Mayo Clinic HIV eCurriculum Series
Essentials of HIV Medicine
Module 4
Transmission and Diagnosis of HIV

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RISK FACTORS FOR HIV TRANSMISSION

Overview: This section presents information on the infectivity of body fluids, the risk of HIV infection with differing types of exposures and factors that modify the risk of HIV transmission. The risk of HIV transmission is determined by the infectivity and volume of the body fluid(s) to which an individual is exposed (e.g., blood, genital secretions or other fluids), the nature of the exposure (e.g., sexual, percutaneous [e.g., needlestick] or other) and the amount of viable virus.

Infectivity of body fluids:

➢ General considerations: HIV does not maintain infectiousness outside its host.
  • Drying of HIV-infected human blood or other body fluids reduces the risk of environmental transmission to essentially zero.
  • Except under specific laboratory conditions, HIV reproduces only in infected patients

➢ Infectivity of specific body fluids
  • All body fluids containing HIV pose a theoretical risk, but some (e.g., tears, urine, and stool) have not been implicated in transmission of the virus
  • Known infectious body fluids
    ◆ Blood
    ◆ Semen
    ◆ Vaginal fluids
    ◆ Breast milk
  • Potentially infectious body fluids
    ◆ Pericardial fluid
    ◆ Synovial fluid
    ◆ Peritoneal fluid
    ◆ Cerebrospinal fluid
    ◆ Pleural fluid
    ◆ Amniotic fluid
  • Infectious only if bloody
    ◆ Feces
    ◆ Nasal secretions
    ◆ Saliva*
Transmission and Diagnosis of HIV

- Sputum
- Sweat*
- Tears*
- Urine
- Vomitus

* Very low quantities of HIV has been found in saliva and tears from some HIV-infected patients. HIV has not been recovered from non-bloody sweat of HIV-infected persons.

Activities that are strongly associated with transmission of HIV infection:

- Sexual exposure to an HIV-infected person
- Mucocutaneous (e.g. splash in eye, mouth or on broken skin) or parenteral exposure to HIV-infected body fluids (e.g., needlestick injuries)
  - Transfusion of HIV-infected blood products; this may account for 10% of AIDS cases in low income countries
  - Sharing of contaminated injection drug equipment
  - Percutaneous exposure to HIV infected material (e.g., needlestick injury); most of the estimated 1000 occupational HIV infections per year associated with sharps injuries occur in sub-Saharan Africa.
  - Splash of HIV-infected fluid into mouth or eye
- Mother-to-child transmission of HIV infection (MTCT): up to 90% of transmission occurs during the last 2 months of pregnancy with up to 65% of MTCT occurring during the intrapartum period.
Table 1. Rate of infection per 10,000 exposures to HIV-positive materials or individuals

<table>
<thead>
<tr>
<th>Activity</th>
<th>Risk per 10,000 exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receipt of HIV infected blood transfusion</td>
<td>9,250</td>
</tr>
<tr>
<td>Needle-sharing injection-drug use</td>
<td>150</td>
</tr>
<tr>
<td>Receptive anal intercourse</td>
<td>50</td>
</tr>
<tr>
<td>Receptive vaginal intercourse</td>
<td>10</td>
</tr>
<tr>
<td>Insertive anal intercourse</td>
<td>6.5</td>
</tr>
<tr>
<td>Insertive vaginal intercourse</td>
<td>5</td>
</tr>
<tr>
<td>Receptive oral intercourse</td>
<td>1</td>
</tr>
<tr>
<td>Insertive oral intercourse</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Table 2. Rate of infection per 10,000 exposures to HIV-infected material

<table>
<thead>
<tr>
<th>Type of exposure to infectious fluid</th>
<th>Infection rate per 10,000 events (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percutaneous (e.g., needlestick or scalp injury)</td>
<td>32 (20 – 50)</td>
</tr>
<tr>
<td>Mucocutaneous (e.g. splash in eye, mouth or on broken skin**)</td>
<td>9 (0.6 – 50)</td>
</tr>
<tr>
<td>Skin (e.g. splash fluid on intact skin)</td>
<td>0.0 (0.0 – 11)</td>
</tr>
</tbody>
</table>

* 95% confidence interval
** The risk of transmission after exposure of non-intact skin to infectious fluid is not well quantified but is estimated to be less than for mucous membrane exposures.

Activities that are rarely or theoretically associated with transmission of HIV infection:

- Tattooing or body piercing: although theoretically possible, HIV transmission has not been reported to occur through tattooing or body piercing
- Acupuncture: One case of HIV transmission from acupuncture has been documented
- Kissing:
  - "French" or open-mouth kissing provides the potential for contact with blood. One case of HIV transmission by "French" or open-mouth kissing has been reported.
Casual contact through closed-mouth or "social" kissing is not a risk for transmission of HIV.

- Biting:
  - Bites causing severe trauma with extensive tissue tearing and damage and presence of blood have resulted in HIV transmission
  - Risk of HIV infection due to a bite by an HIV-infected individual is estimated to be 5% of the risk of infection due to a needlestick injury.

- Skin to skin contact: Infection by exposure of intact skin by exposure to HIV-infected fluids has not been conclusively demonstrated.

