HIV Infection and AIDS

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HIV

H – Human – This particular virus can only infect human beings.

I – Immunodeficiency – HIV weakens your immune system by destroying important cells that fight disease and infection. A “deficient” immune system can’t protect you.

V – Virus – A virus can only reproduce itself by taking over a cell in the body of its host.

Virus

- A virus is an extremely tiny infectious agent that is only able to live inside a cell.
- Basically, viruses are composed of just two parts. The outer part is a protective shell made of protein. This shell is often surrounded by another protective layer or envelope, made of protein or lipids (fats). The inner part is made of genetic material, either RNA or DNA.
- A virus does not have any other structures (called organelles) that living cells have, like a nucleus or mitochondria. These organelles are the tiny organs that maintain a cell’s metabolism (life processes). A virus has no metabolism at all.

http://www.cdc.gov/ncidod/diseases/hanta/hps/noframes/virus.htm
Virus

- Because a virus lacks organelles, it cannot reproduce by itself. To reproduce, a virus invades a cell within the body of a human or other creature, called the host. Each type of virus has particular types of host creatures and host cells that it will invade successfully.
- Once within the host cell, the virus uses the cell’s own organelles to produce more viruses. In essence, the virus forces the cell to replicate the virus' own genetic material and protective shell. Once replicated, the new viruses leave the host cell and are ready to invade others.

http://www.cdc.gov/ncidod/diseases/hanta/hps/noframes/virus.htm

Historical Context

- **Human immunodeficiency virus type 1 (HIV-1)** must have been spreading through the human population long before AIDS was first described in 1981, but very few strains from this ‘prehistoric’ period (pre-1980s) have been characterized.
- HIV-1 strains are divided into three groups, each of which was independently derived from a simian immunodeficiency virus (SIV) that naturally infects chimpanzees in west-central Africa.
- Whereas two of these groups are rare, the third, group M, has spread throughout the world and is the cause of more than 95% of HIV infections globally.


Historical Context

- Acquired immunodeficiency syndrome (AIDS) pandemic was one of the key international health and demographic events of the late 20th century
- By the turn of the century, in some countries, over 30% of adults were living with HIV infection
- The impact of HIV/AIDS has always been greatest in the poorest countries, where over 95% of new infections currently occur
- HIV/AIDS has become a major political issue

Historical Context

- The HIV viruses (HIV-1 and HIV-2) are of zoonotic origin in Africa
- The virus likely emerged around 1930 or before
- Epidemic did not arise until mid-1970’s around Kinshasa
- HIV-2 likely emerged earlier than HIV-1, has been associated with many fewer cases and mostly found in West Africa
- HIV spread to western hemisphere with Haiti appearing to have the oldest epidemic outside sub-Saharan Africa


Historical Context

- Recent analyses suggested the transfer was from Central Africa to Haiti to the United States
- Earliest documented HIV-1 infection in US was in 1977
- From the US, HIV spread by homosexual contact then spread later among injection drug users
- World became aware of clinical entity known as AIDS due to a June 1981 CDC report describing clusters of fatal Pneumocystis carinii pneumonia (PCP) and Kaposi's sarcoma (KS) over the previous 6 months in younger men in California and New York


Historical Context

- Causal pathogen (HIV-1), a T-lymphotropic retrovirus was identified in 1983
- In 1985, a test to screen for antibody to the virus was approved by the FDA
- In May 1987, zidovudine (ZDV, AZT) which is a nucleotide reverse transcriptase inhibitor became the first antiretroviral approved by FDA
- Because single antiretrovirals had limitations including resistance and side effects, highly active antiretroviral therapy (HAART) regimens (cocktails or combination therapy) were introduced in 1995 which transformed HIV disease into a chronic condition requiring long term care

Global Epidemiology

- The global prevalence of HIV-1 has stabilized at 0.8%, with 33 million people living with HIV/AIDS
- 2.7 million new infections, and 2.0 million AIDS deaths in 2007
- Heterosexual spread in the general population is the main mode of transmission in sub-Saharan Africa which remains the most heavily affected region, with 67% of the global burden
- Male–male sex, injection drug use, and sex work are the predominant risk factors in most other regions
- Infection rates are declining in some regions, including some of the most heavily affected countries in Africa, but climbing elsewhere such as in eastern Europe and central Asia

Current Opinion in HIV and AIDS 2009; 2(4):240-246

U.S.A. Epidemiology

- Prevalence is the number of people living with HIV infection at the end of a given year
- At the end of 2006, an estimated 1,106,400 persons (95% confidence interval 1,056,400-1,156,400) in the United States were living with HIV infection, with 21% undiagnosed
- HIV prevalence in US is higher than ever before despite declining incidence because mortality has declined while the annual number of new cases remains stable

https://www.cdc.gov/hiv/topics/surveillance/basic.htm#hivest

U.S.A. Epidemiology

- In 2008, CDC (1) released HIV incidence estimates for 2006 based on a new method of determining incidence (2)
- The new method showed that the HIV epidemic is, and has been, worse than was previously estimated, with 56,300 people newly infected with HIV in 2006. This estimate is significantly higher than CDC’s previous estimate of 40,000 new HIV infections per year (1).
- It is estimated that over one million people in the United States are living with HIV.
- Although there has been great progress in HIV testing rates, approximately 20% of those with HIV infection still do not know they are infected.

