaginosis.

**Benefits of Detection and Early Intervention**

- Asymptomatic Pregnant Women at Low Risk for Preterm Delivery. No direct evidence indicates that screening for bacterial vaginosis reduces adverse health outcomes in asymptomatic pregnant women at low risk for preterm delivery. Good evidence indicates that treatment of bacterial vaginosis in these women lacks benefit.

- Asymptomatic Pregnant Women at High Risk for Preterm Delivery. No direct evidence indicates that screening for bacterial vaginosis reduces adverse health outcomes in asymptomatic pregnant women at high risk for preterm delivery. Evidence from good-quality studies is conflicting with respect to the benefits of treating bacterial vaginosis.

**Harms of Detection and Early Treatment**

- Asymptomatic Pregnant Women at Low Risk for Preterm Delivery. Evidence is poor (because studies are lacking) for harms of screening for bacterial vaginosis in asymptomatic pregnant women at low risk for preterm delivery. Evidence is fair that false-positive results from screening lead to harms due to treatment.

- Asymptomatic Pregnant Women at High Risk for Preterm Delivery. Evidence is poor (because studies are lacking) for harms of screening for bacterial vaginosis in asymptomatic pregnant women at high risk for preterm delivery. Studies on the harms of treatment have conflicting results.

- USPSTF Assessment. The USPSTF concludes that for asymptomatic pregnant women at low risk for preterm delivery, there is moderate certainty that screening for bacterial vaginosis has no net benefit.

- The USPSTF concludes that for asymptomatic pregnant women at high risk for preterm delivery, the evidence is conflicting and the balance of benefits and harms cannot be determined.
Accuracy of Screening Tests

- Bacterial vaginosis is diagnosed by using the Amsel clinical criteria or Gram stain.
- The reliability of the Amsel clinical criteria in community practice is unknown. Gram stain of vaginal discharge may be a more reliable means of diagnosing bacterial vaginosis and offers the added ability to quantify and classify bacterial load. As a result, Gram stain has been the primary means used to diagnose bacterial vaginosis in research studies. However, Gram stain is less commonly used in clinical practice because of the need for laboratory facilities and the delay in receiving diagnostic results.
- No studies of diagnostic assessment in the clinical practice setting were found in the literature. Most studies compared the application of all Amsel clinical criteria with Gram stain in a research setting. In the 2001 USPSTF review, comparisons of the Amsel clinical criteria with Gram stain yielded sensitivities from 62% to 97% and specificities from 66% to 95%, with Gram stain as the criterion standard in diagnosing bacterial vaginosis.
- The 2001 USPSTF evidence review stated that the preferred screening test would predict pregnancy outcomes with the most accuracy. The current update identified studies that evaluated diagnostic tests in predicting preterm birth. A poor-quality meta-analysis (11 studies) showed no difference in accuracy between clinical criteria and Gram stain in preterm delivery.

Effectiveness of Early Detection and Treatment

- Because the evidence is poor, there is no known benefit of early detection in either low-risk or high-risk, asymptomatic pregnant women.
- The USPSTF found good evidence of a lack of benefit from treatment in low-risk, asymptomatic pregnant women. Randomized clinical trials of good quality pooled with 2001 report data showed no treatment effects for asymptomatic women at low risk for preterm delivery at less than 37 weeks.
- Randomized, controlled trials of good quality had conflicting results about treatment benefit in high-risk, asymptomatic pregnant women. There was statistically significant heterogeneity among the trials (P < 0.001). Three of the five trials reported a statistically significant benefit from treatment, one showed a statistically significant harm from treatment, and one showed no benefit.
Potential Harms of Screening and Treatment

- No studies directly addressed the harms of screening (for example, increased risk for preterm delivery).
- The effects of treatment in women with a misdiagnosis of bacterial vaginosis have been indirectly studied and were documented in the 2001 review.
- Two studies of women who tested negative for bacterial vaginosis and received treatment compared with women who tested negative and were not treated found an increase in preterm delivery at less than 34 weeks in the group who tested negative and were treated.
- A recent study also confirmed the potential harm of misdiagnosis (greater spontaneous preterm delivery at < 37 weeks) in women who tested negative for bacterial vaginosis and were treated versus the placebo group, but this finding did not reach statistical significance.

