Chapter 5
Care of HIV Patients

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Historical Perspective and the Evolution of the Current State of the Art

In 1981, a prescient CDC report described five cases of *Pneumocystis carinii* pneumonia (now referred to as *Pneumocystis jiroveci* pneumonia, PJP) that were associated with cytomegalovirus (CMV) infection and mucosal candidiasis occurring in previously healthy gay men [1]. Soon after, the CDC reported 26 gay men with an unusual cancer, Kaposi's sarcoma, also associated with unusual infections that were indicative of defective cell-mediated immunity (PJP, CMV, toxoplasmosis, cryptococcosis) [2]. These sentinel clinical observations suggested an acquired cell-mediated immunodeficiency which became known as the acquired immunodeficiency syndrome (AIDS) in 1982. Infections, which do not occur in normal hosts but which occur by virtue of an immune defect, are termed "opportunistic infections" (OIs). The AIDS-associated OI s were associated with a markedly depressed CD4 (helper T) lymphocyte count

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(<200/mm^3). With time, the spectrum of unexpected OIs and malignancies broadened as did the risk groups affected. Intravenous drug users (IDUs), hemophiliac men and women who were sexual partners of IDUs, hemophiliac or bisexual men, and their offspring also had AIDS. The human immunodeficiency virus (HIV) was isolated in the early 1980s [3, 4, 5]. Since 1985, blood products in the USA have been screened for HIV. Detailed epidemiologic studies showed that HIV was transmitted sexually, by contaminated blood and from infected mother to child during pregnancy, childbirth, or breastfeeding, but not by casual household and family contact [6].

About 2 weeks after exposure to HIV, an acute, intense viremia ensues. This may be associated with a clinical mononucleosis like seroconversion illness, consisting variably of fever, rash, sore throat, lymphadenopathy, diarrhea, and/or aseptic meningitis. Not infrequently, a concurrent sexually transmitted disease (STD) or group A beta strep in the throat obscures recognition of acute HIV. During acute HIV infection, profound CD4 cell destruction in lymphoid tissue, especially in the gut, occurs, and HIV establishes itself in its reservoirs by integrating into the host DNA of CD4-bearing cells. As an immune response supervenes, the acute HIV viremia declines to a "set point" which varies from hundreds to hundreds of thousands. The viral load set point accounts for about half of the variability of HIV progression without treatment and characterizes most of the duration of untreated infection [7, 8, 9]. Acute HIV is highly transmissible compared to chronic HIV in part due to the high-grade viremia of acute HIV but also because the viral strains detected during seroconversion are better adapted for transmission, while the viral strains detected during chronic HIV are better adapted to persistence in the host. Greater severity of seroconversion symptoms is associated with a higher subsequent set point and faster disease progression. The rationale for initiating antiretroviral therapy (ART) during acute infection is to limit the profound immunologic damage associated with acute infection, to reduce the viral reservoirs that are established as

a result of acute infection, and to treat the most infectious stage of HIV infection. This requires a high index of suspicion for acute HIV in high-risk individuals not known to be HIV positive. Suspected acute HIV infection presents an opportunity to initiate pre-exposure prophylaxis (PrEP), if acute HIV is ruled out. HIV antibody appears after seroconversion, so conventional HIV antibody testing, even with a fourth-generation test, may be falsely negative during the acute seroconversion illness. The prevailing view that ART is indicated at any stage of HIV infection derives from a shifting landscape of risk and benefit. With better observational data, HIV has been shown to be associated morbidity and mortality due to diverse causes apart from AIDS-related complications. Further, ART agents have become more potent, less toxic, and less vulnerable to the development of drug resistance. See Table 5.1 for a list of drugs used to treat HIV infection.

Ongoing HIV replication in the presence of the selective pressure of ART can lead to resistance to the ART agents. The likelihood of the developing resistance to a given drug varies according to its "barrier to resistance." Drugs like NNRTIs and lamivudine/emtricitabine have a low barrier to resistance, so resistance is quite likely to emerge during when VL is not fully suppressed. By contrast, PIs and INSTI have a higher barrier to resistance. When the selective pressure of ART is removed, the drug-sensitive virus may come to dominate the viral population, but drug resistant virus may be present as a minority species (archived drug resistance) and can reemerge if the drug to which the virus is resistant is used again. A baseline drug resistance test can identify transmitted drug resistance in patients with newly diagnosed HIV. For ART-experienced patients, results of past resistance tests can demonstrate resistance that may emerge again. Genotypic drug resistance assays identify specific mutations in the viral genes which code for the HIV RT, PI, and integrase which are known to confer resistance. In a phenotypic assay, the relevant genes from the patient's HIV are introduced into a laboratory HIV strain and then introduced into cell cultures with and without ART drugs to assay the effect of the ART drugs in vitro on the patient's strain.