2. JAMA, August 6, 2008;300(5):520
Incidence by Race/Ethnicity

- The chart below shows the breakdown by race or ethnicity of the estimated 56,300 people who were newly infected with HIV in 2006.
- African Americans are the racial/ethnic group most affected by HIV.
- African Americans comprise only 12% of the population of the United States.
- Hispanics/Latinos are also disproportionately affected by HIV.
- Within each racial/ethnic category are individuals with different risk factors for HIV infection, including those who have sex with others who may be at high risk of HIV infection, or people who are injection drug users.
Incidence by Transmission Category

- The epidemic is largely concentrated among men who have sex with men (MSM)
- MSM accounted for 53% of new HIV infections in 2006, even though gay and bisexual men comprise a very small portion of the population
- People infected through heterosexual contact, accounted for almost one-third of new infections, and injection drug users accounted for 12%.

n= 54,230

http://www.cdc.gov/hiv/topics/surveillance/incidence.htm
http://www.cdc.gov/hiv/surveillance/incidence/sote/transmission-category.htm

Incidence by Transmission Category

- MSM, regardless of race or ethnicity, comprise 53% of new HIV infections among whites, blacks, and Hispanics/Latinos
- This fact is critical to understand when fighting the US epidemic. Reaching MSM of all races with life-saving prevention services is as important as it has ever been

n= 54,230

http://www.cdc.gov/hiv/topics/surveillance/incidence.htm

MSM by Race/Ethnicity

- Data emphasize that among white, black, and Hispanic MSM, the majority of new infections – 46% - occurred among white MSM
- Black MSM accounted for 35% of new infections among MSM, and Hispanic MSM 19%

n= 28,720

http://www.cdc.gov/hiv/topics/surveillance/incidence.htm
Heterosexuals by Race/Ethnicity

- This chart shows the race/ethnicity among white, black, and Hispanic/Latino heterosexuals newly infected with HIV in 2006.
- Heterosexual transmission accounted for the second largest route of HIV transmission in the United States in 2006.
- This chart represents 37% of all new HIV infections among whites, blacks, and Hispanic/Latinos in 2006.

n= 16,800

Injection Drug Use by Race/Ethnicity

- This chart represents 12% of all new HIV infections among whites, blacks, and Hispanics in 2006.
- Most new HIV infections in the injection drug group—53%—occurred in blacks. Whites accounted for 30% of new infections, and Hispanics 17%.

n= 6,610

Estimated Number* of New HIV Cases—22 States 2006

*Estimated to the nearest 10. Data have been adjusted for reporting delay.
HIV Surveillance and Reporting

- Surveillance is the routine, ongoing systematic collection and analysis of epidemiologic data to detect both extent of disease spread and also changes in trends of the disease.
- As of April 2008, all 50 states, the District of Columbia, and 5 dependent areas—American Samoa, Guam, the Northern Mariana Islands, Puerto Rico, and the U.S. Virgin Islands—use the same confidential name-based reporting system to collect HIV and AIDS data.

How is HIV Spread?

1. Most cases have resulted from sexual contact.
2. Injecting drug users are at risk from sharing needles and sex.
3. Perinatal (vertical) transmission – childbirth.
4. Transfusion related HIV transmission (effectively halted following 1985 screening).
5. Occupational exposure of healthcare and lab workers.
6. Transmission during invasive procedures (rarely reported).

**How is HIV Spread?**

- HIV is spread through four body fluids:
  1. Semen
  2. Vaginal Fluid
  3. Blood
  4. Breast Milk

- HIV is **NOT** spread through:
  1. Tears
  2. Sweat
  3. Feces
  4. Urine

**HIV Through Sex**

- For HIV to be spread through sex, the semen, vaginal fluids, or blood of an infected person must enter the body of an uninfected person
- Sexual contact that can transmit HIV includes:
  1. **vaginal sex** (penis in the vagina)
  2. **anal sex** (penis in the anus of either a man or a woman)
  3. **oral sex** (penis in the mouth)
- If you have sex, the best thing to do is to practice "safer sex" all the time (condom, dental dam, or other latex barrier and avoid "rough sex")

**HIV Through Blood Exposure**

- You can become infected if you have contact with the blood of someone who is infected with HIV by:
  1. sharing needles when shooting drugs
  2. tattoos or body piercings with unsterilized needles
  3. accidental needle sticks
  4. blood transfusions
  5. splashing blood in your eyes
- HIV is **NOT** spread by blood passed through insect bites.

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**HIV Through Mother to Baby**

- Pregnant women who are HIV positive can give the virus to their babies in the womb, during birth and by breastfeeding
- Taking anti-HIV drugs during pregnancy and childbirth can help lower the risk
- New mothers should try to bottle-feed their babies rather than breast-feed

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**Prevention of HIV Disease**

- Because the most common ways HIV is transmitted is through anal or vaginal sex or sharing drug injection equipment with a person infected with HIV, it is important to take steps to reduce the risks associated with these

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**Prevention of HIV Disease**

**Primary Prevention** – implemented pre-pathogenesis and aim to avert infection by decreasing or eliminating risks

**Secondary Prevention** – implemented after infection and aims to avert/delay disease progression by stopping or slowing pathologic processes

**Tertiary Prevention** – aims to avert the complications of disease and its treatment

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3. [http://www.cdc.gov/hiv/topics/basic/#prevention](http://www.cdc.gov/hiv/topics/basic/#prevention)
Primary Prevention of HIV

- eliminate reservoir of infection (sterile needles, screen blood supply, alternatives to breastfeeding)
- biologic and chemoprophylaxis
  - a) vaccine
  - b) male circumcision
  - c) prevention/treatment of STIs
  - d) pre-exposure prophylaxis
- chemical barriers
  - a) microbicide
  - b) mechanical/barrier methods (e.g., condoms)
- post-exposure prophylaxis

Secondary Prevention of HIV

- "therapeutic" vaccine to slow disease progression
- timely access to antiretroviral therapy and psychosocial interventions
- confidential partner notification

Tertiary Prevention of HIV

- aims to prevent opportunistic infections, adverse effects of medications and other interventions
- counseling
- risk assessment and prophylaxis for opportunistic infections
- immune boosters

General Prevention of HIV Disease

1. Know your HIV status
   Find a testing location at http://www.hivtest.org/
2. If you have HIV, get care
3. Abstain from sexual activity or be in a long-term mutually monogamous relationship with an uninfected partner
4. Limit your number of sex partners. The fewer partners you have, the less likely you are to encounter someone who is infected with HIV or another STD.
5. Correct and consistent condom use. Latex condoms are highly effective at preventing transmission of HIV and some other sexually transmitted diseases.
   http://www.cdc.gov/hiv/topics/basic/#prevention