Estimate of Magnitude of Net Benefit

- In low-risk, asymptomatic pregnant women, the USPSTF found no known benefits of detection and early treatment and concluded with moderate certainty that screening has no net benefit.
- Given the lack of net benefit, the USPSTF recommends against routine screening for bacterial vaginosis in low-risk, pregnant women. The results of studies assessing bacterial vaginosis treatment in high-risk, asymptomatic pregnant women are conflicting. As a result of this significant evidence gap, the USPSTF concluded that the evidence is insufficient to make a recommendation about screening for bacterial vaginosis in high-risk pregnant women.

Recommendations of External Organizations

The following institutions make similar recommendations about screening and treatment of pregnant women with bacterial vaginosis:

- The Centers for Disease Control and Prevention
- The American College of Obstetricians and Gynecologists
- The Cochrane Pregnancy and Childbirth Group
- The British Association for Sexual Health and HIV/Clinical Effectiveness Group
- The American Academy of Family Physicians

All recommend against routine screening for bacterial vaginosis in asymptomatic pregnant women. With respect to women at high risk for preterm delivery, the Centers for Disease Control and Prevention, American College of Obstetricians and Gynecologists, the American Academy of Family Physicians, and British Association for Sexual Health and HIV state that there may be high-risk women for whom screening and treatment may be beneficial. The Centers for Disease Control and Prevention does not recommend the use of clindamycin vaginal cream in the second half of pregnancy.
Pregnancy and Hepatitis C (HCV) Infection
The CDC’s Division of Viral Hepatitis and National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention recommends that as pregnant women have no greater risk of being infected with HCV than non-pregnant women and interventions to prevent mother-to-child transmission are lacking, routine anti-HCV testing of pregnant women is not recommended. However, the CDC suggests that pregnant women with risk factors for HCV infection be tested for anti-HCV.

What is the risk that an HCV-infected mother will spread HCV to her infant during birth?
- Approximately four of every 100 infants born to HCV-infected mothers become infected with the virus. Transmission occurs at the time of birth, and no prophylaxis is available to prevent it. The risk is increased by the presence of maternal HCV viremia at delivery and also is two to three times greater if the woman is coinfected with HIV. Most infants infected with HCV at birth have no symptoms and do well during childhood. More research is needed to find out the long-term effects of perinatal HCV infection.

- Regarding breastfeeding, there is no evidence that breastfeeding spreads HCV. However, HCV-positive mothers should consider abstaining from breastfeeding if their nipples are cracked or bleeding.

When should children born to HCV-infected mothers be tested to see if they were infected at birth?
- Children should be tested for anti-HCV no sooner than age 18 months because anti-HCV from the mother might last until this age. If diagnosis is desired before the child turns 18 months, testing for HCV RNA could be performed at or after the infant's first well-child visit at age one to two months. HCV RNA testing should then be repeated at a subsequent visit, independent of the initial HCV RNA test result.

Screening Tools
Effects of Antenatal Syphilis Screening
One cluster-randomized trial (Munkhuu 2009)\(^{(115)}\) was selected for analysis and evaluated the effects of incorporating on-site rapid syphilis testing and treatment into routine antenatal care (moderate quality evidence).

- Munkhuu et al. compared on-site rapid syphilis testing, treatment and counseling incorporated into antenatal care versus routine antenatal care with off-site testing and treatment at 14 clinics in Mongolia. They showed that the intervention reduced rates of congenital syphilis by over 90% compared with routine antenatal care, with an acceptable level of false positive test results. The one-stop service ensured that almost all women were tested, and significantly increased the treatment rate of syphilis infected women and their partners.
## HIV / STI Screening in Primary Care

### Practice Steps for Implementation of Guideline Recommendations

The guideline recommendations are shown schematically.

<table>
<thead>
<tr>
<th>ASK</th>
<th>Routinely obtain a thorough sexual history from all patients ≥ 12 years of age to assess risk behaviors and stratify for appropriate testing.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SCREEN</strong></td>
<td>Test for human immunodeficiency virus (HIV) and sexually transmitted infections (STIs)</td>
</tr>
<tr>
<td></td>
<td>Screen all at-risk individuals ≥ 12 years old for the following:</td>
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<tr>
<td></td>
<td>Screen all pregnant women for the following:</td>
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<tr>
<td></td>
<td>Early during each pregnancy</td>
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<td></td>
<td>Retest before 36 weeks in pregnant women at risk for exposure to HIV and/or STIs during the course of pregnancy.</td>
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<tr>
<td><strong>Human immunodeficiency virus (HIV)</strong></td>
<td>X</td>
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<tr>
<td><strong>Syphilis</strong></td>
<td>X</td>
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<tr>
<td><strong>Hepatitis B</strong></td>
<td>X</td>
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<tr>
<td><strong>Neisseria gonorrhoea</strong></td>
<td>X</td>
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<tr>
<td><strong>Chlamydia trachomatis</strong></td>
<td>X</td>
</tr>
<tr>
<td><strong>Hepatitis C</strong></td>
<td>X</td>
</tr>
<tr>
<td><strong>Trichomoniasis (for women)</strong></td>
<td>X</td>
</tr>
</tbody>
</table>

Note: “Risk continuum” (high vs. low risk) refers to patients engaging in behaviors that put them at risk for HIV infection and may include: unprotected sex with infected persons; sharing needles with infected people; transmission from HIV-infected mother to child (e.g., in utero or through breast-feeding).

