

Evaluation and Management of HIV-Infected Women

Alexandra M. Levine, MD

The rate of newly diagnosed AIDS in the United States is increasing fastest in women, who are infected with HIV primarily through heterosexual transmission. Approximately 60% of these women are African American, and 18% are Latina. A gynecologic infection is the most common symptom that leads to initial medical evaluation. Specific studies at baseline should include CD4 lymphocyte count, HIV-1 RNA level, and gynecologic examination with Papanicolaou smear. Decisions about initiation of antiretroviral therapy depend on the patient's clinical diagnoses, her willingness to adhere to treatment, and CD4 lymphocyte and HIV-1 RNA levels. Levels of HIV-1 RNA may be somewhat lower in women than in men at the same CD4 count, whereas women have higher CD4 lymphocyte counts at the time of AIDS diagnosis. However, prospective trials have not yet indicated the need to change the threshold CD4 lymphocyte counts or HIV-RNA levels for initiation

of therapy in women. The efficacy of antiretroviral therapy appears to be similar in men and women, although women are more likely to experience toxicities. Abnormal Papanicolaou smears occur in approximately 40% of women at baseline, and 58% are infected with human papillomavirus. The prevalence of both conditions increases with lower CD4 lymphocyte counts and higher HIV-1 RNA levels. Precursor lesions to cervical cancer may be effectively treated, but almost 50% recur within 1 year, mandating careful follow-up. Referral should be sought for specialized gynecologic care and for issues related to HIV itself, since survival is prolonged in patients treated by physicians who are experienced in treating HIV. When they are provided the same access to care, HIV-infected women have similar prognoses as HIV-infected men.

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For the author affiliation and current address, see end of text.

A 32-year-old African-American woman comes to see you because she has had recurrent vaginitis in the past year. She is concerned because the vaginal discharge has recurred only 2 months from the last episode. She has had six sexual partners in the past 10 years, has been married for 5 years, and is monogamous. She has a 4-year-old son who is active and well. She has never used illicit injection drugs and has never had a blood transfusion.

IS THIS PATIENT TYPICAL OF WOMEN WITH HIV INFECTION, AND SHOULD SHE BE TESTED FOR HIV?

The patient is typical of women with HIV infection; she should be counseled and then tested. The rate of AIDS in the United States is increasing fastest among women, who accounted for approximately 7% of AIDS cases in 1985, 22% in 1997, and 30% in 1999 (1-3). The majority of U.S. women with AIDS belong to ethnic minority groups; African Americans account for 62% of cases, and Latinas and Caucasian persons each account for approximately 18% (3).

Pelvic examination reveals a thick white cervical discharge, no masses, and no tenderness on cervical motion. Microscopic examination of the discharge reveals white cells and hyphae. Cervical cultures are ordered, and you prescribe a 3-day course of topical antifungal therapy. The patient is counseled about HIV and agrees to be tested; results confirm the presence of HIV infection.

WHAT IS THIS WOMAN'S PROBABLE SOURCE OF HIV INFECTION?

The patient was probably infected by heterosexual contact, which is now the most common mode of transmission in U.S. women (2, 3). Because HIV infection may be asymptomatic for up to a decade after initial infection, it would not be unusual for the patient to have been unaware of her partners' HIV status.

SHOULD THE PATIENT'S HUSBAND AND SON BE TESTED FOR HIV?

The patient's husband and son should be tested. The chance of heterosexual transmission increases with higher HIV-1 viral load in the positive partner (4); presence of reproductive tract infections (5, 6), cervical ectopy (7), sex during menstruation (8), and lack of circumcision in the male partner (9) may also increase the likelihood of transmission (10). The risk for vertical transmission from an infected mother (not taking antiretroviral therapy) to her infant is approximately 25%; HIV can be transmitted to the child in utero (11), at birth (12-14), or by breast feeding (15-20).

The patient's husband was seen by another physician and was found to be infected with HIV. His CD4 lymphocyte count was 0.65×10^9 cells/L, and his HIV viral load was 2033 copies/mL. Their son was found to be negative for HIV antibody, and his HIV RNA level was nondetect-

