HIV Update: What the Hospital-Based Provider Should Know

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Case Study

45 year old female
- Presented to the ER at the University of Colorado Hospital in 2008 with acutely worsening cough and shortness of breath
- She had noted several months of cough, fatigue, and shortness of breath
- Pulse oximetry on room air 67%
- Chest x-ray: bilateral pneumonia
- No prior HIV testing; rapid HIV test was positive
Case Study (continued)

- Sputum: PCP DFA +
- CD4 count 0 cells/mm³, HIV RNA level 42,500 copies/mL
- Management: intravenous trimethoprim-sulfamethoxazole and prednisone
- Steady improvement during hospital course
- Discharged home on oral trimethoprim-sulfamethoxazole, prednisone, and oxygen

Outline

- HIV Epidemiology and Testing
- Recognizing the Clinical Manifestations of HIV Infection
- Current Principles of HIV Care
- Reasons for Hospitalization and Causes of Death in the Current Era

HIV Epidemiology and Testing
Global Report: Adults and children estimated to be living with HIV, 2009

Total: 33.4 million (31.1 – 35.8 million)

www.unaids.org

Rates of Diagnoses of HIV Infection among Adults and Adolescents, 2009—40 states and 5 U.S. Dependent Areas

Total: 21.1

Rates per 100,000 population
- <150
- 150 - 199
- 200 - 299
- 300+

HIV Prevalence in Adults from Selected Countries in Sub-Saharan Africa and Subpopulations in the United States

Screening for HIV Infection

- In health care settings, HIV screening should be performed routinely in all patients aged 13-64 yrs
- Patients may decline (opt out) of testing
- General informed consent for medical care should suffice; a separate written informed consent for HIV testing is not necessary
- Rapid HIV tests are available to provide preliminary information within 20-30 minutes

Types of HIV Tests

- Most screening tests detect antibody to HIV; these include rapid and conventional HIV screening tests
- All antibody tests are confirmed with a second test, usually the Western Blot
- Tests for the virus itself, usually HIV RNA testing, can be useful during acute or primary HIV infection
- A recently licensed screening test detects both p24 antigen, part of the virus, and HIV antibody

Recognizing the Clinical Manifestations of HIV Infection
Natural History of HIV Infection

Acute or Primary HIV Infection

- Acute febrile illness frequently seen with acquisition of HIV infection
- Synonym: acute retroviral syndrome
- Classic definition: mononucleosis-like illness with or without aseptic meningitis associated with seroconversion to HIV
- Typically occurs 2-4 weeks after HIV exposure
- Occurs in over 50% of patients although it is frequently unrecognized

Common Signs and Symptoms of Acute HIV Infection

- fever 77%
- fatigue 66%
- maculopapular rash 56%
- myalgia 55%
- headache 51%
- pharyngitis 44%
- cervical nodes 39%
- arthralgia 31%
- oral ulcers 29%
- odynophagia 28%
- weight loss 24%
- diarrhea 23%
- oral candidiasis 17%
- photophobia 12%

Clin Inf Dis 1997; 24:965
Rash of Primary HIV-1 Infection


Laboratory Findings in Acute HIV Infection

General lab testing
- Leukopenia with atypical lymphocytes
- Mildly elevated transaminases
- Evidence of aseptic meningitis on LP

HIV-specific lab testing
- Initial antibody testing (ELISA) may be negative and may need to be repeated
- HIV plasma RNA testing (AKA HIV viral load testing) will be positive before antibody tests

Management of Acute HIV infection

- Treatment of this infection is largely supportive with IVFs, management of symptoms, and exclusion of other diagnoses.
- Although antiretroviral therapy can be given, studies have not consistently shown benefit.
- Recognition of acute HIV infection has public health importance as this is the stage of infection where rates of transmission are at their highest.