- Percutaneous injury by discarded needles and syringes found in the community
  - HIV RNA can be detected in 3 – 4% of syringes used for intramuscular or subcutaneous injection in persons known to have HIV infection
  - Viable virus can be found in after 21 – 42 days in 8% of syringes contaminated by HIV-infected blood that are stored at room temperature.
  - However, there are no known reports of HIV infection occurring due to a community exposure to a discarded syringe.

Table 3. Factors that modify the risk of HIV infection following a percutaneous injury

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Adjusted odds ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep injury, i.e., into muscle</td>
<td>15 (6.0 – 41)</td>
</tr>
<tr>
<td>Visibly bloody device</td>
<td>6.2 (2.2 – 21)</td>
</tr>
<tr>
<td>Intravascular device</td>
<td>4.3 (1.7 – 12)</td>
</tr>
<tr>
<td>Terminally ill source patient with advanced HIV disease</td>
<td>5.6 (2.0 – 16)</td>
</tr>
</tbody>
</table>

* 95% confidence interval

Table 4. Risk of MTCT of HIV infection (without antiretroviral therapy or prophylaxis)

<table>
<thead>
<tr>
<th>Type of exposure</th>
<th>Rate of infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-breastfeeding women</td>
<td>15–30%</td>
</tr>
<tr>
<td>Breastfeeding women</td>
<td>20–45%</td>
</tr>
</tbody>
</table>
Activities which are not associated with HIV infection:

- Household activities, i.e., activities in household settings that exclude contacts involving sex or equipment (e.g., needles and syringes) used in injection drug use
  - Anecdotal reports of household transmission have nearly always involved documented or probable blood contact or home nursing care of terminally ill persons with AIDS in which a blood exposure might have occurred
  - Based on studies in the United States and Europe of household exposure of more than 1100 uninfected persons, including more than 326 children, the estimated 95% confidence interval for the rate of transmission is 0.0 to 0.2 infections per 100 patient-years of exposure.
- Food-service businesses:
  - There is no known risk of HIV transmission to co-workers or consumers in food-service establishments
- Personal-services (such as hairdressers, barbers, cosmetologists, and massage therapists):
  - There is no evidence of transmission directly from a personal-service worker to a client or vice versa.
  - HIV could be transmitted if instruments contaminated with blood are not sterilized or disinfected between clients.
- Insect exposure
  - There is no evidence of HIV transmission through insects
  - When an insect bites a person, it does not inject its own or a previously bitten person’s or animal’s blood into the next person bitten.
    - HIV lives for only a short time inside an insect
    - After biting, insects do not immediately bite other people but instead digest their food.
- Aerosol exposure: there is no evidence that HIV has been transmitted to healthcare workers or persons in the community via inhalation of aerosolized body fluids from an infected patient

Risk of transmission of HIV infection during medical procedures

- Infection of patients (nosocomial transmission):
Infection by an HIV-infected healthcare worker.

- Anecdotal reports
  - One instance of HIV transmission from one HIV-infected dentist to six patients
  - Three other instances of intra-operative transmission by HIV-infected healthcare workers have been reported, one case each by an orthopedic surgeon, gynecologist and operating room nurse
- Investigations involving more than 22,000 patients of 63 HIV-infected physicians, surgeons, and dentists have found no other cases of HIV transmission by an HIV-infected healthcare worker during the course of a medical procedure.
- The estimated risk of HIV seroconversion after an invasive procedure by HIV-infected healthcare workers is far less than the risk of other complications of medical procedures.

Table 5. Risk of complications during surgical procedures

<table>
<thead>
<tr>
<th>Event</th>
<th>Risk per Million Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical wound infection (high-risk patient and procedure)</td>
<td>147,000</td>
</tr>
<tr>
<td>Surgical wound infection (low-risk patient and procedure)</td>
<td>10,000</td>
</tr>
<tr>
<td>Anesthesia associated mortality</td>
<td>100</td>
</tr>
<tr>
<td>HIV seroconversion after invasive procedure by HIV-positive surgeon</td>
<td>2.4-24</td>
</tr>
</tbody>
</table>

Infection by transfusion of blood screened for presence of HIV.

- Blood can be screened for HIV infection by antibody testing only, antibody testing plus tests for the presence of the p24 viral antigen or by antibody testing plus nucleic acid-amplification testing (e.g., PCR).
- The use of p24 antigen testing increases the detection of donors who are in the seronegative phase of infection (i.e., before the development of antibodies). Detection of seronegative patients is further enhanced by the use of nucleic acid-amplification testing.
- All blood in the United States is now screened by nucleic acid-amplification testing
Table 6. Risk of infection by blood transfusion versus type of screening

<table>
<thead>
<tr>
<th>Screening technology</th>
<th>Risk per one million transfusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody testing only</td>
<td>2</td>
</tr>
<tr>
<td>Antibody and p24 viral antigen testing</td>
<td>0.66</td>
</tr>
<tr>
<td>Antibody and nucleic acid-amplification testing</td>
<td>0.50</td>
</tr>
</tbody>
</table>