Table 1. Treatment of Gynecologic Infections in HIV-Infected Women

Infection	Treatment
Vaginitis	
Candidiasis	Intravaginal miconazole suppository, 200 mg × 3 d, or 2% cream × 7 days OR Clotrimazole cream (1%) × 7–14 d, or 100 mg/d orally × 7 d, or 500 mg/d orally × 1 d OR Fluconazole, 150 mg/d orally × 1 d
Trichomoniasis	Metronidazole, 2.0 g orally
Bacterial vaginosis	Metronidazole, 500 mg orally twice daily × 7 d
<i>Chlamydia trachomatis</i>	Doxycycline, 100 mg orally twice daily × 7 d OR Azithromycin, 1 g or 1.2 g (two 600-mg tabs) orally × 1
Pelvic inflammatory disease	
Outpatient	Ceftriaxone, 250 mg intramuscularly, or cefoxitin, 2 g intramuscularly, plus probenecid, 1 g orally, followed by doxycycline, 100 mg orally twice daily × 14 d
Hospitalized patients	Cefoxitin, 2 g intravenously every 6 h, plus doxycycline, 100 mg every 12 h, until improved, followed by doxycycline, 100 mg orally twice daily to complete 14 d
Herpes simplex	
Mild	Acyclovir, 400 mg orally three times daily × 7–10 d OR Famciclovir, 250 mg orally three times daily × 7–10 d OR Valacyclovir, 1 g orally twice daily × 7–10 d
Severe or refractory	Acyclovir, 800 mg orally 5 times daily × 7–10 d OR Acyclovir, 5–10 mg/kg of body weight intravenously every 8 h × 7–10 d OR Valacyclovir, 1 g orally twice to three times daily × 7–10 days
Human papillomavirus genital warts	Podophyllin, trichloroacetic acid, cryotherapy
Gonorrhea	Ceftriaxone, 125–250 mg intramuscularly once, OR Spectinomycin, 2 g intramuscularly once
Syphilis	
Early	Benzathine penicillin G, 2.4 million U intramuscularly once
Late	Benzathine penicillin G, 2.4 million U intramuscularly three times weekly
Neurosyphilis	Aqueous penicillin G, 18–24 million U intravenously daily × 10–14 days (3–4 million U every 4 h)

able. The patient's vaginal cultures, which you ordered to rule out other infections, are positive for *Candida* organisms.

SHOULD YOU ALTER THE PRESCRIBED TREATMENT, IN LIGHT OF THE PATIENT'S HIV STATUS?

In general, the patient should receive the same treatment as an HIV-negative woman with candidal vaginitis, although the duration of topical therapy may be extended to 7 to 14 days in the presence of underlying HIV infection. Table 1 shows recommended therapy for common gynecologic infections in HIV-infected women (21, 22).

ARE GYNECOLOGIC INFECTIONS A COMMON INITIAL PRESENTATION IN HIV-INFECTED WOMEN?

The most common reason that HIV-infected women first seek medical attention is development of a gynecologic infection (23). Recurrent candidal vaginitis was the reason for seeking care in 37% of 200 women in one study (23) and has been reported in 3% to 71% of women in published series (24–28); it tends to be seen at relatively high CD4⁺ T-cell counts (29, 30). No firm evidence indicates that vaginal infections with *Candida*

species are more severe in HIV-infected women than in noninfected women, but vulvovaginal candidiasis that is persistent, frequent, or poorly responsive to therapy is considered a clinical category B condition by the Centers for Disease Control and Prevention (31). Gynecologic infections have been diagnosed at a routine study visit in up to 63% of women known to be HIV infected (32) and in 83% at the time of hospitalization, although only 9% were actually hospitalized for a primary gynecologic symptom or diagnosis (32, 33). The presence of infections other than bacterial vaginosis should alert the health care provider to the need for counseling and testing for HIV infection.

Infection with human papillomavirus (HPV) is also common. Compared with 434 HIV-seronegative women at high risk for HIV infection, only HPV infection was statistically more common among the 851 HIV-seropositive women (28% vs. 64%, respectively) (24). Bacterial vaginosis was common in both groups (approximately 34% of patients in each group), and trichomoniasis was diagnosed in 12% of the HIV-infected women (24). Chronic genital infection with herpes simplex virus may be the first manifestation of

Table 2. Initial Assessment of HIV-Positive Women

Comprehensive history and physical examination
Gynecologic examination with Papanicolaou smear
Discussion of safe sex practices and sexual health
Laboratory tests
Complete blood count
Chemistry panel
Antibody for hepatitis B and C
Antibody for toxoplasmosis
Antibody for cytomegalovirus
VDRL and rapid plasma reagin tests for syphilis
Lipid panel before institution of protease inhibitor therapy
Pregnancy test, if indicated
Other
Purified protein derivative skin test (Mantoux, 5 tuberculin units)
Chest radiography

AIDS in women (34). Gonorrhea and infection with *Chlamydia trachomatis* are relatively uncommon (24, 33, 35).

The presentation of pelvic inflammatory disease may be more subtle than usual in HIV-infected women; these patients may have less severe pain and lower leukocyte counts (36, 37). However, body temperature may be higher, and an increased incidence of tubal ovarian abscesses has been reported (38). More intensive therapy for pelvic inflammatory disease is often recommended, with use of parenteral antibiotics (21, 22).

Because your patient has newly diagnosed HIV infection, you order screening blood tests and other baseline evaluations.

WHAT BASELINE TESTS SHOULD BE DONE IN WOMEN WITH NEWLY DIAGNOSED HIV INFECTION?