Undiagnosed HIV Infection

• 1 – 1.2 million persons estimated to be living with HIV infection in the U.S. in 2003
• An estimated 21% of these persons are unaware of their infection
• In 2004, 39% of newly positive HIV patients were diagnosed with AIDS within 1 year
• Persons diagnosed late tend to be persons of color, women, and/or symptomatic

www.cdc.gov

Patients Presenting to University Hospital with PCP and a new HIV Diagnosis

www.cdc.gov
### Pneumonia: Differentiating PCP and Bacterial Pneumonia*

<table>
<thead>
<tr>
<th>PCP</th>
<th>Bacterial</th>
</tr>
</thead>
<tbody>
<tr>
<td>diffuse infiltrates</td>
<td>lobar infiltrates</td>
</tr>
<tr>
<td>subacute presentation</td>
<td>acute presentation</td>
</tr>
<tr>
<td>lower fever</td>
<td>higher fever</td>
</tr>
<tr>
<td>normal or low WBC</td>
<td>relative leukocytosis</td>
</tr>
<tr>
<td>minimal sputum production</td>
<td>purulent sputum</td>
</tr>
</tbody>
</table>

* Findings may overlap in individual cases

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**Images:**
- Mild PCP
- Severe PCP
- Bacterial Pneumonia

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Tuberculosis in HIV Infection

- Patients with normal CD4 counts may present with typical pulmonary TB
- In areas of high TB prevalence, TB is often the most common opportunistic infection in HIV
- TB is an early opportunistic infection requiring little or no immunosuppression to occur
- In advanced HIV infection, TB is more likely to present as a disseminated illness with a predilection for extrapulmonary sites
- TB is relatively uncommon in HIV+ patients in Colorado

Acute Meningitis

- Major distinction is between bacterial meningitis and cryptococcal meningitis
- Immediate therapy is potentially life-saving for bacterial causes
- Consider mass lesions, which are quite common in HIV/AIDS, before LP. In some situations, it may be prudent to empirically treat for bacterial meningitis and get CT scan of head prior to LP

Acute Focal Neurologic Syndrome

- Most CNS mass lesions in AIDS can be visualized by both CT and MRI
- CNS toxoplasmosis, primary CNS lymphoma, and progressive multifocal leukoencephalopathy are the most common causes
- Diagnosis can often be made without brain biopsy based on blood tests (Toxoplasma IgG), LP (cytology, EBV PCR, JCV PCR), and appearance on imaging (CT/MRI, Thallium SPECT)
CNS Toxoplasmosis

FUO in HIV Infection: 72 Episodes in 70 Patients

- DMAC 31%
- PCP 13%
- CMV 11%
- Lymphoma 7%
- Other viral 7% (including HCV, HBV, HSV, and VZV)
- Histoplasmosis 7%
- MTB 5%
- Bacterial 5%
- Drug fever 3%
- Fungal 3%
- Parasitic 3%
- Other 4%


Potential Clinical Clues to Underlying HIV Infection

- weight loss
- generalized lymphadenopathy
- unexplained diarrhea
- thrush
- oral hairy leukoplakia
- severe aphthous ulcers
- severe or recurrent vaginal candidiasis
- severe forms of common skin diseases such as Tinea, Herpes, Zoster, seborrhea, or molluscum
- unexplained lymphopenia
- Pneumococcal bacteremia
- other STDs
- opportunistic Infections
Thrush

Oral Hairy Leukoplakia

Kaposi Sarcoma
Case Study (continued)

- Feels “120 percent” better since her hospitalization for PCP
- Tolerating oral trimethoprim-sulfamethoxaxole and has 1 more week of PCP therapy
- CD4 count 0 cells/mm$^3$, HIV RNA level 42,500 copies/mL
- HIV genotyping: no significant resistance mutations
- She is interested in starting antiretroviral therapy

Treatment for Persons with HIV Infection

1. Antiretroviral therapy
2. Prevention/treatment of opportunistic infections
3. Treatment of AIDS and non-AIDS malignancies
4. Vaccines to prevent other diseases (e.g. Influenza)
5. Treatment of other infections (e.g. Hepatitis, HPV)
6. Mental Health Care
7. Substance Abuse treatment and counseling
8. Treatment of illnesses unrelated to HIV
9. General age and gender-appropriate health care
### Targets for Antiretroviral Drugs

<table>
<thead>
<tr>
<th>Reverse Transcriptase Inhibitors: NRTIs (Nucleosides, Nucleotides)</th>
<th>Protease and Maturaton Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+ T-Cell</td>
<td>HIV-1 Reverse Transcriptase Inhibitor</td>
</tr>
<tr>
<td>Reverse Transcriptase Inhibitors: NRTIs (Nucleosides, Nucleotides)</td>
<td>Integrase Inhibitors</td>
</tr>
<tr>
<td>Protease and Maturaton Inhibitors</td>
<td>Current Antiretroviral Agents</td>
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</table>