- Other medical procedures:
  - HIV infection may occur due to organ transplantation during the seronegative phase of HIV infection (before antibodies are produced) or due to massive blood transfusions and hemodilution. The risk of infection is reduced by use of nucleic acid-amplification testing
  - Artificial insemination during the seronegative phase of HIV infection. The risk of infection is reduced by use of nucleic acid-amplification testing
  - Improper sterilization of needles and syringes:
    - Healthcare associated clusters of HIV transmission due to inadequately sterilized equipment (e.g., needles and syringes) or reused medical equipment (e.g., hemodialysis or plasma donation equipment) are very well-documented.
    - Improper use of multi-dose vials (re-entry of vial with used syringes)
    - Unsafe injections are estimated to cause 5% of HIV cases worldwide.
- Occupational infection of healthcare workers
  - Infrequently reported in the developed world
  - Documented cases: HIV seroconversion documented following occupational exposure to HIV-infected blood, body fluids, or laboratory material in persons with no other risk factor for HIV infection and negative tests for HIV-infection at the time of injury
  - Possible cases: same circumstances as for documented cases except that laboratory testing to confirm HIV seroconversion after exposure was not documented in the possible cases (i.e. testing was not done at the time of the exposure)
• Occupational infection of laboratory workers
  ♦ As of June 1998, CDC had reports of 16 laboratory workers (all clinical) in the United States with documented occupational transmission

**Table 7. Healthcare personnel with occupationally acquired HIV infection**

<table>
<thead>
<tr>
<th>Health-care Occupations</th>
<th>Documented</th>
<th>Possible*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurse</td>
<td>24</td>
<td>35</td>
</tr>
<tr>
<td>Laboratory, Worker, clinical</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Physician, Non-surgical</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Laboratory technician, non-clinical</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Housekeeper/maintenance worker</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Laboratory technician, surgical</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Embalmer/morgue technician</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Health aide/attendant</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Respiratory therapist</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Technician, Dialysis</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Dental health-care worker, including dentist</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Emergency medical technician/paramedic</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Physician, surgical</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Other technician/therapist</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Other healthcare occupations</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>57</strong></td>
<td><strong>139</strong></td>
</tr>
</tbody>
</table>

**Modifiers of risk of HIV Transmission**

Source patient factors

• Stage of disease in source patient
• HIV seroconversion may account for up to 20% of episodes of HIV transmission
• Late stage disease. The risk of infection per coital act with untreated source patients during the two years before death is 4 – 8 times higher the risk per coital act with such persons during the asymptomatic, period of chronic infection
Transmission rate during both the primary infection and the late stages of disease are higher than would be expected on the basis of the plasma viral loads alone.

Table 8. Estimated rate of HIV transmission versus duration of infection

<table>
<thead>
<tr>
<th>Status of infection in index partner</th>
<th>Estimated HIV transmission per heterosexual coital act</th>
<th>Relative risk per heterosexual coital act</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 2.5 months after seroconversion</td>
<td>0.0082</td>
<td>11.7</td>
</tr>
<tr>
<td>6 - 15 months after seroconversion</td>
<td>0.0015</td>
<td>2.1</td>
</tr>
<tr>
<td>Long term infection</td>
<td>0.0007</td>
<td>1.0</td>
</tr>
<tr>
<td>6-25 months before death of index partner</td>
<td>0.0028</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Viral load in source patient:
- Risk of infection is decreased with decreased viral load, but not eliminated even in persons with undetectable plasma viral load.

Table 9. Relative risk of heterosexual transmission of HIV infection per coital act

<table>
<thead>
<tr>
<th>Variable Viral load (HIV-1 RNA copies/mL)</th>
<th>Risk of Acquisition by HIV-partner*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3,500</td>
<td>1.0</td>
</tr>
<tr>
<td>3,500 – 9,999</td>
<td>5.81 (2.25 – 17.91)</td>
</tr>
<tr>
<td>10,000 – 49,999</td>
<td>6.84 (2.93 – 19.97)</td>
</tr>
<tr>
<td>&gt;50,000</td>
<td>12.55 (5.28 – 36.99)</td>
</tr>
<tr>
<td>Risk per 10-fold increase viral load</td>
<td>2.45 (1.86 – 3.26)</td>
</tr>
</tbody>
</table>

* Rate ratio adjusted for all other variables

Table 10. Estimated rate of HIV transmission in persons with virological suppression*

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Estimated yearly HIV transmission (100 coital acts/year)</th>
<th>New infections per 10 year period (10,000 serodiscordant partnerships)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female-to-male transmission</td>
<td>0.0022</td>
<td>215</td>
</tr>
<tr>
<td>Male-to-female transmission</td>
<td>0.0043</td>
<td>425</td>
</tr>
<tr>
<td>Male-to-male transmission</td>
<td>0.0430</td>
<td>3524</td>
</tr>
</tbody>
</table>

* < 10 HIV-1 RNA copies/mL.
- Sexually transmitted disease in source patient
• The presence of genital tract infection increases the amount of HIV in the genital tract

• Presence of genital ulceration may increase the probability of heterosexual transmission of HIV by a factor of four