Table 5.1 HIV drugs

Drug class	Drug names	Mechanism of action	Complications/ interactions	Advantages	Dosing
NRTI, nucleoside analogue reverse transcriptase inhibitor	Lamivudine(3TC), emtricitabine, abacavir(ABC), tenofovir disoproxil fumarate(TDF), alafenamide (TAF)	Compete with nucleosides, terminating DNA formation	Abacavir causes systemic hypersensitivity reaction in patients with the HLA B5701 gene	TAF has less mitochondrial toxicity and less renal toxicity than TDF	Dual NRTI backbone: abacavir/lamivudine (ABC/3TC) 600 mg/300 mg—1 daily (Epzicom)—check HLA B5701 for ABC hypersensitivity reaction (HSR) TDF 300 mg/emtricitabine 200 mg (TDF DF/EMT)—once daily (Truvada) TAF la* 25 mg/emtricitabine 200 mg (TAF/EMT)—once daily (Descovy) *TAF is preferred over TDF—less renal/bone toxicity

PI, protease inhibitor	darunavir*(DRV)*, atazanavir*(ATZ)*, fosamprenavir, nelfinavir, indinavir	Blocks virion assembly	Hyperglycemia, hyperlipidemia	*DRV* is the drug of choice as it can be used in patients with PI resistance and requires fewer pills daily	*DRV* 800 mg, must use with booster ritonavir 100 mg RTV or coformulated with booster cobicistat (Prezcobix)—once daily, with food. *ATV,* unboosted 400 mg (2 × 200 mg caps) or boosted 300 mg with 100 mg ritonavir or coformulated with booster cobicistat as Evotaz—once daily, with food. Less hyperlipidemia. Asymptomatic unconjugated hyperbilirubinemia common. Renal stones. Must use boosted with *TDF, EFV*
PI booster	Ritonavir*(RTV)*, cobicistat	Blocks hepatic metabolism of PI	Hyperglycemia, hyperlipidemia	Permits once daily PI dosing	

(continued)

Table 5.1 (continued)

Drug class	Drug names	Mechanism of action	Complications/ interactions	Advantages	Dosing
NNRTI, non-nucleoside reverse transcriptase inhibitor	Nevirapine(*NVP*), efavirenz*(EFV)*, rilpivirine*(RPV)*, etravirine*(ETR)*	Inhibits reverse transcriptase enzyme	*NVP* should not be initiated if CD4 count is above 400/ mm^3 (women) and 250/mm^3 (men) due to risk for severe hypersensitivity. *EFV* is associated with neuropsychiatric side effects	*ETR* is tasteless and dissolvable for patients with swallowing difficulties	*EFV*—600 mg once daily. Transient neuropsychiatric side effects, teratogenic first trimester *NVP* 400 mg once daily—not started at higher CD4 counts-- in men CD4 > 400, women CD4 > 250 due to potential for HSR/Stevens-Johnson syndrome. *RPV* 25 mg—once daily, MUST be taken with food. Not recommended for HIV PCR > 100,000/mL. TINY tablet. (Edurant) *ETR*—200 mg BID or 400 mg q day, after a meal. Easily dissolves in water, tasteless

INSTI, integrase strand transfer inhibitors	raltegravir (*RAL)*(RAL), dolutegravir(*DTG)*, elvitegravir*(ELV)*, (bictegravir—anticipated approval)	Blocks incorporation into proviral DNA	Class with few side effects *DTG*, bictegravir is preferred due to less resistance *ELV* must be given with a booster	Well tolerated	*RAL* 400 mg twice daily *DTG* 50 mg once daily *ELV* 85 mg or 150 mg—Always given with booster

These pivotal studies are the basis for the recommendation to treat everyone, at all CD4 counts. Patients should appreciate the solid basis for treatment guidelines:

- SMART (2001–2006)—continuous ART is better than intermittent CD4-guided ART in patients with CD4 > 350/mm [10].
- START—ART initiation at CD4 > 500 is better than initiation at CD4 > 350/mm^3 [11].
- HPTN 052—ART reduced HIV transmission in serodiscordant couples [12].