Screening blood work should include a complete blood count, with special attention to the hemoglobin and platelet counts (Table 2). Anemia was found in 37% of 2056 HIV-infected women studied as part of the Women's Interagency HIV Study (39). Factors independently associated with anemia included African American ethnicity, mean corpuscular volume of erythrocytes less than 80 fl, CD4 lymphocyte count less than 0.2×10^9 cells/L, higher HIV RNA levels in plasma, current use of zidovudine, and history of a clinical AIDS-defining condition (39). Anemia has been associated with decreased survival in HIV-infected persons (40–43). Thrombocytopenia is also common: It occurs in approximately 40% of patients during the course of infection and is the first manifestation of HIV in 10% (44, 45).

Serum chemistry panels, including glucose, and baseline levels of cholesterol and triglycerides are valuable because many HIV-infected patients eventually receive multiple medications, many of which cause renal, liver, or metabolic toxicity. In addition, up to 75% of HIV-infected patients have abnormal liver enzyme levels on initial evaluation (46).

The U.S. Public Health Service/Infectious Diseases Society of America guidelines suggest initial screening for hepatitis B and C. Hepatitis B vaccination should be considered in patients who do not show immunity to the virus. Co-infection by hepatitis C virus and HIV has been associated with increased levels of hepatitis C virus RNA (47) and more rapid progression of HIV disease (48).

A VDRL or rapid plasma reagin test should be ordered because of the high likelihood of co-infection by HIV and syphilis (49). Biological false-positive results on these tests may be seen in up to 6% of HIV-infected patients (46). Treponemal and nontreponemal tests should be interpreted in the usual manner (22).

An initial assessment of toxoplasmosis IgG can determine the potential risk for reactivation of latent infection (50) and the potential need for future prophylaxis against toxoplasmosis (51). A positive result for toxoplasmosis on IgG antibody testing may also aid in the differential diagnosis of central nervous system disease later in the course of HIV infection (50).

Antibody screening for cytomegalovirus is suggested, since absence of previous cytomegalovirus infection might aid in future decisions about prophylaxis against cytomegalovirus in the setting of severe CD4 lymphocyte depletion ($<0.5 \times 10^9$ cells/L) and might identify patients who should receive cytomegalovirus antibody-negative or leukocyte-depleted blood cell products (51).

A purified protein derivative skin test should be done (Mantoux, 5 tuberculin units); a positive result is 5 mm of induration (52). The purified protein derivative test should be repeated annually in HIV-infected persons at risk for tuberculosis, since the chance of reactivation is approximately 7% to 10% per year (53). Baseline chest radiography is also suggested (54).

A gynecologic examination with Papanicolaou (Pap) smear should be performed at baseline, repeated at 6 months, and then repeated annually, as long as results are normal (51). A pregnancy test should be considered.

Table 3. Indications for Initiation of Antiretroviral Therapy from the U.S. Public Health Service, Department of Health and Human Services*

Clinical Category	CD4 Lymphocyte Count, $\times 10^9$ cells/L	Plasma HIV-1 RNA Level, copies/mL	Recommendation
AIDS	Any value	Any value	Treat
Symptomatic HIV infection or AIDS	Any value	Any value	Treat
Asymptomatic	≤ 0.35	Any value	Treatment usually offered; may delay in patients with HIV-1 RNA level $< 20\,000$ copies/mL
Asymptomatic	> 0.35	$> 30\,000$ on branched DNA assay or $> 55\,000$ on reverse transcription polymerase chain reaction	Some controversy; either treat or defer and monitor CD4 lymphocyte count

* Data from reference 61.

Because your patient has newly diagnosed HIV infection, you order measurements of viral load (HIV-1 RNA level) and CD4 lymphocytes in the blood. One month after resolution of candidal vaginitis, the CD4 lymphocyte count is 0.279×10^9 cells/L and the HIV viral load is 134 000 copies/mL.

After discussing the critical importance of adherence to HIV treatment and assessing the patient's willingness to do so, you initiate antiretroviral therapy with zidovudine plus lamivudine (Combivir [Glaxo SmithKline, Research Triangle Park, North Carolina]) and efavirenz.

WHAT FACTORS SHOULD BE CONSIDERED WHEN DECIDING TO INITIATE ANTIRETROVIRAL THERAPY?

Before considering the biological factors that influence the decision to begin antiretroviral therapy, the patient's acceptance of such therapy and her willingness and ability to take all medicines properly must be determined. Lack of almost perfect adherence to antiretroviral therapy has been associated with development of drug resistance and resultant drug failure (55–57). Before starting a specific therapeutic regimen, it is critical to determine whether the patient is willing to adhere to the requirements of such therapy.