Table 11. Effect of genital tract infection on HIV shedding

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Odds ratio for detection of HIV mean (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urethritis</td>
<td>3.1 (1.1 - 8.6)</td>
</tr>
<tr>
<td>Cervicitis</td>
<td>2.7 (1.4 - 5.2)</td>
</tr>
<tr>
<td>Cervical discharge or mucopus</td>
<td>1.8 (1.2 - 2.7)</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>1.8 (1.2 - 2.7)</td>
</tr>
<tr>
<td>Chlamydial infection</td>
<td>1.8 (1.1 - 3.1)</td>
</tr>
<tr>
<td>Vulvovaginal candidiasis</td>
<td>1.8 (1.3 - 2.4)</td>
</tr>
<tr>
<td>Genital ulcer disease**</td>
<td>2.4 (1.2 - 4.9)</td>
</tr>
<tr>
<td>Bacterial vaginosis</td>
<td>1.0 (0.7 - 1.5)</td>
</tr>
<tr>
<td>Trichomoniasis*</td>
<td>0.9 (0.7 - 1.3)</td>
</tr>
</tbody>
</table>

* Although trichomoniasis was not found to affect the frequency of detection of HIV in the genital tracts of women, trichomoniasis has been found to increase viral concentrations in semen.

- Suppressive treatment of HSV-2 with acyclovir or valacyclovir reduces seminal and cervical HIV-1 levels in HIV-1/HSV-2 co-infected patients.

- Use of condom: Male condom use decreases rate of HIV transmission by 95%

Recipient factors:

- Circumcision
  - Uncircumcised men are approximately 2 – 9 times more likely to acquire HIV
  - Male circumcision reduces the risk of acquiring HIV infection by 50 – 60%

- Genetic factors
  - Strong evidence: persons who are homozygous for a 32 base-pair deletion in the gene coding for chemokine receptor CCR5 are protected against infection by HIV-1 isolates that rely upon CCR5 as the coreceptor for HIV-1 infection but not against infection by virus that uses CXCR4 as the coreceptor
Weaker evidence: mutations in the gene encoding the stromal-derived factor (SDF-1), the natural ligand of the CXCR4 molecule, which is a co-receptor for HIV-1, or in the gene for the chemokine receptor CCR2b (CCR2-64I) may also protect against HIV infection.

Mother-to-child transmission (MTCT) of HIV infection

- In utero events:
  - Increased risk of infection with performance of amniocentesis and amnioscopy

- Intra-labor transmission
  - Maternal factors
    - CD4+ cell count:
      - Decreased risk of infection with higher CD4+ cell counts
    - Viral load:
      - Decreased rate of infection with decreased maternal viral load.
      - For any viral load the MTCT rate is lower among women receiving antiretroviral drugs.
    - Low maternal vitamin A levels:
      - Increased MTCT rate with low maternal vitamin A levels
    - HIV replication capacity:
      - Increased MTCT rate with higher replication capacity (ability of virus to multiply) of maternal HIV isolate
  - Labor-related events: risk of MTCT is increased by each of the following factors
    - Performance of invasive procedures that breach the infant skin, e.g., fetal scalp electrodes, fetal blood sampling
    - Premature membrane rupture
    - Hemorrhage in labor, bloody amniotic fluid
    - Low birth weight
    - Decreased gestational age

- Breastfeeding:
  - The overall risk of transmission through breast milk is 15 – 30%
  - Factors that increase the risk of transmission via breast feeding
◊ Maternal HIV infection during the post-partum period
◊ Higher viral load
  ▪ Higher maternal plasma viral loads predict higher breast milk viral loads
  ▪ HIV infected breast milk cells play a more important role in HIV transmission than does cell-free virus in breast milk
  ▪ The concentration of infected breast milk cells is higher in colostrum and early milk than in mature milk
◊ CD4 count: Lower maternal CD4+ cell count
◊ Presence of nipple lesions, mastitis or breast abscess
◊ Infant oral thrush
◊ Duration of breastfeeding
◊ Type of breast feeding: feeding of foods other than breast milk in early infancy (e.g., within the first 3 months of life) damages the gastrointestinal tract, with a concomitant increase in the permeability of the gastrointestinal tract to HIV in breast milk
  • Overall, in utero, and breast milk HIV-1 transmission increased with increased HLA concordance between mother and child

**DIAGNOSIS**

**Benefits of routine HIV testing**

• Benefits to individual, infected persons
  ◆ Persons whose HIV status is not known cannot benefit from antiretroviral therapy
  ◆ Antiretroviral therapy is more successfully at reconstituting the immune system in HIV-infected persons with higher CD4+ cells counts
  ◆ By decreasing the proportion of patients with delayed diagnoses, more comprehensive HIV testing programs can extend average survival for HIV-infected patients by 1.5 years

• Benefits to society
  ◆ Decreased plasma viral load decreases likelihood of further transmission of HIV infection
Upon notification of their status, HIV-infected individuals frequently change their behaviors, again decreasing the risk of further HIV transmission.

**Cost-effectiveness of HIV testing**

- Except in very low risk populations, routine testing for HIV is as cost-effective as screening for hypertension, colon cancer, and breast cancer.
- Cost-effectiveness from an individual perspective: For an individual from a population with a prevalence of HIV infection of 1%, the cost of one-time screening for HIV infection is estimated to be $38,000 – $41,736 per quality-adjusted life-year gained.
- Cost-effectiveness from a societal perspective: Analyses that consider the relationship of diagnosis, treatment and behavior change with decreased HIV transmission show that the cost of routine HIV screening remains <$50,000 per quality-adjusted life-year gained until the prevalence of previously undiagnosed HIV infection is <0.05%.