With current ART, a progressive and fatal disease has become easily manageable. Those whose HIV infection is discovered in the latest stages can experience a return to health lasting decades with ART. Older patients, with newly discovered HIV infection, may fear ART due to knowledge of earlier more toxic and less effective therapy. The new generation of newly infected younger patients may have little awareness of deadly potential of untreated HIV and may fail to adhere to therapy, thereby jeopardizing their own health and further fueling the current epidemic.

Testing for HIV in the Primary Care Setting

Educate

Before offering HIV testing, common misconceptions should be explicitly addressed. Worldwide, the most common mode of HIV transmission is heterosexual sex. HIV can be transmitted unknowingly by healthy, asymptomatic individuals. The clinical latency between infection and illness is years to decades, so current sexual activity is not the only indicator of risk. An individual whose partner is HIV negative should not conclude that he/she must also be HIV negative. Also, HIV can be transmitted by unrecognized blood exposures—for example, tattoos, ritual practices, unregulated medical practices, etc. Individuals who do not perceive themselves as "pro-

miscuous" or drug using may erroneously assume that they are not at risk and may decline testing. Higher-risk individuals, like men who have sex with men and drug users as well as their partners, have ongoing risk and so should be tested at frequent intervals. Higher-risk individuals can be informed of the availability of PrEP to prevent HIV acquisition. Engaging high-risk individuals in medical care can reduce HIV risk both through PrEP and with STD screening and treatment, since STDs facilitate HIV transmission and acquisition.

Testing for HIV

Universal screening: HIV testing can be offered in the context of all routine age-appropriate screening. HIV screening has an excellent cost/risk to benefit ratio. HIV screening is mandatory for blood/organ donation, organ transplantation, and purchase of life insurance.

Pregnancy: All pregnant women are offered HIV testing. ART during pregnancy is safe and prevents mother-to-child HIV transmission during pregnancy and childbirth. Pregnancy is an indication for HIV treatment.

Newborns: All newborns are screened at birth for passively transmitted maternal HIV Ab. This is default mandatory screening of mothers.

High-risk groups, due to social, demographic, and behavioral attributes: Members of high-risk groups include men who have sex with men (MSM), transgender women, IDUs and ex IDUs, sex partners of persons in high-risk group, sex partners of a person with uncontrolled HIV, victims of sexual assault, and vulnerable individuals (homeless, cognitively impaired, incarcerated, refugee, hearing impaired, sexually abused). Risk is also conferred by unregulated tattooing, unregulated medical practices, and ritual practices involving blood.

Patients with medical conditions suggesting risk of HIV acquisition: Receipt of blood or blood product transfusion before routine HIV screening (1985 in the USA), hemodialysis, hepatitis C

(often associated with prior IDU, exposure to contaminated blood), any STD (syphilis, gonorrhea, chlamydia, herpes simplex, hepatitis B, trichomonas, and genital/anal warts), cervical dysplasia, and infections with pathogens transmitted by fecal oral route like ameba, giardia, salmonella, shigella, campylobacter, and hepatitis A.

Patients with medical conditions, symptoms, and signs that can be symptoms of HIV-related immunodeficiency but non-AIDS defining: Bacterial pneumonia, dermatomal zoster, chronic kidney disease with proteinuria, pulmonary/extrapulmonary TB, cervical dysplasia, HPV-related cancers (cervix, anus, mouth, throat), lymphoma, onychomycosis, seborrheic dermatitis, eczema, unprovoked ear or sinus infections, and stroke. Symptoms such as encephalopathy, dementia, chronic diarrhea, chronic cough, and chronic skin disorder. Signs such as lymphadenopathy, splenomegaly, weight loss, oral thrush, and skin rashes. Any patient with unusual infections or recurrent infections should be screened for immunodeficiency conditions, including HIV.

Patients with laboratory abnormalities suggestive of HIV: Anemia, leukopenia, thrombocytopenia, polyclonal gammopathy, and monocloncal gammopathy.