The HIV-1 viral load and CD4 lymphocyte count are important biological factors that help guide treatment decisions. The amount of HIV-1 RNA in plasma is directly related to the probability of progression to clinical AIDS in the subsequent 5 years (58, 59). As initially reported in the Multicenter AIDS Cohort Study, a viral load less than 5000 copies/mL on branched DNA testing or less than 10 000 copies/mL

on reverse transcriptase polymerase chain reaction is associated with an 8% risk for progression to AIDS in the subsequent 5 years, but an HIV RNA level greater than 36 000 copies/mL is associated with a 5-year risk for progression to AIDS of 62% (59). Current Public Health Service/Department of Health and Human Services guidelines (60) for initiation of antiretroviral therapy (Table 3) are somewhat more conservative than previous guidelines (61) in terms of the threshold level of HIV-1 RNA at which treatment should be considered in asymptomatic patients with higher CD4 cell counts ($> 0.35 \times 10^9$ cells/L). These changes are based on the acknowledgment that HIV infection is currently incurable and that antiretroviral therapy is associated with significant toxicity and difficulty in terms of adherence.

The CD4 lymphocyte count also provides useful information for determining the need for antiretroviral therapy. Antiretroviral therapy should be initiated in asymptomatic patients with CD4 lymphocyte counts less than 0.35×10^9 cells/L (60, 61). When the CD4 lymphocyte count is less than 0.2×10^9 cells/L or 14%, the risk for AIDS-defining opportunistic infections or neoplasms increases substantially, a condition termed *immunologic AIDS* (31). In patients with immunologic AIDS, prophylaxis against various infections should be initiated, as outlined in Table 4 (51, 62, 63).

Measurement of viral load and CD4 lymphocyte count provides further prognostic information; the risk for AIDS increases in a stepwise manner as the CD4 lymphocyte count decreases to less than 0.5, 0.35, and 0.2×10^9 cells/L at the same HIV RNA level (64). These data have led to the development of guidelines for initiation of therapy in HIV-infected persons (Table 3).

Since the patient in this hypothetical case is eager to begin treatment and since her viral load is high (with CD4 lymphocyte count $<0.35 \times 10^9$ cells/L), it is reasonable to initiate antiretroviral therapy with three agents, including two reverse-transcriptase inhibitors (zidovudine and lamivudine) and a third reverse-transcriptase inhibitor (abacavir), a non-nucleoside reverse-transcriptase inhibitor (efavirenz), or a protease inhibitor

(Table 5). The antiretroviral regimen should be chosen on the basis of its complexity in terms of numbers of pills and the frequency of dosing, as well as potential toxicities and drug interactions. Combivir consists of only one pill taken twice daily, and efavirenz is taken once daily; there are no restrictions on food intake for either medication. The combination is known to be efficacious and may avoid the potential complication of

Table 4. Abbreviated Recommendations from the U.S. Public Health Service for Use of Prophylactic Antimicrobial Agents*

Infection	Threshold for Initiation of Prophylaxis	Agent Used as Prophylaxis	Criteria for Discontinuation of Prophylaxis
<i>Pneumocystis carinii</i> pneumonia	CD4 lymphocyte count $<0.2 \times 10^9$ cells/L Previous <i>P. carinii</i> infection HIV-related thrush Fever of unknown origin for 2 weeks	Trimethoprim, 160 mg + sulfamethoxazole, 800 mg/d OR Dapsone, 100 mg/d OR Aerosolized pentamidine, 300 mg/mo by Respigard II nebulizer† OR Atovaquone, 750 mg orally twice daily with meals	Patients with increases of CD4 lymphocyte count to $>0.2 \times 10^9$ cells/L for 3–6 months may safely discontinue <i>P. carinii</i> prophylaxis
<i>Toxoplasma gondii</i>	CD4 lymphocyte count $<0.1 \times 10^9$ cells/L and positive result for <i>T. gondii</i> on IgG antibody testing	Trimethoprim, 160 mg + sulfamethoxazole, 800 mg/d OR Dapsone, 50 mg + pyrimethamine, 50 mg/wk + leucovorin, 25 mg/wk OR Dapsone, 200 mg/wk orally + pyrimethamine, 75 mg/wk + leucovorin 25 mg/wk orally	May discontinue primary prophylaxis when CD4 lymphocyte count is $>0.1 \times 10^9$ cells/L for ≥ 3 –6 months
<i>Mycobacterium avium</i> complex	CD4 lymphocyte count $<0.5 \times 10^9$ cells/L	Clarithromycin, 500 mg orally twice daily OR Azithromycin, 1200 mg/wk orally OR Rifabutin, 300 mg/d orally OR Azithromycin, 1200 mg/wk + rifabutin, 300 mg/d orally	May discontinue prophylaxis if CD4 lymphocyte count is $>0.1 \times 10^9$ cells/L for 3–6 months in patients without previous <i>M. avium</i> complex bacteremia
<i>M. tuberculosis</i>	Positive result on purified protein derivative test (≥ 5 mm of induration) or recent contact with person with tuberculosis	Isoniazid (INH), 300 mg/d + pyridoxine, 50 mg/d for ≥ 270 doses (9 mo or up to 12 mo with interruption) OR Isoniazid, 900 mg + pyridoxine, 100 mg twice weekly with directly observed therapy to ≥ 76 doses (9 mo or up to 12 mo with interruption) OR In patients not receiving a protease inhibitor or non-nucleoside reverse transcriptase inhibitor: rifampin, 600 mg/d + pyrazinamide, 20 mg/kg of body weight daily for ≥ 60 doses (2 mo or up to 3 mo with interruptions)	
<i>Streptococcus pneumoniae</i>	All patients	Pneumovax‡, one 0.5-mL dose; consider re-vaccination at 5 years or at time of CD4 cell count increase to $>0.2 \times 10^9$ cells/L, if initial vaccination occurred at CD4 cell count is $<0.2 \times 10^9$ cells/L	
Hepatitis B	Negative result on anti-hepatitis B core screening test	Recombivax HB‡, 10 μ g intramuscularly $\times 3$ doses, OR Energix-B§, 20 μ g intramuscularly $\times 3$ doses	
Influenza	All patients	Influenza vaccine, 0.5 mL intramuscularly; repeat annually	
Varicella	Exposure to chicken pox or herpes zoster in patients negative by history or antibody to varicella	Varicella zoster immune globulin, 5 vials (6.25 mL) intramuscularly within 48–96 hours of exposure	