### Current Antiretroviral Agents

<table>
<thead>
<tr>
<th>Nucleoside/tide RTIs</th>
<th>Fixed Dose Combos</th>
<th>Protease Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>current Antiretroviral Agents</td>
<td></td>
<td>tipranavir, TPV (2005)</td>
</tr>
<tr>
<td>Nucleoside/tide RTIs</td>
<td></td>
<td>darunavir, DRV (2006)</td>
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<tr>
<td>non-nucleoside RTIs</td>
<td></td>
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<tr>
<td>nevirapine, NVP (1996)</td>
<td></td>
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<tr>
<td>delavirdine, DLV (1997)</td>
<td></td>
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<tr>
<td>efavirenz, EFV (1998)</td>
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<tr>
<td>etravirine, ETR (2008)</td>
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<td>rilpivirine, RPV (2011)</td>
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<tr>
<td>fixed drug combinations</td>
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<tr>
<td>ZDV/3TC (1997)</td>
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<tr>
<td>ZDV/3TC/ABC (2000)</td>
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<td></td>
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<tr>
<td>ABC/3TC (2004)</td>
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<td>TDF/FTC (2004)</td>
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<td>TDF/FTC/EFV (2006)</td>
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<td>TDF/FTC/RTV (2011)</td>
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<tr>
<td>entry inhibitors</td>
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<tr>
<td>maraviroc, MVC (2007)</td>
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<tr>
<td>integrase inhibitors</td>
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<td></td>
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<tr>
<td>raltegravir, RAL (2007)</td>
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<tr>
<td>protease inhibitors</td>
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<td></td>
</tr>
<tr>
<td>saquinavir, SQV (1995)</td>
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<td></td>
</tr>
<tr>
<td>ritonavir, RTV (1996)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>indinavir, IDV (1996)</td>
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<tr>
<td>nelfinavir, NFV (1997)</td>
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<td>amprenavir, APV (1999)</td>
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<tr>
<td>lopinavir, LPV/r (2000)</td>
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<td>atazanavir, ATV (2003)</td>
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<tr>
<td>fosamprenavir, FPV (2003)</td>
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<td></td>
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<tr>
<td>tipranavir, TPV (2005)</td>
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<tr>
<td>darunavir, DRV (2006)</td>
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</tr>
</tbody>
</table>

### Fixed Dose Combos

- ZDV/3TC (1997)
- ZDV/3TC/ABC (2000)
- ABC/3TC (2004)
- TDF/FTC/EFV (2006)
- TDF/FTC/RTV (2011)
- maraviroc, MVC (2007)
- raltegravir, RAL (2007)

### Protease Inhibitors

- saquinavir, SQV (1995)
- ritonavir, RTV (1996)
- indinavir, IDV (1996)
- nelfinavir, NFV (1997)
- amprenavir, APV (1999)
- lopinavir, LPV/r (2000)
- atazanavir, ATV (2003)
- fosamprenavir, FPV (2003)
- tipranavir, TPV (2005)
- darunavir, DRV (2006)
Initiating Antiretroviral Therapy in Treatment-Naïve Patients

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS-defining illness</td>
<td>Treat</td>
</tr>
<tr>
<td>CD4 count &lt; 350 cells/mm²</td>
<td>Treat</td>
</tr>
<tr>
<td>CD4 count 350-500 cells/mm²</td>
<td>Treat: 55% of panel (A); 45% of panel (B)</td>
</tr>
<tr>
<td>CD4 count &gt; 500 cells/mm²</td>
<td>Treat: 50% of panel (B) Optional: 50% of panel (C)</td>
</tr>
<tr>
<td>Pregnancy, HIV-associated nephropathy, or Hepatitis B that needs treatment</td>
<td>Treat regardless of CD4 count: pregnancy, HIVAN, Hepatitis B</td>
</tr>
</tbody>
</table>

A = strong recommendation
B = moderate recommendation
C = optional


Limitations of Antiretroviral Therapy
- Drug toxicity
- Drug interactions
- Drug resistance
- Adherence issues
- Cost