Test to Detect HIV [13]

Tests to diagnose and to confirm of HIV are listed below:

- *IgG—positive 6–12 weeks after infection, chronic HIV
- *IgM—positive 3 weeks after infection and then wanes
- *p24 antigen (Ag)—positive 11–14 days after infection and then wanes
- *Rapid test—detects IgG, IgM (OraQuick), chronic HIV
- *Fourth-generation assay—detects IgG + IgM + p24 Ag, chronic and early HIV
- *HIV PCR—first test positive after infection, test of choice in acute HIV infection

HIV testing in some locales requires informed consent.

Clinical Management

Evaluation of HIV Asymptomatic or Symptomatic HIV Seroconversion Illness or Following an OI

Obtain baseline CD4 count, HIV PCR, and HIV resistance test. Also, check CBC, chemistry, serology for HBV, HCV, syphilis, and STD screen (GC, chlamydia from urine (all), cervix (F), throat, rectum (MSM), and tuberculosis screen (PPD, QFT, targeted TB history)).

START ART—assure insurance coverage for ART.

CHOICE of ART—guidelines see www.aidsinfo.nih.gov and IAS-USA in JAMA 2016:316:191.

ART for ALL patients; any CD4. See Fig. 5.1 and Table 5.2.

For patient with unknown ART history, a boosted PI, INSTI and 2 NRTIs can be used pending RES testing.

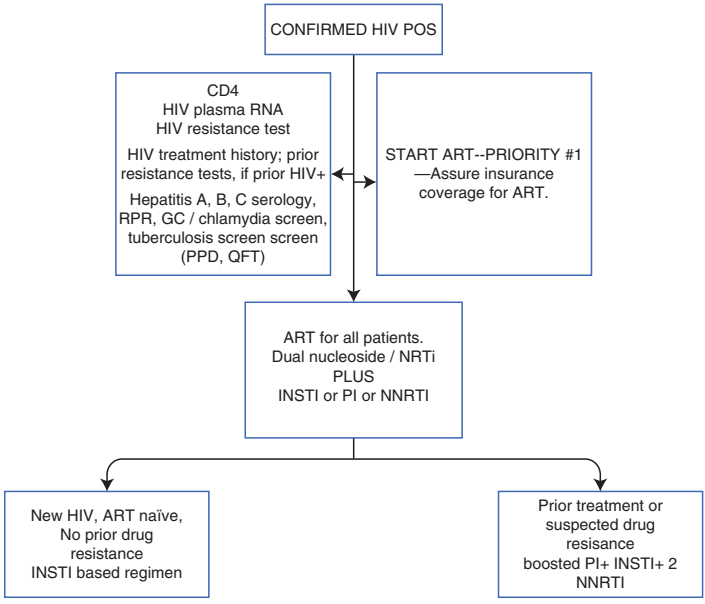

Fig. 5.1 Suggested starting regimens

Table 5.2 Preferred combined pill regimens

Initial preferred regimen	Single tablet regimens, without booster	Single tablet regimens, with booster
Descovy*(EMT/TAF)*/ Tivicay*(DTG)*—1 small pill each/once daily. No food issues. No booster, so fewer drug interactions	Atripla—*EFV/TDF/EMT*; big pill	Stribild—*ELV/cobi/TAF/EMT*
	Complera—*RPV/TDF/EMT*. Well tolerated. MUST take with food, for VL < 100,000/mL	Genvoya—same as Stribild, but with*TAF*
	Odefsey—same as Complera but with TAF instead of TDF. Well tolerated. MUST take with food. VL < 100,000/mL	
	Triumeq—*DTG/ABC/3TC*; BIG pill, no food restrictions. MUST check HLA B5701	

Rilpivirine and etravirine may be effective even if there is resistance to efavirenz and nevirapine.

Guidelines see www.aidsinfo.nih.gov and IAS-USA in JAMA 2016:316:191.

Care Recommendations at/near the First Visit

*CD-4 < 200/mm^3—screen for PCP, use PCP prophylaxis (trimethoprim sulfa 1 DS tab daily or every other

day)—can be stopped once CD4 > 100, with undetectable HIV PCR.

*CD 4 < 50/mm^3—screen for disseminated *Mycobacterium avium* complex disease (DMAC), wasting syndrome, and oral thrush (Table 5.3).