6. Get tested and treated for STDs and insist that your partners do too.
7. Male circumcision has been shown to reduce the risk of HIV transmission from women to men during vaginal sex
8. Do not inject drugs. If you inject drugs, you should get counseling and treatment to stop or reduce your drug use. If you cannot stop injecting drugs, use clean needles and materials when injecting.
   http://www.cdc.gov/hiv/topics/basic/#prevention

9. Obtain medical treatment immediately if you think you were exposed to HIV. Sometimes, HIV medications can prevent infection if they are started quickly. This is called post-exposure prophylaxis.
10. Participate in risk reduction programs. Programs exist to help people make healthy decisions, such as negotiating condom use or discussing HIV status. Your health department can refer you to programs in your area.
   http://www.cdc.gov/hiv/topics/basic/#prevention
Other Prevention Strategies

- Universal blood and bodily fluid precautions in clinical settings
- Provider-initiated HIV counseling/education
- Sex education in schools
- World AIDS Day

Pathophysiology of HIV - Overview

- The causative organism, HIV, is classified within Lentivirus (Latin: lenti = slow) subgroup of a new family of viruses, Retroviridae
- During replication of these viruses, the flow of genetic information is in the opposite direction (from RNA to DNA), hence, they are called retroviruses
- Their unique enzyme reverse transcriptase copies the viral RNA into DNA, which is eventually inserted into the genome of the host cells
- Hence, the virus persists within the host cells for years and cannot be eradicated from the host cells with any of the currently available ARV drugs

Lentiviruses

Lentiviruses include:

1. HIV-1
   a. HIV-1 is the most prevalent human retrovirus in the world
   b. HIV-1 has three virus groups (M,N,O) which are further divided into subgroups (clades)
   c. M is the main group and has 11 clades A – K
2. HIV-2
   a. primarily localized to Western Africa
3. Simian immunodeficiency virus (SIV)
   a. linked to AIDS-like disease in monkeys
Basic structure of a Retrovirus:

• All retroviruses (including HIV) have a diameter of about 100 nm
• All retroviruses have an outer lipoprotein envelope, which encloses a core made of other viral proteins, within which lie two single strands of viral RNA (RNA viruses) and the enzyme reverse transcriptase (RNA-dependent DNA polymerase)

Structure of Retrovirus
• reverse transcriptase transcribes RNA into DNA
• 3 common genes: env, pol, gag
• able to incorporate viral DNA into genome of host target cells
• incorporated retroviral DNA can be transcribed to produce budding viruses

Structure of HIV
• HIV is an enveloped icosahedral sphere (i.e. a solid with 20 plane faces)
• Diameter of the virus is 80–120 nm
• Two identical, non-complementary strands of HIV RNA (the viral genome) and three enzymes (reverse transcriptase, integrase, and protease) are packaged in a coneshaped protein core
• Core is surrounded by a protein coat called "capsid".
• Role of capsid is to form protective shell around the nucleic acid core, and introduce the viral genome into host cell by adsorbing readily to host cell surfaces
Structure of HIV

- Lipid envelope contains the glycoproteins – gp120 and gp41
- The HIV genome contains 3 genes called **env**, **pol**, and **gag**
  - **env** codes for gp120 and gp41
  - **pol** codes for the 3 enzymes (e.g., protease)
  - **gag** codes for p24, p6, p7, p17

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HIV – What it looks like

Electron microscope photo of HIV in cell (dark black) and HIV budding from cell surface (lower right-hand corner).

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This highly magnified transmission electron micrographic (TEM) image revealed the presence of mature forms of the human immunodeficiency virus (HIV) in a tissue sample under investigation. The Human Immunodeficiency Virus (HIV), a retrovirus, was identified in 1983 as the etiologic agent for the Acquired Immunodeficiency Syndrome (AIDS). AIDS is characterized by changes in the population of T-cell lymphocytes that play a key role in the immune defense system. In the infected individual, the virus causes a depletion of subpopulation of T-cells, called T-helper cells, which leaves these patients susceptible to opportunistic infections, as well as certain malignancies.
HIV Replication Basics

• Receptors are present on the surface membrane of all living cells
• The receptor is compared to a lock, into which a specific key (called "ligand") will fit
• HIV binds to at least two specific receptors on the host cell: the primary receptor, called the CD4+, and a secondary receptor, a chemokine co-receptor, such as CXCR4 or CCR5
• CD4 receptor: A protein present on the outside of infection-fighting white blood cells. CD4 receptors allow HIV to bind to and enter cells.

http://www.apin.harvard.edu/Chapter7.pdf

HIV Replication Basics

• After infection, there is a cascade of events within the host cell. The end results are production of new viral particles, death of the host cell, and destruction of the immune system of the host.
• In an infected individual, the replication of HIV occurs rapidly and continues throughout the course of the disease, unless checked by ARV drugs.
• HIV infected CD4 cells have an average life span of 2.2 days. High rate of destruction of CD4 cells leads to a decline in the CD4 cell count.

http://www.apin.harvard.edu/Chapter7.pdf

HIV Lifecycle

1. Binding and Fusion
2. Reverse Transcription
3. Integration
4. Transcription
5. Assembly
6. Budding
1. Binding and Fusion

HIV infection of a lymphocyte begins with attachment of the virus, via its gp120, to the cell membrane through both CD4 receptor and co-receptor.

The virus then fuses with host cell. Following fusion, the contents of the virus are emptied into the cytoplasm of the host cell.

2. Reverse Transcription

Reverse transcriptase converts single stranded viral RNA into viral DNA duplex. In case there are errors in reading the viral RNA sequence, the viral progeny may have molecular differences in their surface membrane and enzymes, which may lead to production of drug-resistant and immunological escape mutants in each cycle of viral replication.

3. Integration

The viral DNA is integrated into the DNA of the host cell. This process is facilitated by the viral enzyme integrase. The integrated DNA is called a “provirus”.