Potentially Serious and/or Life-Threatening Toxicities with Antiretroviral Agents
- Nucleoside analogue RTIs: syndrome of lactic acidosis and hepatic steatosis
- Zidovudine: anemia, leukopenia
- Didanosine: pancreatitis
- Abacavir: hypersensitivity reaction
- Nevirapine: hepatotoxicity
- NNRTIs: skin rash/erythema multiforme
- Protease inhibitors: diabetes mellitus, hyperlipidemia
Drug-Drug Interactions

- Protease inhibitors, through inhibition of cytochrome p450 enzymes, may lead to higher levels of co-administered drugs => certain drugs are contraindicated.
- Nevirapine and efavirenz, through induction of cytochrome p450 enzymes, may reduce levels of co-administered drugs => certain co-administered drugs may be less effective.
- Co-administered drugs that induce hepatic metabolism (e.g. rifampin) may compromise the antiretroviral regimen.  
- The absorption of several antiretroviral drugs are reduced with H2 blockers and PPIs.

Immune Reconstitution Inflammatory Syndrome (IRIS)

Initiation of ART leads to worsening or altered clinical manifestations of opportunistic infections

- Clinical progression of Pneumocystis pneumonia
- CMV vitritis
- MAC lymphadenitis
- Flares of Hepatitis B and C
- Worsening of tuberculosis: sepsis syndrome, worsening respiratory status, and meningitis
- Worsening cryptococcal meningitis

Case Study (continued)

- Enrolls in a clinical trial of fixed dose tenofovir/emtricitabine with the integrase inhibitor, raltegravir, partly because of the costs of her insurance coverage
- Returns for follow-up 1 month later; doing well
- CD4 has increased to 24; HIV VL undetectable
- In addition to antiretroviral therapy, she is also on medications to prevent opportunistic infections
Case Study: Conclusion

- CD4 Count vs. Time
- CD4 steadily rising, HIV viral undetectable
- Remains on TDF/FTC and raltegravir

University of Colorado HIV/AIDS Clinical Program: Incidence of PCP, 1995-2010

- No cases of PCP among 1513 HIV+ Patients Seen in 2010

University of Colorado HIV Clinical Program: AIDS-Related Deaths, 1995-2010

- 1450 HIV+ Patients in Care in 2010

- AIDS Deaths
Persons with HIV Infection seen at the University of Colorado Hospital

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 18-44</td>
<td>43%</td>
</tr>
<tr>
<td>Age 45-49</td>
<td>24%</td>
</tr>
<tr>
<td>Age 50 and Over</td>
<td>33%</td>
</tr>
</tbody>
</table>

University of Colorado HIV/AIDS Clinical Program
N = 1470, Time Period = 9/1/09-8/31/10

Organ Transplantation in HIV+ Patients at the University of Colorado HIV Program

<table>
<thead>
<tr>
<th>Patient Summary</th>
<th>Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Well-controlled HIV infection and hemophilia; active Hepatitis C with ESLD</td>
<td>Liver transplant June 2006 (UCH)</td>
</tr>
<tr>
<td>2. Well-controlled HIV infection; HIV nephropathy with ESRD</td>
<td>Kidney transplant December 2006 (NIH)</td>
</tr>
<tr>
<td>3. Well-controlled HIV infection; ESRD from Alport Syndrome</td>
<td>Kidney transplant August 2007 (UCH)</td>
</tr>
<tr>
<td>4. Well-controlled HIV infection; active Hepatitis B with Hepatocellular carcinoma</td>
<td>Liver transplant November 2007 (UCH)</td>
</tr>
<tr>
<td>5. Well-controlled HIV infection; Type I diabetes mellitus with ESRD</td>
<td>Kidney-pancreas transplant February 2008 (UCSF)</td>
</tr>
<tr>
<td>6. Well-controlled HIV infection; Hepatitis C with ESLD and Hepatocellular CA</td>
<td>Liver transplant April 2009 (UCH)</td>
</tr>
<tr>
<td>7. Well-controlled HIV infection; ESRD from acute interstitial nephritis</td>
<td>Kidney transplant September 2010 (UCH)</td>
</tr>
</tbody>
</table>

To enter a cell, HIV uses the CD4 receptor and a co-receptor, either CCR5 or CXCR4

The Berlin Patient

- HIV+ patient who developed acute myelogenous leukemia.
- Subsequent treatment including chemotherapy and two stem cell transplants.
- The transplanted stem cells were from a CCR5 Δ32/Δ32 donor.
- The patient is now off antiretroviral therapy and still has an undetectable HIV viral load.
- He appears to be cured.