* Information from reference 63.

† Manufactured by Marquest Medical Products, Inc., Englewood, Colorado.

‡ Manufactured by Merck & Co., West Point, Pennsylvania.

§ Manufactured by GlaxoSmithKline, Research Triangle Park, North Carolina.

Table 5. Available Antiretroviral Agents

Class	Drug	Dosing	Comments
Nucleoside reverse transcriptase inhibitors	Zidovudine	300 mg twice daily	Pills must be chewed; empty stomach; powder also available
	Didanosine	Weight \geq 60 kg: 200 mg twice daily or 400 mg/d; weight < 60 kg: 125 mg twice daily or 250 mg/d	
	Lamivudine	150 mg twice daily	2 mg/kg of body weight twice daily for weight <50 kg
	Stavudine	40 mg twice daily; 30 mg twice daily if <60 kg; 20 mg twice daily with peripheral neuropathy	Should not be used with zidovudine
	Dideoxycytidine	0.75 mg three times daily	
	Abacavir	300 mg twice daily	
	Combivir* (zidovudine + lamivudine)	1 tab twice daily	
	Trizivir* (zidovudine + lamivudine + abacavir)	1 tab twice daily	
Non-nucleoside reverse transcriptase inhibitors	Nevirapine†	200 mg twice daily	Start with 200 mg/d \times 14 d to avoid rash
	Delaviradine‡	400 mg three times daily	Separate dosing of didanosine or antacids by 1 h
	Efavirenz	600 mg/d	Take at bedtime to reduce early central nervous system side effects
Nucleotide reverse transcriptase inhibitors	Tenofovir§	300 mg/d	Take with food
Protease inhibitors	Ritonavir†	600 mg twice daily	Dosage of 100–400 mg twice daily when used with another protease inhibitor; increase initial doses over first 14 days for gastrointestinal tolerance
	Saquinavir (Invirase)¶	400 mg twice daily with ritonavir, 400 mg twice daily	
	Saquinavir (Fortovase)‡	1200 mg three times daily	Preferred because of better oral bioavailability
	Indinavir	800 mg every 8 h	Take while fasting or with light, nonfat meal; must drink \geq 48 oz of fluids daily to prevent renal stones
	Nelfinavir†	750 mg three times daily or 1250 mg twice daily	Take with food
	Amprenavir†	1200 mg twice daily	
	Kaletra (lopinavir + ritonavir)†¶	3 capsules twice daily (133.3/33.3 mg)	

* Manufactured by Glaxo SmithKline, Research Triangle Park, North Carolina.

† These drugs should not be used with oral contraceptive pills, since they result in decreased ethinyl estradiol levels and increased risk for pregnancy.

‡ No information is available on interactions with oral contraceptives.

§ Manufactured by Gilead Sciences, Inc., Foster City, California.

¶ Manufactured by Roche Laboratories, Nutley, New Jersey.

|| Manufactured by Abbott Laboratories, North Chicago, Illinois.

lipodystrophy, reported primarily with use of protease inhibitors (65). The ease of administration may facilitate adherence to therapy.

ARE INDICATIONS FOR ANTIRETROVIRAL THERAPY THE SAME IN MEN AND WOMEN?