**Prevalence of undiagnosed HIV infection**

- 21% of the 1.2 million HIV-infected persons in the United States are unaware of their status.
- 10-25% of HIV-infected people report no high-risk behaviors.
- Despite frequent opportunities for earlier HIV testing during patient visits to outpatient clinics, urgent care clinics, emergency rooms and hospitals, the average CD4⁺ cell count at the time of the diagnosis of HIV infection is approximately 200 cells/μL.
- Although the prevalence of undiagnosed HIV infection is decreased in older patients, HIV testing is less frequently done in this population and available data indicates that older persons have a prevalence of HIV infection above the 0.10% threshold at which routine testing is cost-effective when societal benefits are considered.

### Table 12. Undiagnosed HIV Infection in Outpatients: VA Medical Centers 2000–2002

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Seroprevalence of Undiagnosed Infection (95% Confidence Limits)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 - 44</td>
<td>1.60% (0.80% - 2.70%)</td>
</tr>
<tr>
<td>45 - 54</td>
<td>0.90% (0.40% - 1.60%)</td>
</tr>
<tr>
<td>55 - 64</td>
<td>0.70% (0.20% - 1.70%)</td>
</tr>
<tr>
<td>65 - 74</td>
<td>0.50% (0.20% - 1.20%)</td>
</tr>
<tr>
<td>&gt;= 75</td>
<td>0.10% (0.001% - 0.60%)</td>
</tr>
</tbody>
</table>
Current recommendations for HIV testing

- Routine, non-risk based testing for the general population
  - Unless the prevalence of undiagnosed HIV infection in the target population is known to be <0.1% the United States Centers for Disease Control and Prevention (CDC) and the American College of Physicians (ACP) recommend one-time testing for all adults aged 13 – 64 (CDC) or with no upper age cut-off (ACP) regardless of the presence of known risk factors for HIV infection
  - Unless there are no positive results after 4,000 consecutive tests, there is a greater than 5% probability that the true prevalence of undiagnosed HIV infection is over 0.1%

- Routine testing in during pregnancy:
  - All pregnant women should be promptly tested for the presence of HIV infection
  - A second HIV test during the third trimester, preferably <36 weeks of gestation, is cost-effective even in areas of low HIV prevalence. It is particularly important for women who:
    ◊ receive health care in areas with elevated incidence of HIV or AIDS among women aged 15–45 years or in facilities in which prenatal screening identifies at least one HIV-infected pregnant woman per 1,000 women screened
    ◊ are known to be at high risk for acquiring HIV
    ◊ have had a new or more than one sex partner during this pregnancy
    ◊ have signs or symptoms consistent with acute HIV infection.
  - Testing during labor: any woman with undocumented HIV status at the time of labor should be screened with a rapid HIV test

- Indications for more frequent HIV testing in asymptomatic patients
  - Tuberculosis (active or latent infection): all patients with should be screened or re-screened for HIV infection
  - All patients seeking treatment for sexually transmitted diseases (STDs) should be screened for HIV during each visit for a new complaint
  - High risk patients should be offered yearly HIV testing
Table 13. Risk Factors for HIV Infection

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unprotected contact with sexual partners whose HIV status is not known</td>
</tr>
<tr>
<td>Injection drug use</td>
</tr>
<tr>
<td>Blood transfusions in the developed world between 1978 and 1985 (routine testing of the blood supply in developed countries started in 1985)</td>
</tr>
<tr>
<td>Surgery or blood transfusion in a developing country at any time</td>
</tr>
</tbody>
</table>

- Diagnostic testing
  - All patients with signs or symptoms consistent with HIV infection or an opportunistic illness characteristic of AIDS should be tested for HIV
  - When acute retroviral syndrome (i.e., the HIV seroconversion reaction) is a possibility, a nucleic acid amplification test should be used in conjunction with an HIV antibody test to diagnose acute HIV infection

**Laboratory tests available for diagnosis of HIV infection**

- **Enzyme immunoassay (EIA):** standard screening test for detection of antibodies to HIV-1 or HIV-2
  - Time to become positive: 2 to 6 weeks after time of infection depending on the version of the test

- **Standard format assays:**
  - Use serum
  - Results usually not available for at least several hours. However, recent technical advances have allowed for EIA assays to be done in highly automated multi-analyzer systems that can generate results within one hour
  - Considered preliminarily positive if confirmed by repeat assay on the same specimen

- **Differences between test versions:**
  - First and second generation assays detect only IgG antibodies against HIV-1
  - Third generation assays detect IgM and IgG antibodies against HIV-1 as early as 2 weeks after infection. Some assays also detect HIV-2 and HIV-1 group O.
  - Fourth-generation combination EIAs
Detect both HIV antibody and p24 antigen
- Can identify HIV infection within 2 weeks of infection
- FDA approval is pending; widely used in other developed countries