![Risk Continuum Diagram](image)

**Lower Risk**
- ADVISE on HIV and STI risk factors and basic prevention messages (see below).

**Higher Risk**
- ADVISE on risk of infecting partners while waiting for test results.

### INTERVENE

**Treat diagnosed HIV and STI** (as per regional and national protocol, and practice resources), and conditions contributing to high-risk behaviors (substance use/abuse, depression, etc.)

#### HIV-INFECTED
- REFER for care as per regional policies and procedures.
- ADVISE on the risk of infecting partners and the prevention of other STIs.

#### HIGH-RISK HIV-UNINFECTED
- COUNSEL patients on ways to stay “infection free” & on changing high-risk behavior.
- Develop a recurring testing schedule to retest for HIV & STIs based on risk.
- Develop an action plan to reduce risk behaviors.
- Refer to substance abuse treatment programs.
- Treat depression or refer to mental health.

#### LOW-RISK HIV-UNINFECTED
- ADVISE patients on ways to stay negative. (Make sure they have understanding of basic prevention messages.)
The practice steps further explained:

1. **ASK:** It is strongly recommended that clinicians routinely obtain a thorough sexual and substance use history from all patients ≥ 12 years of age to assess risk behaviors and stratify for appropriate testing.

   Regular discussions for new and continuing patients under care should include questions about sexual behavior and substance use, including illicit drug use.
   a. Clinicians should use language that reflects culturally competent care to enable appropriate discussion and terms that patients will understand.
   b. Clinicians must inquire about changes in patient's sexual behavior and substance use, which can change during the course of a patient's life and experiences.

   Effective HIV and STI prevention begins with a full understanding of each member’s substance use and sexual activity and any risks these activities may create. Patient history (past STIs), current clinical signs and symptoms, and sexual and substance use risk assessments must all be combined to evaluate the need for prevention interventions. Risks to be addressed for intervention include, but are not limited to:

   - Anyone who acknowledges having had unprotected sexual activity.
   - Patients with multiple sexual partners.
   - Patients with current or previous STIs.
   - Patients with sexual partners with current or previous STIs.
   - Patients with history of recreational or intravenous drug use (IDU), particularly methamphetamines.
   - Patients with chronic alcohol abuse.
   - Patients with hepatitis B or hepatitis C.
   - Men who have exchanged money or drugs for sex, who have been incarcerated, or who have had sex with other men.
   - Women who have exchanged money or drugs for sex.

   There are many simple and direct questions providers can use for effective risk assessment.

**Sexual History for All Patients:**

“I'd like to ask you some questions related to your sexual health that I ask all my patients.”

1. Are you sexually active? If no, have you ever had sex?
2. How many lifetime sexual partners have you had? Timeframe?
3. Are/were your sexual partners men, women, or both?
4. Did/do you have vaginal, anal, and/or oral sex?
5. Have you ever been diagnosed with an STD or thought you might have one? Has your partner?
6. Have you ever been tested for HIV or advised to be tested? Has your partner?
7. How do you protect yourself from STIs and HIV?
Sexual History for Married Patients and Couples:

“I'd like to ask you a few questions related to your sexual health. These are questions that I ask all my patients regardless of the type of relationship they are in."

1. Do you or your partner have sex with other people outside of your marriage?
   How do you protect yourself from STIs and HIV?
2. Have you or your partner ever been diagnosed with an STI?
3. Have you or your partner ever been tested for HIV?
4. How long have you been married/together?
5. Before you were a couple did you have sex with other people?
   If yes, with men, women, or both?
6. Before you were married, did your partner have sex with other people?
   If yes, with men, women, or both?

Simple and validated risk assessment tools exist to help the busy clinician conduct effective risk assessments. KP HealthConnect and kp.org will create easy-to-use assessment tools for providers and patients with consistent documentation and monitoring of risks over time with minor impact on clinician workload.