During pregnancy, antiretroviral therapy is routinely advised in an attempt to prevent vertical transmission of HIV (66, 67). Aside from this circumstance, the recommendations for initiation of antiretroviral therapy are similar for men and women (60, 61). However, the threshold CD4 lymphocyte counts and HIV-1 RNA levels for initiation of antiretroviral therapy are somewhat controversial and may differ between men and

women. The CD4 lymphocyte count may be higher at the time that AIDS is first diagnosed in women versus men (68), suggesting that antiretroviral therapy should perhaps be initiated at a lower threshold value in women. Furthermore, the level of HIV-1 RNA in plasma may be lower in women than in men at similar CD4 lymphocyte counts (69–74), and lower HIV-1 RNA levels have been associated with progression to AIDS in women (71, 73, 74). Although not all studies have confirmed these findings (75, 76), the bulk of current evidence indicates a real difference in the level of HIV-1 RNA associated with disease progression in men versus women. Since women appear to have lower RNA levels (69–74) and higher CD4 lymphocyte counts

when AIDS is first diagnosed (68), it is possible that women should be treated earlier in the course of infection. Prospective clinical trials are required to address this matter.

WHAT IS THE EFFICACY AND TOXICITY OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY IN HIV-INFECTED WOMEN COMPARED WITH MEN?

Most studies indicate that the efficacy of antiretroviral therapy is equivalent in women and men (77–83). Ritonavir in combination with reverse transcriptase inhibitors has been studied in 90 women and 996 men (77). Although the efficacy of the drug appeared to be similar in both groups, women were more likely than men to experience nausea (63% vs. 56%), vomiting (49% vs. 31%), malaise and fatigue (47% vs. 34%), and numbness and tingling around the mouth (37% vs. 27%). In contrast, men were more likely than women to experience diarrhea (62% vs. 49%). Use of antiretroviral therapy, especially protease inhibitors, has also been associated with abnormal accumulations of body fat and elevated cholesterol, triglyceride, and glucose levels, with development of insulin resistance (65, 84–88). These abnormalities, which represent more than a single entity, are termed *the lipodystrophy syndrome*. Women with the lipodystrophy syndrome (87) are more likely than men to experience increases in abdominal fat (93% vs. 76%) and breast size (74% vs. 31%), whereas men are more likely than women to develop lipoatrophy in the limbs (69% vs. 53%) and buttocks (60% vs. 45%). Men are also more likely than women to develop elevated levels of triglycerides (63% vs. 26%) and cholesterol (50% vs. 26%).

A retrospective review of 200 men and 76 women attempted to ascertain the value of highly active antiretroviral therapy (HAART) regimens in a “real-world” clinical setting (79). At 7 to 14 months after initiation of a HAART regimen containing a protease inhibitor, 37% of patients had nondetectable plasma HIV-1 RNA levels; the regimen’s effectiveness did not differ significantly in men and women. However, women had a statistically increased risk for adverse drug effects compared with men (37% vs. 25%) ($P = 0.008$). Of the protease inhibitors, ritonavir had a higher toxicity profile compared with indinavir or nelfinavir; adverse effects consisted primarily of gastrointestinal symptoms.

These data indicate that various antiretroviral agents and combinations are equally efficacious in HIV-infected men or women, although the toxicity profiles may differ.

The patient and her husband do not wish to have more children, and she has been taking oral contraceptives for birth control. She asks if the HAART that you have prescribed will interfere with these oral contraceptives.

ARE THERE ANY KNOWN DRUG INTERACTIONS BETWEEN HAART AND ORAL CONTRACEPTIVES?

Drug interactions may be complex, especially when protease inhibitors are involved (21, 89, 90). Several antiretroviral agents interfere with metabolism of oral contraceptives and should be avoided (Table 5). Because efavirenz may be associated with severe birth defects (91), it is critical to discuss the importance of effective contraceptive measures while patients are taking efavirenz.

You measure the patient’s HIV-1 viral load after 1 and 3 months and find that the level is now nondetectable (<0.5 copies/mL), while the CD4 lymphocyte count has increased to 0.499×10^9 cells/L. Serologic testing for hepatitis, toxoplasmosis, cytomegalovirus, and syphilis is negative, and the tuberculosis skin test is nonreactive. The patient has no anemia or thrombocytopenia, and her liver and renal functions are normal. You ask her to continue taking her antiretroviral medications and to return in 3 months.

HOW OFTEN SHOULD HIV-1 RNA LEVELS AND CD4 LYMPHOCYTE COUNTS BE RECHECKED?

The CD4 lymphocyte count and HIV-1 RNA levels should be measured every 3 to 4 months. The same laboratory and testing methods should be used. In the case of markedly divergent results, the tests should be repeated to ensure their accuracy. Any persistent increase in HIV-1 RNA viral load greater than $0.3 \log_{10}$ (50% or more) is considered significant, warrants further evaluation, and may indicate the need to change antiretroviral therapy. Follow-up HIV-1 RNA measurements should be obtained when the patient is clinically stable and has had no intercurrent infection or immunization within the past 4 weeks, both of which may transiently increase the viral load (92–94).