*FU HIV PCR after 2 weeks ART—expect one to two log drops in HIV PCR; expect undetectable HIV PCR by 6 weeks.

*Integrate age/risk/behavior specific health promoting interventions (see Table 5.3).

Evaluation of Symptomatic Patients with New HIV and CD-4 < 200/mm^3

Patients who are HIV tested due to symptoms must be evaluated to for the presence of an OI as the cause of the symptoms that prompted the HIV test. All patients should have CBC, chemistry, LDH, routine blood cultures, blood culture for *Mycobacterium avium* complex (MAC), serum cryptococcal antigen (CrAg), RPR, chest X-ray, relevant exposure history for TB, and endemic mycoses. See Table 5.4 for a description of OIs.

Timing of ART After an OI

ART started in the context of a recognized OI or in the presence of unexplained symptoms can lead to the paradoxical worsening of the OI or the unmasking of a previously occult OI. This is referred to immune reconstitution inflammatory syndrome (IRIS). ART, by improving immune competence, can cause a profound inflammatory response to an underlying OI, thereby paradoxically worsening symptoms. In general, OIs involving the CNS need to be treated longer prior to ART initiation since IRIS can be potentially catastrophic when it occurs in the confines of the brain or spinal cord. Further, OI s which cannot be speedily eliminated (TB, MAC,

Table 5.3 Ancillary interventions

Smoking cessation	HBV vaccine (all)[a], high dose	HAV vaccine (MSM, liver disease, other risks)[a]	Pneumococcal vaccine (all—Prevnar, followed by 23 valent Pneumovax)[a]	HPV (female and MSM < 26 years old)
Screen for latent tuberculosis with symptom screen, tuberculin skin test or interferon gamma release assay. If positive, obtain chest X-ray.	Regular STD screening—GC/chlamydia/syphilis common in MSM, treatable	Regular cervical cancer screening	Regular anal cytology[b]	

[a]For vaccines, can wait until CD4 rises >500/mm^3 or plateaus
[b]Plausibly beneficial

Table 5.4 Common opportunistic infections

Infection	Symptoms	Diagnostic test
Pneumocystis jirovecii pneumonia (PJP)	Fever, progressive exertional dyspnea (weeks), leading to hypoxia that worsens with exercise, dry cough without pleuritic pain	Chest XR shows typical diffuse interstitial infiltrates, without dense consolidation, effusions, or lymphadenopathy. LDH is elevated, WBC normal or low. Organisms can be seen in sputum or bronchoalveolar lavage fluid
Central nervous system (CNS) toxoplasmosis	Focal neurologic deficits that can be mistaken for stroke	Contrast-enhanced CT and MRI show characteristic multiple ring-enhancing abscesses. A positive serum toxoplasma titer is evidence of prior infection
Progressive multifocal leukoencephalopathy (PML)	Slowly progressive focal neurologic deficits which may be mistakenly attributed to "stroke"	JC PCR in CSF
Cryptococcus neoformans	Subtle and minimally localizing symptoms—headache, incoordination, with or without fever	Positive serum/CSF cryptococcal antigen or direct visualization of yeast by CSF microscopy

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Table 5.4 (continued)

Infection	Symptoms	Diagnostic test
Disseminated *Mycobacterium avium* complex (DMAC)	Fever, weakness, often with abdominal pain and diarrhea	Mycobacterial blood culture
Oral candidiasis	Cottage cheese-like plaque on the buccal mucosa and soft palate, difficulty swallowing solids more so than liquids	Resolution with antifungal treatment (fluconazole) Microscopic or pathologic exam of typical plaque
Tuberculosis (TB)	Productive cough, ascites, lymphadenopathy, fever	Culture of sputum, blood, bone marrow, or tissue biopsy (lymph node, liver, or other affected tissues)
Disseminated histoplasmosis	Pancytopenia, high LDH, fever, pulmonary infiltrates, abdominal pain, diarrhea, shock in patient with geographic risk[a]	Urine antigen or culture of sputum or blood
Coccidioidomycosis	Diffuse or localized pulmonary infiltrates, meningitis, lymphadenitis, or skin disease in patient with geographic risk[b]	Culture of sputum or blood Serology from blood or CSF

[a]Ohio River Valley, Caribbean, Central America, Africa
[b]Sonoran life zone—arid desert in Arizona, Nevada, California, Mexico border

Cryptococcus) or easily recognized (DMAC) prior to starting ART are the ones most commonly associated with IRIS.