4. Transcription

Upon activation of infected cells, viral DNA is transcribed along with the host DNA into mRNA. The mRNA codes for the production of virus proteins. The new viral RNA also acts as the genetic material for the next generation of viruses.

5. Assembly

Protease cuts the long chains of HIV proteins into smaller proteins. As the smaller HIV proteins come together with copies of HIV’s RNA genetic material, a new virus particle is assembled.

6. Budding

During budding, the new virus takes part of the cell’s outer envelope. This envelope, which acts as a covering, is covered with protein/sugar combinations called HIV glycoproteins. These HIV glycoproteins are necessary for the virus to bind CD4 and coreceptors. The new copies of HIV then move on to infect other cells.
Normal Immunology

Cells of the immune system - Types of Leukocytes:
1. Neutrophils
2. Eosinophils
3. Basophils
4. Monocytes and Macrophages
5. Lymphocytes
   i) B cells
   ii) T cells
   iii) Natural killer (NK) cells

T cells

- represent 70-90% of all circulating lymphocytes
- identified by different surface markers (e.g. CD4, CD8, CD3)
- T-helper/inducer cells carry the CD4 surface marker
- normal absolute count of CD4 cells is 950–1,700 per mm3 of peripheral blood.
Normal Immunology

Immune response characteristics:
1. Nonspecific immunity
   i) physical, mechanical, chemical, microbial barriers
   ii) phagocytosis
   iii) inflammatory response
2. Specific immunity
   i) humoral immunity (B-cell)
   ii) cell-mediated immunity (T-cell)
   iii) NK cells

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Immune System Response to HIV

1. CD4 T cells are the targets for HIV infection
   a) if sexual transmission, HIV enters via macrophages in semen or vaginal secretions
   b) chemokine receptors are required for cell infection
   c) CD4 T cells become reservoirs of latent virus early
   d) progressive decline in CD4 cell numbers over time
   e) progressive loss in proliferation and cytokine secretion by CD4 – TH1 cells
   f) hyperactivation of CD4 – TH2 cells

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Immune System Response to HIV

2. CD8 T-cytotoxic cells
   a) increase in number during acute infection
   b) activated CD8 T cells are cytotoxic to HIV-infected CD4 cells with env, gag or pol proteins
   c) decline in numbers at time of diagnosis
   d) ↑ expression of cell surface activation markers
   e) ↓ HIV-specific cytotoxic lymphocyte activity over time
Immune System Response to HIV

3. NK cells
   a) produce perforins (contact dependent mechanism to kill virus-infected cells) that insert into cell membrane and create channels in membrane leading to death
   b) NK cells can be cell reservoirs for latent virus

4. B lymphocytes
   a) expression of cell surface activation markers
   b) ↑ levels of HIV-specific immunoglobulins
   c) differentiate into plasma cells to produce antibody against HIV virus proteins
   d) antibody-dependent cellular cytotoxicity – antibodies help clear virus by macrophages + NK

5. Mononuclear phagocytes
   a) targets for HIV infection
   b) macrophages can be reservoir of latent virus
   c) reduced migration to inflammatory stimulus
   d) reduced phagocytosis and killing of bacteria

6. Granulocytes – no consistent alterations

7. Lymphoid organs – main sites for early and latent infection
Natural History of HIV infection

Primary infection (time 0)
- Period immediately after HIV infection
- ↑ levels of viremia and immune activation
- Viral load usually exceeds 100,000 copies/ml but often exceeds 1 million copies/ml
- CD4 and CD8 cells decrease initially followed by lymphocytosis
- Acute retroviral syndrome: 30-50% of people around a month after infection and lasts 2-4 weeks, fever, joint pain, myalgia, lymphadenopathy, pharyngitis, anorexia, antibodies develop after 2-5 weeks

Chronic infection
- Decreased level of viremia, resolved acute syndrome
- A balance between viral replication and immune control results in a steady state (set point)
- After the set point, HIV progresses in this way:
  1. Clinical latency – 12 wks to 8 years
     a) HIV sequestered mostly in lymph tissue
     b) chronic immune activation
     c) continued spread of virus
  2. Symptomatic HIV disease – typically 8-10 yrs
     a) signs and symptoms begin to emerge
     b) viral replication
     c) deteriorated lymphoid environment
     d) CD4 cell count between 200-500 cells/mm³ with decreasing CD4 lymphocytes
Chronic infection

3. Advanced HIV disease (AIDS) – period after primary infection (usually 10-11 years) in which T cell count is < 200 cells/mm³ or there is AIDS indicator condition as defined by CDC. Period is characterized by:
   a) failure of immune system to control virus replication
   b) major immunodeficiency, with CD4 lymphocytes between 0-200 cells/mm³

4. Clinical progression of HIV disease is dependent on numerous factors: genetics, viral virulence, response to antivirals etc.

5. A small proportion (less than 5%) of HIV-infected people remain asymptomatic with no sign of disease progression
HIV Testing Overview

• Updated CDC guidelines (2006) recommend screening of all patients aged 30 to 64 years at least once for HIV (without regard to reported risk factors for HIV acquisition)
• CDC encourages the use of an "opt-out" approach to testing. This means patients are advised that HIV testing will be performed unless they decline it. The CDC also recommends that HIV testing be considered part of a patient's general consent for medical care. Law in many states requires a separate consent form.
• CDC recommends HIV testing of all pregnant women and, at minimum, annual testing of patients who are at high risk


HIV Testing Overview

Purpose of Testing - screening (do they have HIV-1 or HIV-2) and diagnosis (quantifying amount or 'viral load')

The 3 Cs:
1. Consent – opt out vs. opt in
2. Confidentiality
3. Counseling – pretest, post-test


HIV Testing Overview

Approaches to HIV Testing
1. Voluntary counseling and testing (VCT)
2. Provider-initiated HIV counseling and testing
3. Anonymous unlinked HIV testing
4. Mandatory testing
   a) screening for transfusions
   b) screening of donor bodily fluids
   c) some countries for military personnel
   d) immigrants and federal prisoners