At the patient’s next quarterly evaluation, her HIV-1 RNA level is still nondetectable and her CD4 lymphocyte count is 0.501×10^9 cells/L. The patient states that she

Table 6. Guidelines for Performance of Follow-up Papanicolaou Smears and Colposcopy in HIV-Infected Women*

Baseline Abnormality	Recommended Follow-up
Normal Pap smear Severe inflammation ASCUS or atypia	Repeat in 6 mo, then annually Evaluate for infection: repeat Pap smear in 2–3 mo Repeat Pap smear every 6 mo until 3 consecutive negative smears; then yearly follow-up
Low-grade squamous-cell intraepithelial lesion or low-grade cervical intraepithelial neoplasia (CIN I)	Colposcopy with second report of ASCUS Pap smear every 6 mo, and colposcopy with directed biopsy if repeated Pap smear is abnormal; some clinicians proceed directly to colposcopy, especially if patient is likely to be lost to follow-up
High-grade squamous intraepithelial lesion or high-grade cervical intraepithelial neoplasia (CIN II or III)	Colposcopy with biopsy followed by definitive therapy (conization or loop excision) and follow-up every 6 mo; careful examination for squamous intraepithelial lesions at other anogenital sites

* Information from reference 21. ASCUS = atypical squamous cells of uncertain significance; Pap = Papanicolaou.

feels well, with no intercurrent vaginitis. You explain the importance of obtaining a Pap smear now that the vaginitis has cleared.

The patient's gynecologic examination is normal, but the Pap smear is abnormal, showing a Bethesda system low-grade squamous intraepithelial lesion.

DO HIV-INFECTED WOMEN COMMONLY HAVE ABNORMAL PAP SMEARS?

Abnormal Pap smears are common in HIV-infected women; they were documented in 40% of 2054 HIV-positive women and 17% of HIV-negative women in the Women's Interagency HIV Study cohort (95). Abnormal Pap smears are associated with HIV infection, CD4 lymphocyte count less than 0.2×10^9 cells/L, HPV infection, and infection with high-risk types or multiple types of HPV (95). The relationship between HIV infection (96–99) or lower CD4 lymphocyte counts (100) and increased likelihood of cervical intraepithelial neoplasia (CIN) is well documented. Higher HIV-1 RNA levels have also been associated with increased risk for CIN (101).

SHOULD THE PATIENT UNDERGO TESTING FOR HPV?

Since the patient has an abnormal Pap smear, you elect to test her for presence and type of HPV infection by using polymerase chain reaction for HPV DNA.

Infection with HPV is common in HIV-infected women; in one study, it was detected in 58% of 2015 seropositive women and 26% of matched seronegative controls (102). The prevalence of HPV is even higher in women with CD4 lymphocyte counts less than 0.2×10^9 cells/L (103) and those with high HIV-1 viral

load (102). Of note, HIV-infected women are also likely to have persistent HPV infection over time (104, 105), a factor associated with development of invasive cervical cancer in HIV-negative women (106). Routine testing for HPV in HIV-infected women is not yet recommended.

WHY IS HPV INFECTION IMPORTANT IN TERMS OF CERVICAL CANCER?

Aside from its relationship to invasive cervical cancer, HPV is associated with the advanced precursor lesions CIN II and CIN III (107, 108). Multiple types of HPV have been identified, including HPV 6 and 11, which are associated with viral condyloma or mild dysplastic changes (CIN I) that do not progress to frank neoplasia (109). In contrast, HPV types 16, 18, 31, 33, and 35 are often associated with more advanced precursor lesions and are found in most cases of invasive carcinoma (110, 111).

You explain to the patient that her Pap smear does not reveal cervical cancer but that she might have a precancerous lesion, which will require specialized assessment. You refer her to a gynecologist with experience in the care of HIV-infected women. Colposcopy confirms the presence of low-grade cervical intraepithelial neoplasia (CIN I); infection with HPV type 6 is also present.

WHAT IS THE COURSE OF CIN IN HIV-INFECTED WOMEN, AND HOW SHOULD CIN BE TREATED AND FOLLOWED?

No specific therapy is required for CIN I, since this grade of lesion may regress spontaneously. However,

careful follow-up is required (Table 6). If CIN II or III is found on colposcopy, treatment is needed to prevent eventual progression to invasive cervical carcinoma (108). Various therapies are efficacious; loop electrical excision procedure and cervical conization (cone biopsy) are the procedures most commonly performed in HIV-infected women (108). In HIV-negative women with CIN II or III, the risk for persistent CIN or CIN recurring 1 year after specific therapy is approximately 10%, whereas the recurrence rate approaches 40% to 60% in HIV-infected women (112). In preliminary studies, use of 5% topical 5-fluorouracil cream, administered at a dosage of 1 g every 2 weeks for 6 months, has been associated with a statistically significant reduction in recurrence (28% of treated women and 47% of controls) (113). No significant systemic toxicities were observed, and rates of local toxicity were similar in both groups. Other experimental approaches are currently under study.