2. SCREEN: It is strongly recommended that patients be appropriately screened for HIV infection and STIs based on their individual risk assessment.

The testing recommendations demonstrate who should be targeted for HIV/STI screening with appropriate HIV antibody testing and other age- and risk-based assessment of other STI laboratory exams. The STI laboratory tests may include: screening for syphilis (RPR or Treponema pallidum IgG+IgM), Chlamydia (urine or genital tract swab with Chlamydia PCR amplified probe), gonorrhea (urine or genital tract swab [and if appropriate anal and throat swab] with gonorrhea PCR amplified probe), hepatitis B and C antibodies.

Screen and promptly treat all identified individuals ≥ 12 years of age at risk for the following STIs:
- Human immunodeficiency virus (HIV)
- Neisseria gonorrhoea
- Chlamydia trachomatis
- Syphilis
- Hepatitis B
- Hepatitis C
- Trichomoniasis (for women)

NOTE: Evidence suggests that the presence of other STIs, including herpes simplex, increases the risk of HIV transmission and acquisition.¹

¹ The USPSTF recommends against serological screening for herpes simplex virus (HSV) in asymptomatic adolescents and adults (USPSTF Screening for Genital Herpes, 2010).
Screen all pregnant women for HIV antibody, syphilis, and hepatitis B early during each pregnancy. Screen at-risk pregnant women for gonorrhea, Chlamydia and hepatitis C. Retest before 36 weeks in women at risk for exposure to HIV and/or any other STIs during the course of pregnancy. Risk factors include HIV-infected partner or partner at risk for HIV, new or multiple sex partners during pregnancy, illicit drug use, exchanges sex for money or drugs, history of STI during this pregnancy or one year prior to pregnancy, signs or symptoms of acute HIV infection. Pregnancy risk for exposure may include a newly diagnosed STI during pregnancy, documented or suspected injection drug use, or partner with known HIV infection.

The probability of contracting HIV during a high-risk encounter is significantly higher if an STI is present, including herpes simplex and trichomoniasis (in women). Therefore prompt diagnosis and successful treatment of an STI is an effective prevention strategy and has been shown to reduce transmission of HIV.

3. INTERVENE: It is strongly recommended that patients be given brief, evidence-based, and culturally sensitive HIV/STI prevention counseling.

   a. Prevention counseling will be based on the individual patient’s risk and present behaviors.
   b. Follow-up testing and counseling is based on the patient’s ongoing behaviors.

Initial HIV Prevention Messages

An initial screen for HIV infection can offer an opportunity to educate patients to modify their behavior even before the results are available. There are many “simple” but effective messages clinicians can provide to their patients, including but not limited to:

- Condoms are effective for preventing HIV and most STIs.
- Oral contraceptives do not prevent HIV or an STI.
- Substance use during sexual activity can increase risk of contracting HIV or an STI.
- Having an active STI (including herpes) can greatly increase one’s chance of contracting HIV.

If a patient has a higher probability of receiving a positive result for HIV or STI testing, the above messages still apply but can also include advice on the risk of infecting partners while waiting for their results.

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2 The USPSTF (Recommendations for STI Screening, 2008) recommends that providers determine at risk individuals based on high-risk sexual behavior and age.


4 Health Education Departments, HIV multi-disciplinary teams and/or other departments can establish programs targeting high-risk patients based on clinician referral and clinicians assessment of patient’s risk. Several medical centers currently offer one-on-one sessions with clinical health educators or other members of an HIV multi-disciplinary team. The HIV Interregional Initiative and kp.org will develop tools and programs to assist with these prevention and counseling efforts. Another excellent evidence-based resource with the CDC DEBI Project, available at: http://www.cdc.gov/hiv/topics/research/prs/evidence-based-interventions.htm. The CDC DEBI Project offers approaches that are consistent with Kaiser Permanente operations and resources.
Providing Test Results and Post-Test Counseling

CDC Diffusion of Effective Behavioral Interventions Project (DEBI) demonstrates that appropriate follow-up and referral to targeted prevention interventions based on HIV antibody results status and risk behaviors can be very effective in HIV prevention. However, evidence for the effectiveness for post test counseling for behavior change and risk reduction has been mixed, and varied by target population. Meta-analysis of post-test counseling interventions have shown that greater reduction in unprotected sex occurred in those receiving positive test results vs. negative, the older vs. younger populations, and those who sought testing vs. being offered by a provider.