**Rapid format assays:**
- May be done using saliva, whole blood or urine
- Results available within one hour
- Assays that use blood generally have slightly better specificity than assays that use saliva
- Many of the rapid tests are waived from requirements imposed by the Clinical Laboratory Improvement Amendments (CLIA), which facilitates making testing available in both medical and non-medical, community settings.
- Results of both standard and rapid format tests require a confirmatory test using a second assay. Rapid format EIA tests occasionally detect HIV infection in persons with negative standard format EIA tests; therefore a confirmatory Western blot or should be performed on all persons with positive rapid format tests regardless whether a standard format EIA test is positive

**Western blot:** recommended by the United States Centers for Disease Control and Prevention to confirm the results of screening assays (EIA, p24 antigen, or nucleic acid amplification and detection tests). Although far less often used, an immunofluorescent antibody assay can also be used to confirm HIV infection. The standard Western blot assay reliably detects infection only for HIV-1. Special HIV-2 Western blots are available.

- **Positive** Western blot result: requires reactivity to at least 2 of the following antigens (bands): p24, gp41, gp120/160.
- **Negative** Western blot result: absence of recognition of any antigens (bands).
- **Indeterminate** Western blot result: presence of reactivity to 1 or more antigens, but not fulfilling the criteria for positivity

- indeterminate results may be due technical artifact, laboratory error, nonspecific reactions, hypergammaglobulinemia, the presence of an antigenic variant of HIV-1, early HIV-1 infection (recent generation EIA
assays detect HIV infection earlier than does the Western blot, late-stage
disease or infection by HIV-2.
◊ Low risk patients: repeat testing is recommended 1 – 3 months later.
◊ High risk patients: timely performance of a nucleic acid amplification test
to rule out HIV seroconversion and/or performance of an HIV-2 Western
blot is recommended
◊ Many individuals with indeterminate Western blots have the identical
profile for long periods of time (years) and never seroconvert.

- **Nucleic acid amplification tests** (NAAT), i.e., viral load assays performed using signal
amplification technology (e.g., branched chain DNA detection) or real time polymerase
chain reaction assays
  - Become positive 7 – 10 days after infection by HIV-1
  - Nucleic acid amplification tests do not reliably detect HIV-2
  - Qualitative or quantitative HIV-1 nucleic acid amplification test with a
  sensitivity of 50 - 100 RNA copies/mL can detect HIV infection earlier than the
  p24 antigen test or EIA assays, including third and fourth generation tests
  - If both an HIV EIA and nucleic acid amplification test is positive, HIV infection
  is confirmed and Western blot testing is unnecessary.

- **HIV p24 antigen assays:**
  - Become positive about 2 to 3 weeks after infection
  - Use has been largely replaced by nucleic acid amplification tests

*Sensitivity, specificity and predictive value of laboratory assays*

- **Acute HIV infection**
  - Within 2 to 4 weeks after infection approximately two thirds of acutely infected
  individuals develop a mononucleosis-like seroconversion reaction, which is
  characterized by fever, mucosal ulceration, lymphadenopathy, rash and
  occasionally aseptic meningitis and other neurological abnormalities. After
  several weeks, these findings spontaneously resolve and infected individuals
  enter a period of clinical latency wherein symptoms and signs of HIV infection
  are largely absent.
  - HIV infection is undetectable for 7 to 10 days following exposure.
Nucleic acid amplification tests should be used to diagnosis suspected HIV seroconversion reactions

- **Quantitative assays:**
  - Low titer HIV-1 RNA measurements (<5,000 RNA copies/mL) are likely to represent false-positive results.
  - Values greater than 100,000 HIV-1 RNA copies/mL are characteristic of persons with true acute seroconversion reactions

- **Qualitative assays:** Only a single qualitative nucleic acid amplification test has been approved for diagnostic use by the United States Food and Drug Administration (FDA).
  - Sensitivity: reported as being 100% (95% confidence limits 99.5 – 100%) in samples with a viral load of 100 HIV-1 RNA copies/mL and 98.5% (95% confidence limits 97.3 – 99.2%) in samples with a viral load of 30 HIV-1 RNA copies/mL.
  - Specificity: reported as being 99.83%.

All patients who are diagnosed with HIV infection solely on the basis of viral load results (e.g., nucleic acid amplification tests) should subsequently undergo standard serological testing to confirm that the diagnosis is correct.

- **Chronic HIV infection**
  - The FDA draft guidance for manufacturers seeking licensure of individual tests recommends demonstration that the lower bound of the one-sided 95% confidence interval for sensitivity and specificity exceed 98%.

- **Special circumstances**
  - **HIV-2:**
    - Current status of testing in the United States
      - Many but not all FDA-approved HIV EIA assays detect both HIV-1 and HIV-2.
      - The standard Western blot assay in the United States only detects infection by HIV-1.
      - There are no FDA approved assays for determination of HIV-2 viral loads
- Non-FDA approved Western blot and nucleic acid amplifications assays are available for HIV-2.

- Fewer than 100 cases of HIV-2 have been verified in the United States, most of which have been linked to West Africa.