Since the likelihood of both HPV infection and CIN correlate with HIV-1 viral load and CD4 lymphocyte count, use of HAART may be associated with improvements in the clinical course of HPV or CIN. Although results are conflicting, some studies have shown a significant decrease in the prevalence of CIN after HAART (114, 115).

Your patient remains well. However, approximately 1 year after institution of HAART, her HIV-1 RNA level has increased to 76 000 copies/mL and her CD4 lymphocyte count has decreased to 0.32×10^9 cells/L. You repeat these tests in 2 weeks, with similar results. You question her carefully about the possibility of any intercurrent illness or vaccination, which she denies. You explain that her HIV-1 may have become resistant to the medicines she is taking and ask how many times she forgot to take her antiretroviral pills in the past week. She seems uncomfortable and says that she stopped taking her medicines 3 weeks ago because she found it too hard to remember to take them while trying to manage her household.

WHAT IS THE IMPACT OF INADEQUATE ADHERENCE TO ANTIRETROVIRAL MEDICATIONS, AND WHAT LEVEL OF ADHERENCE IS REQUIRED FOR OPTIMAL EFFECT?

Inadequate adherence to antiretroviral therapy may result in development of increasing HIV-1 viral load (55–57, 116, 117), development of antiretroviral drug resistance (118), and decreased survival (118–120).

Some studies have shown optimal retroviral suppression at compliance levels as low as 70% (121), although the majority of recent studies indicate that adherence rates of 95% or greater are associated with better outcomes in terms of viral suppression (55–57).

Factors associated with decreased adherence include increasing complexity of the regimen (122), lack of belief that the regimen might work (56, 123), lack of social support, current abuse of alcohol or recreational drugs (56, 124), change in daily routine (125), forgetfulness, higher CD4 lymphocyte counts (56, 123), and psychiatric illness or depression (126–129). Increased experience with HIV disease by the treating physician has been statistically associated with improved patient adherence (129).

Your patient starts to cry, stating that she is extremely depressed and worried about dying, leaving her son as an orphan. She doesn't have enough energy to care for herself and her family properly. She doesn't believe that the medicines will prevent her death from AIDS, and she feels overwhelmed by all of the difficulties in her life.

SHOULD YOUR PATIENT BE REFERRED TO A MENTAL HEALTH PROFESSIONAL? WHICH MANAGEMENT ISSUES SHOULD BE REFERRED TO A SPECIALIST?

Your patient should be referred to a mental health professional. Significant depression has been reported in as many as 60% of HIV-infected women (130), who often feel overwhelmed and exhausted with the burdens of caring for children, running a household, and meeting financial obligations. In these circumstances, HIV-infected women often neglect their own health care, with the inherent difficulties of transportation, cost, and lack of child care facilities, choosing instead to spend their energy caring for children or others who are dependent on them. Professional psychological care would be of benefit, in terms of adherence to medical therapy (129) and other quality-of-life issues.

Referral to other specialists may also be required in other circumstances throughout the course of your patient's care, such as development of specific gynecologic disorders or cancer; decisions and care regarding potential pregnancy; and management of various malignant, hematologic, or other organ-specific complications. Guidance from specialists in HIV disease will also probably be required. Referral to an HIV specialist is indicated if

the patient's virologic or immunologic profile suggests failure of therapy or if questions about potential drug toxicities or interactions arise. Patients who receive their care from physicians experienced in HIV disease have been shown to fare better and live longer (131–134).

Your patient expresses her fears about the long-term care of her son. She asks you about her long-term prognosis compared with that of her husband.

DOES THE PROGNOSIS OF HIV INFECTION DIFFER IN WOMEN AND MEN?

Although an improved prognosis for women versus men with HIV infection has been reported (25), most early studies documented significantly shorter survival in women with AIDS (135, 136). When these latter analyses were restricted to patients who were taking antiretroviral therapy, no difference in survival was found between men and women (135). After adjusting for baseline CD4 lymphocyte counts and ensuring that both women and men had the same access to care, Chaisson and colleagues (137) demonstrated conclusively that survival of women with HIV disease was similar to that in men. Others have since confirmed that finding (138, 139). These data suggest that earlier reports of decreased survival in women with HIV or AIDS may have resulted from decreased access to care, a problem that persists among HIV-infected women in the United States (140–144). When used properly, effective antiretroviral therapy has been associated with a reduction in mortality of approximately 50% among patients with AIDS and a reduction in development of clinical AIDS-defining conditions of approximately 75% among patients with HIV (145, 146).

Several books and articles (21, 22, 51, 60, 61, 66, 90) and Web sites (147–150) provide additional details on practical issues in the management of HIV-infected women.

From Keck School of Medicine, University of Southern California, Los Angeles, California.

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Requests for Single Reprints: Alexandra M. Levine, MD, USC/Norris Cancer Hospital, 1441 Eastlake Avenue, Room 3468, Los Angeles, CA 90033.

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