HIV Testing Overview

When to Test?
• Whenever S/S of illness that could be HIV related
• Risk based, voluntary testing
• Provider initiated counseling and testing
• Benefits of integrating testing into routine care

Testing frequency?
• every 6-12 months for those with risky behaviors
• early in every new pregnancy


HIV Tests

Tests for diagnosis of HIV infection include:
a) specific tests for HIV infection
b) detecting immune deficiency
c) diagnosing opportunistic infections and malignancies

Specific tests for diagnosis of HIV infection are screening tests - "E/R/S":
a) Enzyme linked immunosorbent assay (ELISA)
b) rapid assays
c) simple agglutination assays

Confirmatory or supplemental assays:
a) immunoblot or Western blot (WB)
b) immuno-fluorescence assay (IFA)
c) radio-immunoprecipitation assay (RIPA)
d) radio-immuno assay (RIA)

Tests for detecting HIV antigen, viral nucleic acids, viral components, or the virus itself: detection of p24 viral antigen, RT assay, virus culture, and detection of HIV nucleic acids.

ELISA (enzyme-linked immunosorbent assay)
• this is the initial screening assay (test) for HIV
• may be used to test blood, urine, oral fluid (not saliva)
• most ELISA kits detect both HIV-1 and HIV-2
• highly sensitive test (99.5%)
• negative result at this step is considered definitive unless within a month of infection

HIV Tests

Western blot assay
- positive ELISA result requires confirmation with Western blot assay because other infections or autoimmune disorders can result in false-positive ELISA results
- Western blot is the standard confirmatory assay
- tests for antibodies to individual, discrete HIV proteins and therefore is less prone to false +
- positive result on this test is considered definitive indication of HIV infection.

Rapid Screening Tests
- More recently, rapid screening tests that use technology similar to ELISA tests have been developed for use outside clinical settings. These tests can provide results in 15 to 30 minutes using blood or oral fluid samples.
- Rapid tests have sensitivity and specificity characteristics similar to laboratory-based ELISA tests.
- A negative test result is considered definitive, but a positive rapid test result must be confirmed with a laboratory-based Western blot test, as is the case with a positive standard ELISA test result.

HIV Stages

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<thead>
<tr>
<th>Stage</th>
<th>Medical evidence</th>
<th>Clinical evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None required</td>
<td>None required (but no AIDS defining condition)</td>
</tr>
<tr>
<td>2</td>
<td>None required</td>
<td>None required (but no AIDS defining condition)</td>
</tr>
<tr>
<td>3</td>
<td>Laboratory test of HIV infection and CD4 T lymphocyte count of 200 or below, or CD4 T lymphocyte percentage of 14% or below</td>
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<td>4</td>
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http://www.cdc.gov/mmwr/PDF/rr/rr5710.pdf
HIV “Classification”

Persons are usually termed as being “HIV positive (HIV+)” after two consecutive HIV enzyme-linked immunosorbent assay (ELISA) tests are positive, and these findings have been confirmed by a Western blot.

An HIV+ patient is said to have AIDS (acquired immunodeficiency syndrome) if CD4+ T-lymphocyte count of <200 cells/μL or CD4+ T-lymphocyte percentage of total lymphocytes of <14 or documentation of an AIDS-defining condition (Appendix A).

http://www.cdc.gov/mmwr/PDF/rr/rr5710.pdf

Appendix A

AIDS-Defining Conditions

- Bacterial infections, multiple or recurrent
- Candida infections, oral or vaginal
- Cryptococcal meningitis
- Cytomegalovirus retinitis
- Herpesvirus or mycobacterial or fungal disease
- Hepatitis B or C
- Progressive multifocal leukoencephalopathy
- Human T-lymphotropic virus, type 1 (HTLV-1) infection
- Lymphomas, primary or secondary to HIV infection
- Cancers or leukaemias secondary to HIV infection
- Other neoplasms secondary to HIV infection
- Any opportunistic infection that compromises immune function
- Any opportunistic infection in the past 3 months

http://www.cdc.gov/mmwr/PDF/rr/rr5710.pdf

HIV Infection: Baseline Assessment

- Health history
- STD history
- Surgical history
- Drug/medication history
- Vaccinations
- Family history
- Social/sexual history

http://www.cdc.gov/mmwr/PDF/rr/rr5710.pdf
HIV Infection: System Review/Exam


**General** – fever, weight loss, fatigue, shaking, night sweats can be initial findings of significant illness

**Skin** – nearly all HIV-infected will eventually be affected secondary to dermatologic disorders

**Lymph Nodes** – generalized adenopathy may be present in acute HIV infection

**Head, Eyes, Ears, Nose, Throat**

**Cardiopulmonary** – include peripheral vascular assessment

**Gastrointestinal** – diseases are increasingly frequent as HIV progresses

**Genitourinary, Obstetric, Gynecologic** – evidence of STD’s?

**Neurologic** – cognitive function and sensory neuropathies can be common

**Musculoskeletal** – myalgias, weakness, wasting

**Laboratory testing** is often the only way to establish or confirm diagnosis

**Follow-up studies** can monitor patient change

The following should be obtained at baseline assessment:

- Immunology profile (CD4/CD8 absolute and % cell counts)
- HIV viral load testing (HIV polymerase chain reaction or branched DNA)
- complete blood count (CBC)
- multichemistry panel (fasting) – lipids, trigs, cholesterol, glucose
- urinalysis
- pregnancy testing with Pap smear
- STD testing if indicated

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8/29/2012
HIV Infection: Baseline Lab Studies

- Tuberculin skin testing (PPD) if patient has not had a positive test in the past
- If PPD positive, chest x-ray should be obtained

The following tests should be done if results not available:

- Hepatitis A antibody
- Hepatitis B surface antigen, surface antibody, core antibody
- Hepatitis C antibody
- Toxoplasmosis, cytomegalovirus, varicella antibody testing
- Glucose-6-phosphate dehydrogenase level (G6PD) to ensure no contraindications to medications
- Vaccinations as may be indicated
- Resistance testing if indicated