- Indications for HIV-2 testing: testing should be done in patients who
  - Are from areas of high prevalence, i.e. Western Africa
  - Share needles or have sexual partners known to be infected with HIV-2 or are from endemic areas
  - Received transfusions or other non-sterile medical care from endemic areas
  - Are children of women with risk factors for HIV-2 infection
  - In persons where a clinical history is not available and there is high-suspicion of HIV infected and negative or indeterminate serology for HIV-1.

- HIV-1 group O:
  - Some EIA assays do not detect infection by HIV-1, Group O.
  - This group of viruses is found primarily in West Africa (Cameroon and Gabon)

- Causes of false negative tests
  - Recent exposure: repeat testing is recommended 3 months after the initial or potential exposure
  - Dilution of antibody concentrations due to receipt of large volume blood transfusions or plasmaphoresis

- Causes of false positive HIV tests
  - Recent Influenza vaccination
  - Systemic lupus erythematosus and other autoimmune diseases

- Participation in HIV vaccine trial:
  - Participants in preventive HIV vaccine may have vaccine-induced antibodies detected by EIA or Western Blot assays
  - Participants whose test results show the presence of HIV antibodies should undergo special confirmatory testing as recommended by their particular study to determine their HIV status.
Infants

- Antibody testing is unreliable due to passive transfer of maternal-to-child antibodies; antibody may persist for one year after birth
- Nucleic acid amplification and detection tests can be done from birth onwards to exclude in utero or subsequent transmission of HIV-1

**Recommended reading list**


HIV Transmission and Diagnosis

Post-Test

1. A young man who has sex with men presents to an urgent care clinic with fever, a diffuse macular rash, sore throat and cervical lymphadenopathy. His most recent sexual encounter was 10 days earlier at which time he had unprotected sex with a new partner. He is concerned that he may have acquired HIV infection. What test should be performed?
   a. HIV Western Blot
   b. Determination of the presence of plasma HIV RNA-1 copies/mL of plasma by means of a nucleic acid amplification test (viral load)
   c. Standard format HIV enzyme immunoassay (EIA) using a blood specimen
   d. Rapid format HIV enzyme immunoassay using a blood specimen
   e. Rapid format HIV enzyme immunoassay using an oral fluid specimen

2. An asymptomatic 40-year-old, sexually active patient is referred to you from an outside clinic for further management. The patient recently participated in a community-based HIV screening program and was found to have a positive rapid format HIV enzyme immunoassay done using an oral fluid specimen. To confirm this result, the outside clinic performed a standard HIV enzyme immunoassay (EIA) using a blood specimen. This confirmatory test was negative and the patient is now referred to you for further counseling and management. Which of the following accurately summarizes the patient’s status and the best course of action?
   a. Since the standard format HIV EIA is negative, the rapid format HIV EIA is a false-positive result. No further testing is required.
   b. Since the standard format HIV EIA is negative and the rapid format HIV EIA was positive, the patient is most likely in the HIV seroconversion period. A standard format HIV EIA test should be obtained in 1 – 3 months.
   c. HIV infection is still a serious concern as a Western Blot test should have been performed to confirm the positive rapid format HIV EIA test.
d. The rapid format HIV EIA test does not require confirmatory testing. The standard format HIV EIA test is very likely a false-negative test and the patient should be told that he or she has HIV infection.

e. Since the standard format HIV EIA is negative and the rapid format HIV EIA was positive, the patient should be tested for HIV-1 type O and HIV-2.

3. Your hospital is considering establishing a program to routinely offer an HIV test to all previously untested patients regardless whether they have known risk factors for HIV infection. An administrator at the hospital is very concerned about the cost-effectiveness of such a program and wants your advice as to whether any groups of patients should be excluded from this program. Your best advice is to say that

a. Routine offers of HIV tests generally remain cost-effective for persons up to at least the age of 74 who have partners to whom they could transmit HIV

b. Routine offers of HIV tests to patients over the age of 64 are unlikely to be cost-effective compared to other medical interventions

c. All positive screening tests should be confirmed with a nucleic acid amplification test

d. If there are 1000 consecutive negative tests at the beginning of the screening program, the prevalence of undiagnosed HIV infection in the local community is less than 0.1%. If this is found, the program should be abandoned because routine HIV screening is very unlikely to be cost-effective in the local community.

e. Persons over the age of 64 should only be offered HIV testing if they are known to have engaged in high-risk activities.

4. Which of the following is the most likely cause of a false-negative HIV test in the United States?

a. Infection by HIV within one year prior to testing

b. A viral respiratory tract infection

c. Recent influenza infection

d. Infection by HIV-1 group O or infection by HIV-2

e. Receipt of corticosteroid therapy
5. Which of the following is true about the risk of HIV infection for a man who has engaged in unprotected insertive vaginal intercourse with an HIV-infected woman?
   a. The risk of becoming HIV infected is approximately the same as for insertive oral intercourse
   b. There is no measurable risk of HIV infection if the woman’s viral load is undetectable (i.e., less than 50 HIV-1 RNA copies/mL)
   c. The risk of acquiring HIV infection is increased if his partner has evidence of infection by chlamydia
   d. The risk of acquiring HIV infection is approximately the same as for a healthcare worker who suffers a needlestick injury by a needle use to draw blood from an HIV-infected patient
   e. The risk of acquiring HIV infection is increased if his partner has evidence of bacterial vaginosis