Reasons for Hospitalization and Causes of Death in the Current Era

University of Colorado HIV/AIDS Clinical Program: Number of UCH Inpatient Days per Patient per Year, 1995-2010

<table>
<thead>
<tr>
<th>Year</th>
<th>Days</th>
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<tbody>
<tr>
<td>1995</td>
<td>3</td>
</tr>
<tr>
<td>1996</td>
<td>2.5</td>
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<td>1997</td>
<td>2</td>
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<td>2008</td>
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<tr>
<td>2009</td>
<td>1.5</td>
</tr>
<tr>
<td>2010</td>
<td>1.5</td>
</tr>
</tbody>
</table>
Co-morbidities in HIV Infection

- Depression
- Bipolar Disease
- Other Mental Illness
- Alcohol use
- Tobacco use
- Other Drug use
- Hepatitis B
- Hepatitis C
- Human Papillomavirus
- Coronary Disease
- Hyperlipidemia
- Diabetes mellitus
- Hypertension
- Aging

University of Colorado Hospital: Reasons for Hospitalization in 2009

- 264 admissions leading to 1309 hospital days
- 165 (10%) of 1622 HIV+ patients had one or more admissions
- Common reasons for hospitalization
  - Cancer-related: N = 29, including 19 chemotherapy-related admissions
  - Pneumonia/Influenza: N = 23
  - Cardiovascular: N = 20 including 4 MIs, 3 CVAs, and 2 PEs
  - Pathologic fractures and orthopedic surgeries: N = 13
  - Pregnancy-related hospitalizations: N = 10
  - Many other reasons for admissions: pancreatitis, liver diseases (Hep B and C), skin/soft tissue infections, sepsis, alcohol-related admissions, seizures, etc.

University of Colorado HIV/AIDS Clinical Program Mortality, 1999-2010

1513 patients in care in 2010
**University of Colorado HIV/AIDS Clinical Program Mortality 2006-2010**

- 33%
- 20%
- 15%
- 17%
- 4%
- 11%

AIDS Conditions
- Mental Health
- Liver Disease
- Non-AIDS Cancers
- Other
- Other

89 deaths out of 2494 HIV+ patients seen over the last 5 years

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**Hepatitis C Prevalence in HIV**

Sherman et al, Clin Infect Dis, 2002

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**Incidence of Non-AIDS Cancers among HIV+ Persons Compared to General U.S. Population**

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Standardized Rate Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal Cancer</td>
<td>42.9</td>
<td>34.1 - 53.3</td>
</tr>
<tr>
<td>Vaginal Cancer</td>
<td>21</td>
<td>11.2 - 35.9</td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>14.7</td>
<td>11.6 - 18.2</td>
</tr>
<tr>
<td>Liver Cancer</td>
<td>7.7</td>
<td>5.7 – 10.1</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>3.3</td>
<td>2.8 – 3.9</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2.8</td>
<td>1.9 - 3.6</td>
</tr>
<tr>
<td>Oropharyngeal Cancer</td>
<td>2.6</td>
<td>1.9 - 3.4</td>
</tr>
<tr>
<td>Leukemia</td>
<td>2.5</td>
<td>1.6 - 3.8</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>2.3</td>
<td>1.8 – 2.9</td>
</tr>
<tr>
<td>Renal Cancer</td>
<td>1.8</td>
<td>0.4 – 0.8</td>
</tr>
</tbody>
</table>

Non-AIDS Malignancy as a Cause of Death at UCH, 2006-2010; 19 cancer deaths out of 89 total deaths, N = 2494 HIV+ patients

Summary

- HIV infection is common in the United States and 1 in 5 do not know their diagnosis.
- All adults should be tested for HIV infection with subsequent testing based on risk.
- Clinical manifestations of HIV can be related to acute infection, opportunistic diseases, complications of treatments, or co-morbidities.
- HIV treatments are very effective. Many patients have the potential to live a normal lifespan.
- Non-AIDS illnesses, including co-morbidities, are the leading causes of hospitalization and death.