- According to Swanson et al (2010), health encounters should focus on: self-care, relationships, staying healthy

**Self Care**

- Promotion of personal responsibility through empowerment
- Connecting with relationships
- HIV/AIDS care must be holistic
- Focus is on healing – mental, physical, emotional
- Development of wellness plan
- Should be re-evaluated regularly

**Relationships**

- Re-evaluate your own clinical behaviors
- Open discussion about: beliefs, sexual behaviors, culture

---

Health, Wellness, Prevention Promotion

**Staying Healthy**

A) Physical activity

- Aerobic activity may boost immunity
  - Performing constant or interval aerobic exercise, or a combination of constant aerobic exercise and progressive resistive exercise for at least 20 minutes, at least three times per week for four weeks appears to be safe and may lead to significant reductions in depressive symptoms and potentially clinically important improvements in cardiopulmonary fitness (Cochrane Database Syst Rev. 2009 Apr 8;(2):CD001796)

- Resistance training

---

Staying Healthy

B) Nutrition

- predictor of survival
- plays role in slowing disease progression
- malnutrition related to adverse outcomes
- 88% of people with AIDS considered malnourished
- dietary changes difficult for people to make

C) Adherence

- staying healthy requires adherence
- alliance between practitioner and patient

Health, Wellness, Prevention Promotion
The Effects of Specific Upper Cervical Adjustments on the CD4 Counts of HIV Positive Patients


HIV/AIDS: nutritional implications and impact on human development

Eis Colenbach

HIV/AIDS is associated with biological and social factors that affect the individual's ability to consume and utilize food and to acquire food. These biological and social factors lead to poor nutrition and nutrition-related illness. Malnutrition is associated with HIV, resulting in a poor quality of life, weight loss, or an impaired prognosis of survival from AIDS. The links between nutrition and HIV/AIDS amplify the impact of HIV infection or human development at individual, household, community, and national levels. For many developing countries, the incidence of HIV/AIDS and opportunistic infections is limiting population development. The social consequences of the HIV/AIDS epidemic are widespread, including economic, educational, and health-related losses. To improve nutrition for populations living with HIV/AIDS is also a greater priority.
Antiretroviral Therapy

• Antiretroviral therapy in the developed world has resulted in substantial reductions in HIV-associated morbidity and mortality, changing an HIV diagnosis from a likely death sentence into a manageable chronic infection
• Currently, over 25 antiretroviral drugs and several fixed-dose drug combinations are available in most developed countries
• Individual agents target many of the critical steps in the HIV replication cycle—entry, reverse transcription, integration, and proteolytic processing
• Newer regimens offer greater convenience and less toxicity
• Antiretroviral therapy should be initiated earlier during the natural history of HIV infection than was previously recommended

Approved ARV Drugs

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>NNRTIs</th>
<th>PIs</th>
<th>Entry Inhibitors</th>
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<tbody>
<tr>
<td>Zidovudine</td>
<td>Nevirapine</td>
<td>Enfuvirtide</td>
<td>Etravirine</td>
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<tr>
<td>Didanosine</td>
<td>Efavirenz</td>
<td>CCR5 antagonist</td>
<td>TMC114</td>
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<tr>
<td>Stavudine</td>
<td>Indinavir</td>
<td>Maraviroc</td>
<td>TMC278</td>
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<tr>
<td>Lamivudine</td>
<td>Nelfinavir</td>
<td>Integrase inhibitor</td>
<td>Tipranavir</td>
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<tr>
<td>Emtricitabine</td>
<td>Saquinavir</td>
<td>Raltegravir</td>
<td>Darunavir</td>
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<td>Abacavir</td>
<td>Ritonavir</td>
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<tr>
<td>Tenofovir</td>
<td>Indinavir</td>
<td></td>
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<tr>
<td>Combinations available as single pill:</td>
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<tr>
<td>Zidovudine/lamivudine</td>
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<tr>
<td>Abacavir/lamivudine</td>
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<td>Tenofovir/emtricitabine</td>
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<tr>
<td>Zidovudine/lamivudine/abacavir</td>
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<tr>
<td>Tenofovir/emtricitabine/efavirenz</td>
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</table>

When to initiate antiretroviral therapy in adolescents and adults

Parameters for recommendation of initiation of therapy
• History of AIDS-defining illness
• Symptomatic HIV disease
• CD4+ T-cell count of less than 500/μl
• HIV-infected pregnant woman
• HIV-associated nephropathy
• HBV (hepatitis B) infection (when HBV treatment is indicated)

Parameter for optional/split-panel recommendation for initiation of therapy
• CD4+ T-cell count of greater than 500/μl

1. JOURNAL OF Virology, June 2010, p. 5458–5464
What antiretrovirals to start?

Preferred regimens
Two NRTIs plus either an NNRTI, a ritonavir-boosted PI, or an INSTI (raltegravir)

Preferred NNRTI
Efavirenz

Preferred ritonavir-boosted PIs
Atazanavir
Darunavir

Preferred regimen for pregnant women
Lopinavir/ritonavir with zidovudine and lamivudine

Lab Monitoring During Antiretroviral Therapy

- regular monitoring of CD4 count and plasma viral loads
- viral load should decrease by more than 1 log_{10} by 4 weeks and be <50 copies by 24 weeks given the potency of currently recommended regimens
- CD4 counts may raise more slowly but in general should be monitored along with viral load measurements
- resistance testing—either genotype and or phenotype should be performed at baseline and generally results should be reviewed prior to initiating ART

Immune Reconstitution Inflammatory Syndrome

- immune reconstitution inflammatory syndrome (IRIS) occurs in a subpopulation of HIV-infected patients after the introduction of antiretroviral therapy (ART)
- the immunopathogenesis of IRIS is characterised by a dysbalance of the immune system resulting in pathological inflammation
- risk factors are low baseline CD4+ cell count, an excellent virological response, an increased antigenic burden of an opportunistic infection and early initiation of ART after an opportunistic infection
Immune Reconstitution Inflammatory Syndrome