PCP should be treated for a week before starting ART. CNS infections should be well controlled before starting ART. Patients with PML should start ART immediately. If they develop IRS, they should get steroids immediately. Patients who start ART in the presence of undiagnosed occult MAC may develop focal MAC IRIS after ART.

IRIS is usually managed symptomatically with anti-inflammatory medication (NSAIDS or steroids), continuation of ART, and antimicrobial agents appropriate to the OI.

Prevention of HIV

Safer sex using barrier protection—condoms, male and female.

Pre-exposure prophylaxis (PrEP)—for those at ongoing regular risk for HIV exposure who are unwilling to regularly use barrier precautions. The two-drug combination of TDF has been shown to reduce HIV acquisition in MSM—but only in those with detectable levels of drug in their blood. TDF is a particularly effective drug in MSM* since it concentrates in rectal mucosa. It is believed to be effective in women as well [10].

Post-exposure prophylaxis (PEP)—with 72 hours of known or suspected exposure to HIV using 30 day ART, usually INSTI plus Truvada (or according to drug resistance information if known from source case).

ART during pregnancy prevents vertical transmission from an HIV infected mother to child. Suppressive ART during pregnancy reduces transmission during pregnancy and childbirth. Where infant formula is available, breastfeeding is not recommended. Usual ART regimens are suitable for pregnancy.

Treatment of an HIV+ partner is prevention for HIV-negative partner in a serodiscordant couple.

Since young males who have sex with males (MSM) have reemerged as the dominant risk group for HIV acquisition in urban centers, education and prevention efforts targeted to this group are especially important.

Finally, a Bit of Humanity

For any patient with newly diagnosed HIV, irrespective of indication for testing, the initial encounter must address the patient's unspoken fears. Patients in the throes of a symptomatic OI may think that they are dying of AIDS. They can be reassured that most OIs are curable and that many years of good health can be reasonably expected. With current ART, the impact of HIV on physical well-being for most people is minimal.

The diagnosis of HIV can be emotionally devastating. Many people may fear stigma and ostracism. Women may fear that they cannot have children. Dating, sex, pregnancy, and intimacy are colored by HIV. Patients who themselves may have harbored negative views of HIV may now find those same stigmatizing attitudes among family and friends painfully personal.

The conversation about the unstated is usually the one that patients want to have. CD4, viral load, safe sex, condoms, and OIs may be a blur of irrelevance during that first encounter. The initial shock of an HIV diagnosis progressively wears off as the reality sets in of just how little life actually changes and just how asymptomatic HIV really is once ART is started. The process occurs over days, weeks, months, years, and, yes, decades. Talking about the distant future may help patients understand that HIV is a life sentence not a death sentence. Recognizing the fragility of life may actually be an epiphany.

For those concerned about death and longevity, we can honestly counsel that ART is very simple and very well tolerated and keeps people healthy for as long as we have been using it (decades). As far as sex, HIV is rarely transmitted by those who maintain an undetectable HIV VL, possibly even

without barrier protection. And for women, the fact that pregnancy is safe for mother and baby must be stated unequivocally. The fact that HIV is not transmitted by casual household contact (sharing food, living space, bathroom, etc.) needs to be communicated explicitly so patients are not afraid to care and be cared for by those close to them. This also serves to address sadly prevalent misconceptions among those who stigmatize HIV the most. Undocumented persons and others without insurance should be reassured, if appropriate, that programs exist which guarantee free care and medications. Young gay men need to have their specific concerns addressed. Concerns about privacy, disclosure, rejection, and safety, including the potential for intimate partner violence, should be sought and addressed. Patients need to emerge from that first encounter with optimism about their future. That optimism starts with a provider who is optimistic.

Clinical Pearls

- Maintain a high index of suspicion for HIV disease as it can masquerade as other illnesses.
- Compliance with medications is extraordinarily necessary for suppression of viral reproduction to elicit patients' concerns about the disease and its treatments.

Don' Miss This!

- Acute HIV infection can present like a cold or tonsillitis.
- Don't miss the chance to prevent infection in at-risk patients.

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