Specific follow-up and referral strategies should be tailored to the following groups, based on test results:

I) Diagnosed HIV-Infected
A) With a diagnosed STI
B) Without a diagnosed STI

Rationale: Identification of a previously undiagnosed HIV positive patient offers several opportunities for prevention. Patients who know they are infected are more likely to adopt behaviors that prevent transmission. Prompt and successful treating of an incident STI prevents transmission. Patients taking effective antiretroviral therapy may be less infectious and transmit HIV less often or possibly not at all.

Recommendation: Prompt treatment of any STI and prompt referral to HIV specialty team (as per regional practices and policies) is essential. Reinforcing prevention messages is useful.

II) Diagnosed HIV-Uninfected
A) Lower Risk (No or Past STI, Past Risk Behaviors, and Now Practicing Protected Sex).

Rationale: Patients receiving a negative test result with past history of risk behaviors or STIs need reinforcement to maintain current strategies for prevention. Sexual behavior and substance use can change throughout a patient's life, and discussion with and counseling patients about these topics is an ongoing process.

Recommendations: Advise patients on ways to stay negative. Reinforce basic prevention messages, and emphasize specific preventative behaviors applicable to the patient. Reassess risk at future visits, and retest if any risk behavior persists.

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5 Health Education Departments, HIV multi-disciplinary teams and/or other departments can establish programs targeting high-risk patients based on clinician referral and clinicians' assessment of patient's risk. Several medical centers currently offer one-on-one sessions with clinical health educators or other members of an HIV multi-disciplinary team. The HIV Interregional Initiative and kp.org will develop tools and programs to assist with these prevention and counseling efforts. Another excellent evidence-based resource with the CDC DEBI Project, available at: http://www.cdc.gov/hiv/topics/research/prs/evidence-based-interventions.htm. The CDC DEBI Project offers approaches that are consistent with Kaiser Permanente operations and resources.
II) Diagnosed HIV-Uninfected (continued)
B) Higher Risk with One or More of:
   1. Active STI
   2. Current History of Unprotected Sexual Activity
   3. Alcohol Abuse
   4. Non-IV Drug Use
   5. IV Drug Use

Rationale: Patients engaging in high-risk activities but recently tested negative for HIV are the most important population to target for evidence-based prevention strategies and will yield the greatest impact on HIV transmission rates. Care must be taken to keep the negative test from reinforcing the risk behaviors, or being cited as "proof" by the patient that they are not at risk. Untreated depression has been associated with high-risk behavior in gay men, and persistent substance use contributes to transmission both as a disinhibitor to safer practices and as a direct transmission route in inject drug use.

Recommendations: Promptly treat any diagnosed STI. Screen and treat, or refer for possibility of substance use or depression. Stress prevention messages in a culturally appropriate way. Help patient establish a personalized action plan to reduce risk. Establish periodic testing schedule for ongoing HIV and STI testing. Refer to HIV prevention programs at local medical center or to external community resources.

Ways to assist the patient in creating a personalized plan for HIV risk reduction:
• Avoid language that may be insensitive to patient’s background and which may impair further disclosure.
• Motivate patients for behavioral change.
• Offer latex condoms and information on appropriate handling and lubricants to all sexually active persons.
• Counsel regarding drug use, including alcohol, methamphetamine, and injection drug use.
• Remind that oral contraceptives do not prevent HIV or an STI.
• Advise to seek prompt treatment for any suspected STI, or known exposure to an STI even in the absence of symptoms.
  • Reassess sexual practices at future visits and plan for repeat testing as appropriate.
  • Avoid false reassurance.
Appendix J - Ask Screen Intervene (ASI)

ASI was developed by The Centers for Disease Control and Prevention, the Health Resources and Service Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Disease Society of America who put forth the following recommendations to better incorporate HIV prevention into the medical care of persons living with HIV. (116)

- **Assess:** Ask about/assess behavioral health risk(s) and factors affecting choice of behavior change goals/methods.

- **Advise:** Give clear, specific, and personalized behavior change advice, including information about personal health harms/benefits.

- **Agree:** Collaboratively select appropriate treatment goals and methods based on the patient's interest in and willingness to change the behavior.

- **Assist:** Using behavior change techniques (self-help and/or counseling), aid the patient in achieving agreed-upon goals by acquiring the skills, confidence, and social/environmental supports for behavior change, supplemented with adjunctive medical treatments when appropriate (e.g., pharmacotherapy for tobacco dependence, contraceptive drugs/devices).

- **Arrange:** Schedule follow-up contacts (in person or by telephone) to provide ongoing assistance/support and to adjust the treatment plan as needed, including referral to more intensive or specialized treatment.
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158

National HIV/STI Clinical Practice Guideline


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