- the differential diagnosis of iris is complex
- treatment options include discontinuation of ART, corticosteroids or pathogen-specific therapy
- diagnosis can be difficult, because IRIS may manifest with a diverse range of clinical presentations
- adopting one case definition and performing more research regarding diagnosis and treatment of IRIS are important recommendations for future studies


Antiretroviral Therapy in the Clinic

Aske T, N. Tubbs and Martin S. Hirsch

Antiretroviral therapy in the developed world has resulted in substantial reductions in HIV-associated morbidity and mortality, changing HIV diagnoses from a likely death sentence into a manageable chronic illness. However, the extensive use of antiretroviral therapy has highlighted the importance of the recognition of IRIS. The full implications of the co-occurrence of IRIS and drug toxicity can lead to increased morbidity and mortality. Numerous factors, including drug resistance, treatment regimens, and drug interactions, can influence the efficacy of antiretroviral therapy and account for the potential for drug toxicity. In particular, the use of highly active antiretroviral therapy (HAART) has demonstrated a role in influencing the development of IRIS. The converse also holds true: the presence of IRIS can influence the efficacy of HAART. This review will examine the current classification and diagnostic criteria for identifying IRIS, which has led to the development of a grading system for IRIS. The review will also consider the current management of IRIS and the prevention of drug toxicity.

Antiviral Research

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AIDS

• in contrast with normal hosts, in which many infectious diseases are usually self-limited, in immunocompromised patients such infections have the potential of becoming serious illnesses characterized by high morbidity and mortality rates
• there are also the opportunistic infections (OI) that occur almost exclusively in immunocompromised hosts such as patients with HIV disease
• OIs can occur all over the body and be relatively localized, systemic or disseminated (spread)
• Whether and when you become susceptible to OIs is often related to the CD4 count.


AIDS

• The impaired immunity of patients with HIV disease frequently results in HIV-associated opportunistic infections and co-infections
• These life-threatening conditions are caused by a wide range of microorganisms, including protozoa, viruses, fungi, and bacteria, and often are associated with the progression from early to advanced HIV disease (AIDS)
• Diseases caused by these pathogens are less common nowadays in AIDS patients receiving highly active antiretroviral therapy (HAART); however, the incidence of co-infections with hepatitis C virus (HCV) or tuberculosis has increased, especially in countries where the risk of co-infection is high.


Types of Opportunistic Infections

A partial list of the most common HIV-related opportunistic infections and diseases includes:

• bacterial diseases such as tuberculosis, MAC, bacterial pneumonia and septicaemia (blood poisoning)
• protozoal diseases such as toxoplasmosis, microsporidiosis, cryptosporidiosis, isopsoriasis and leishmaniasis
• fungal diseases such as PCP, candidiasis, cryptococcosis and penicilliosis
• viral diseases such as those caused by cytomegalovirus, herpes simplex and herpes zoster virus
• HIV-associated malignancies such as Kaposi’s sarcoma, lymphoma and squamous cell carcinoma

http://www.avert.org/hiv-opportunistic-infections.htm
AIDS

• AIDS-defining infections such as Pneumocystis pneumonia (caused by P. jiroveci) tend to occur later in the course of HIV infection when there is substantial depletion of the CD4 cells

• The late emergence of P. carinii pneumonia (PCP) relates to the relatively low pathogenicity of P. carinii compared with other organisms like Mycobacterium tuberculosis

• Mycobacterium tuberculosis can cause disease earlier in the course of HIV infection

Sequence of opportunistic infections during the natural history of HIV infection

<table>
<thead>
<tr>
<th>Declining cell-mediated immunity</th>
</tr>
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<tbody>
<tr>
<td>Herpes zoster</td>
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<tr>
<td>Herpes simplex</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Oral candida</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
</tr>
<tr>
<td>Pneumocystis pneumonia</td>
</tr>
<tr>
<td>Toxoplasma</td>
</tr>
<tr>
<td>Mycobacterium avium intracellulare</td>
</tr>
<tr>
<td>Cryptosporidium</td>
</tr>
</tbody>
</table>

500 cells/mm³ to 200 cells/mm³
- Candidiasis (Thrush), Kaposi's Sarcoma

200 cells/mm³ to 100 cells/mm³
- Pneumocystis jiroveci (PCP), Histoplasmosis, Coccidiomycosis, Progressive Multifocal Leukoencephalopathy

100 cells/mm³ to 50 cells/mm³
- Toxoplasmosis, Cryptosporidiosis, Cryptococcosis

50-100 Cells/mm³
- Cytomegalovirus (CMV)

Less than 50 Cells/mm³
- Mycobacterium Avium Complex (MAC)

Candidiasis (Thrush)

- This is a fungal infection that is normally seen in patients with low CD4 counts
- Treatable with antifungal medications
- A trained provider can usually diagnose thrush with a visual examination
- Thrush is a yeast infection that causes white patches in your mouth
- Esophagitis is thrush that spreads to your esophagus
- Women can get vaginal yeast infections, causing itchiness, pain and discharge
- Yeast infections of the skin cause itching and rashes
- Yeast infections in your bloodstream can be life-threatening

Kaposi’s Sarcoma

- Kaposi’s sarcoma is a cancer that causes patches of abnormal tissue to grow under the skin, in the lining of the mouth, nose, and throat or in other organs
- KS is caused by Human Herpes Virus-8
- Before the introduction of antiretroviral therapy, as many as 1 in 5 patients with AIDS had KS
- Treatment plans can include chemotherapy to shrink the lesions, as well as antiretroviral therapy to increase CD4 cell count
- A diagnosis is typically made by inspecting a lesion and performing a direct biopsy on it
Kaposi’s Sarcoma

The patches are usually red or purple and are made of cancer cells and blood cells. The red and purple patches often cause no symptoms, though they may be painful. If the cancer spreads to the digestive tract or lungs, bleeding can result. Lung tumors can make breathing hard.