6. One of your HIV-infected patients has a CD4⁺ count of 750 cells/μL and a viral load of 47,000 HIV-1 RNA copies/mL. He has never been on antiretroviral therapy. He has lost his job and to conserve funds has been invited to live with his sibling and her family, which includes a healthy teenage daughter who has received a kidney transplant and son who is in pre-school. Your patient asks you what the risks are for sharing the same household and whether any special precautions need to be taken. Your advice is that
   a. There is no evidence of intra-household transmission of HIV infection among persons who are not sexual partners or exposed to blood-contaminated materials.
   b. He should immediately start antiretroviral therapy to decrease his viral load and decrease the likelihood of inadvertent household transmission of HIV infection.
   c. Caution should be taken that there are no opportunities for mosquitoes to bite the patient and then another family member.
   d. He should have his own set of glasses and dining utensils to decrease the risk of HIV transmission.
   e. Under no circumstances should he kiss his niece’s cheek.

7. A 60-year-old man with no known risk factors recently received 2 units of blood while undergoing surgery at a hospital in the midwestern United States. Four months later he
received an influenza vaccination and then 1 month after that accepted an offer of a routine standard format HIV EIA test. The EIA is positive but the Western Blot is negative (no bands are present). He is concerned that he may be undergoing an HIV seroconversion reaction due to receipt of infected blood. You advise him that:

a. The risk of receiving an HIV-infected unit of blood in the United States is approximately 1 in 10,000 units of blood.

b. An HIV nucleic acid amplification test should be immediately done to rule-out HIV seroconversion.

c. A negative Western Blot 5 months after the receipt of the blood transfusion indicates that he was not infected by HIV due to this event.

d. Influenza vaccination temporarily interferes with the interpretation of the Western blot; this test should be repeated after 3 months.

e. Specific testing should be done to rule-out infection by HIV-2

8. A patient of yours recently travelled to Cameroon to participate in a medical missionary program as a non-medical, lay assistant. While in Cameroon she was in a motor vehicle accident and required urgent surgery and two units of blood. It is now three months later and she is concerned that she may have acquired HIV infection due to the blood transfusion. She has not had any fever, chills, lymphadenopathy or other constitutional symptoms following her accident. You inform her that

a. The risk of receiving an HIV-infected unit of blood in Cameroon is much higher than in the United States.

b. Standard HIV testing as performed in the United States is always sufficient to diagnose all forms of HIV (HIV-1 including group O and HIV-2) that might be found in Cameroon.

c. The risk of HIV infection from a unit of blood is the same as the risk from sharing syringes used by an HIV infected patient.

d. HIV-2 is common in West Africa but is not detected by any HIV EIA assays that are routinely available in the United States.

e. Since she has not had any symptoms or signs of the acute retroviral syndrome, the risk of HIV infection is negligible. No testing is warranted.
9. A 9-year-old boy is brought in to an urgent care center by his family who learned that he and his friends had searching for “treasures” in a refuse camp at a homeless camp. His family is very worried that he might have cut himself and been exposed to body waste from HIV-infected persons. Your best advice to the family is as follows:
   a. HIV is readily transmitted by dried blood or other body waste.
   b. HIV is transmitted by contact with urine from HIV-infected persons.
   c. HIV is transmitted by contact with feces from HIV-infected persons.
   d. HIV infection often occurs due to a community exposure to a discarded syringe.
   e. With this type of exposure, assuring adequate tetanus prophylaxis for dirty wounds is far more important than HIV post-exposure prophylaxis.

10. Which of the following healthcare exposures is associated with the highest risk of HIV transmission?
   a. Healthcare worker’s ungloved hands exposed to non-bloody stools of HIV-infected patient
   b. Healthcare worker’s ungloved hands exposed to non-bloody urine of HIV-infected patient in the clinic
   d. Psychotic HIV patient spat at a healthcare worker with some spit contaminating the open mouth of the healthcare worker
   e. Healthcare worker’s ungloved hands exposed to peritoneal fluid of HIV-infected patient

11. Which of these activities has the lowest risk for HIV transmission?
   a. The transfusion of one screened unit of red blood cells in the USA in 2009.
   b. Blood from HIV-infected patient splashed into the eye of a healthcare worker.
   c. Unprotected insertive vaginal intercourse with an HIV-infected female.
   d. Unprotected receptive anal intercourse with an HIV-infected male.
   e. Receipt of a transplanted organ from a patient who hemorrhaged to death following an motor vehicle accident.

12. A 40-year-old woman born, raised and living in the Midwestern United States is referred by her primary care physician for evaluation of her HIV blood tests. She is concerned
that she may have acquired HIV infection from her husband with whom she has not had
sexual relations for twelve months. She has no other risk factors for HIV infection. Her
blood tests (done two weeks earlier) show that the HIV EIA was positive. The HIV-1
Western Blot was indeterminate with a single p24 band. What test(s) do you recommend?

a. Repeat HIV EIA (and Western Blot if positive) in 1 - 3 months
b. Order HIV-2 Western Blot
c. HIV Culture for HIV-1 group O
d. HTLV-I and HTLV-II antibody
e. None; no further testing is necessary since her last sexual exposure to her husband
   was 12 months ago