Credits: Paul A. Volberding, MD, University of California San Francisco

Pneumocystis Jirovecii

- PCP is a fungal infection and is the OI that most often causes death in patients with HIV
- It is treatable with antibiotic therapy and close monitoring
- If necessary, prophylaxis is available for patients who are at risk for PCP, but who are not ready to start antiretroviral medication
- Diagnosing PCP usually involves a hospital stay to ensure proper testing and treatment without complications


Pneumocystis Jirovecii

Description: Chest radiograph of an HIV-infected patient, CD4 count of <200 cells/µL, revealing bilateral, predominantly central, granular opacities and 3 thin-walled air-containing cysts (pneumatoceles) (arrows). This combination of findings is strongly suggestive of Pneumocystis jiroveci pneumonia, which was microscopically confirmed by examination of bronchoalveolar lavage fluid.

Credits: Laurence Huang, MD, University of California San Francisco
Histoplasmosis and Coccidioidomycosis

- Histoplasmosis is caused by a fungus found in the central and eastern United States (Mississippi and Ohio River Valley), eastern Canada, Mexico, Central America, South America, Africa, and Southeast Asia.
- They often present as severe, disseminated illnesses in patients with low CD4 counts.
- Diagnosis consists of blood tests and evaluation for possible exposures related to geographical areas.
- Most infected persons have no apparent ill effects.
- The acute respiratory disease is characterized by respiratory symptoms, a general ill feeling, fever, chest pains, and a dry or nonproductive cough.


Histoplasmosis and Coccidioidomycosis

Description: Chest radiograph of an HIV-infected patient, CD4 count <50 cells/µL, demonstrating a miliary pattern that is suggestive of either mycobacterial or disseminated fungal disease (clinical information may help in assigning the relative probabilities).

Credits: Laurence Huang, MD, University of California San Francisco

Progressive Multifocal Leukoencephalopathy (PML)

- PML is a severe neurological condition that is caused by the JC virus and typically occurs in patients with CD4 counts below 200.
- While there is no definitive treatment for this disease, it has been shown to be responsive to antiretroviral therapy.
- In some cases, the disease resolves without any treatment.

Progressive Multifocal Leukoencephalopathy (PML)

PML is a demyelinating disease of the CNS that can occur in patients with severe immunosuppression.

Credits: Pediatric AIDS Pictoral Atlas, Baylor International Pediatric AIDS Initiative

Toxoplasmosis

• an infection due to the parasite Toxoplasma gondii
• it is a widespread intracellular parasite infecting a wide range of birds and mammals, including humans
• the sexual cycle of the organism takes place in the intestinal epithelium of the cat, which is the definitive host
• transmission of infection is caused by ingestion of either parenteral cysts (trophozoites) from raw, infected meat, or oocysts from feces of domestic pets (cats), by transplantation of infected organs, by tainted blood transfusion, or even by accidental inoculation in a laboratory setting


Toxoplasmosis

Toxoplasma gondii: CT scan showing cerebral abscess

Credits: Paul A. Volberding, MD, University of California San Francisco
Cryptosporidiosis

- Cryptosporidium has emerged as an important cause of diarrheal illness worldwide
- Usually presenting as a gastro-enteritis-like syndrome, disease ranges in seriousness from mild to severe and signs and symptoms depend on the site of infection, nutritional and immune status of the host, and parasite-related factors
- caused by infection with protozoan parasites of the Apicomplexan genus Cryptosporidium

Cryptococcal Infection

- Cryptococcus neoformans is a yeast-like fungus that is pathogenic to both animals and humans
- a saprophytic organism found in soil, in a variety of fruits, and in pigeon nests (feces)
- Infection with C. neoformans is usually acquired by inhalation
- no observation of human-to-human transmission of the disease
- Cryptococcosis may develop as an acute, subacute, and chronic pulmonary, systemic, or meningal mycosis

Cryptococcal Infection

Description: A 9-year-old HIV-infected girl with cutaneous Cryptococcus neoformans infection. Skin lesions can be single or multiple and may appear as small papules, pustules, nodules, or ulcers with a base of granulation tissue.

Credits: Pediatric AIDS Pictoral Atlas, Baylor International Pediatric AIDS Initiative

Cytomegalovirus (CMV)

• Cytomegaloviruses are ubiquitous pathogens that commonly infect animals and humans
• CMV belongs to the Betaherpesvirinae subfamily of Herpesviridae, which also includes Roseolovirus
• Transmission is by direct or indirect person to person contact
• After a primary infection, CMV remains latent in the cells
• similar to other herpesviruses, CMV can reactivate in immunosuppressed hosts

[Cytomegalovirus retinitis]

Credits: Paul A. Volberding, MD, University of California San Francisco

Mycobacterium Avium Complex (MAC)

- Mycobacterium avium complex (MAC) includes at least two species, Mycobacterium avium and Mycobacterium intracellularum.
- These organisms belong to a much larger group of bacteria referred to as nontuberculous mycobacteria (NTM), environmental mycobacteria, atypical mycobacteria, or mycobacteria other than tuberculosis.
- Disease manifests as chronic pneumonia; disseminated infection; skin, soft tissue, and bone infection; and acute hypersensitivity pneumonitis.
- Unlike tuberculosis, MAC is not transmitted from person to person.
- Organisms are present in the environment.

http://www.cdc.gov/EID/content/15/1/53-F.htm

Common Opportunistic Infections

- Remember that the CD4 (T-helper) lymphocyte count is the most important indicator of immunocompetence of a HIV-infected individual.
- **P. jiroveci** is the most common life-threatening infection in patients with AIDS.
- **Toxoplasmosis** is an important cause of focal brain lesions.
- **Cryptococcosis** is the cause of the most common life-threatening meningitis in AIDS.

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<thead>
<tr>
<th>HIV RESOURCES ON THE WEB</th>
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<tr>
<td>• <a href="http://www.aidsinfo.nih.gov">http://www.aidsinfo.nih.gov</a></td>
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