



# IMPROVING PATIENT OUTCOMES IN **HIV/AIDS**

## The Role of the Primary Care Clinician

OCTOBER 2009

**N**ew incidence estimates indicate that HIV infection is more prevalent than previously thought. The Centers for Disease Control and Prevention (CDC) has suggested that the earlier estimate of approximately 40,000 cases per year was not representative of the true severity of the epidemic.<sup>1</sup> Indeed, in its reanalysis, the CDC determined that there were actually 56,300 new HIV infections in the United States in 2006 (95% confidence interval [CI]; 48,200–64,500).<sup>1</sup>

While the complexity of therapy for HIV and AIDS most often requires consultation with infectious disease specialists, it is important that primary care providers be able to implement routine HIV screening strategies, recognize the signs and symptoms of infection, counsel HIV-positive patients on therapeutic options and strategies to minimize transmission, and provide appropriate referrals to specialty care.

### OPT-OUT HIV SCREENING: WHAT AND WHY

Of the approximately 1 million Americans currently living with HIV, about 25% remain unaware of their status.<sup>2</sup> These individuals account for approximately 54% of new cases.<sup>2</sup> This fact underscores the significance of a recent recommendation from the CDC—that universal “opt-out” testing be adopted in all health care settings.

The value of HIV screening extends beyond the individual to the community as a whole. Given the high risk for transmission by those unaware of their status, identifying HIV-positive individuals ensures that interventions may be implemented to prevent or reduce the chances of infecting others. To better identify infected individuals, clinicians need to recognize the changing demographics of the epidemic and abandon stereotypes about traditional risk groups. Toward this end, the CDC recommends that all patients aged 13 to 64 years be screened for HIV, regardless of the health care setting, unless an individual opposes it.

Patients should be informed that HIV testing will be performed as part of the routine panel of tests, unless patients wish

to “opt-out.” It is not required to obtain separate medical consent; rather, the test is simply part of the medical evaluation. Patients would need to decline the test in order to avoid taking it. Prevention counseling is recommended for individuals at high risk for infection, but should not be linked to HIV testing in a general health care setting.<sup>3</sup> Individuals at high risk should be re-tested at least annually.<sup>3</sup> Such patients include men who have sex with other men and are non-monogamous; those with sexually transmitted infections (STIs); and all men and women with multiple sexual partners.

Evidence to support the utility of routine testing comes from the San Francisco Department of Public Health Medical Care System. Traditionally, clinicians had been required to complete a separate laboratory requisition form and obtain written documentation of informed consent before ordering an HIV test. However, beginning in May 2006, HIV antibody testing was added to the routine laboratory requisition form. After the policy change, the monthly rate of HIV screening increased steadily from 13.5 tests per 1000 patient-visits in June 2006 to 17.9 tests per 1000 patient-visits in December 2006. The mean number of positive tests per month increased from 20.6 to 30.6.<sup>4</sup>

Some state health organizations have not adopted “opt-out” testing recommendations, and laws may require separate consent and/or prevention counseling. Furthermore, some states may have ordinances or rules that preclude following these recommendations.<sup>2</sup> Where such policies exist, clinicians should consider strategies to best implement routine screening within current parameters.

### HIV TESTS

Diagnosis of HIV infection is made on the basis of serologic testing. There are several available diagnostic tests, including the HIV enzyme-linked immunosorbent assay (ELISA) and the confirmatory Western blot, which detect host antibodies to the HIV virus. The ELISA is the most commonly used initial screening



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**Provider:** American Academy of Physician Assistants and Haymarket Medical Education

**Sponsor:** American Academy of Physician Assistants

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### NEEDS ASSESSMENT

Significant changes have occurred in the management of HIV/AIDS since the disease was first identified nearly three decades ago; it is now considered a preventable—and treatable—chronic illness. While the prognosis for patients with HIV/AIDS has certainly improved, more treatment challenges exist now than ever. In addition to identifying patients at risk, screening early and effectively, and initiating treatment as soon as possible, the fact that patients are living longer raises a new set of management issues, not least of which is how these patients can best be managed over the long term. Advances in highly active antiretroviral therapy (HAART) have led to significant decreases in HIV-related morbidity and mortality<sup>1</sup> but have also created new clinical challenges.<sup>1</sup>

While the complexity of therapy for HIV and AIDS often requires consultation with infectious disease specialists, primary care providers remain instrumental in screening/diagnosis and providing ongoing management and care coordination, as well as in the prevention of HIV transmission. Therefore, it is important that these clinicians be able to recognize the signs and symptoms of HIV/AIDS, encourage testing in all patients at risk, and counsel infected individuals on therapeutic options and strategies to minimize the risk for transmission.

In this educational activity, experts in the treatment of HIV/AIDS will present evidence-based strategies for disease management in primary care, from screening to initial treatment to HIV complications. As a result of taking part in the educational activity, PAs will be better equipped to manage patients with HIV/AIDS, and to improve the long-term health outlook and quality of life for these individuals.

### REFERENCE

1. Grinsztajn B, Veloso VG, Pilotto JH, et al. Comparison of clinical response to initial highly active antiretroviral therapy in the patients in clinical care in the United States and Brazil. *J Acquir Immune Defic Syndr*. 2007;45:515-520.

### TARGET AUDIENCE

Physician Assistants

### LEARNING OBJECTIVES

As a result of this activity, participants should be better able to:

- List two benefits of routine screening for HIV infection
- Identify two strategies to reduce the risk of HIV transmission
- Explain two critical factors in the selection of highly active antiretroviral therapy (HAART)
- Describe two key concepts in the management of patients with HIV/AIDS

### SPONSORSHIP AND APPROVAL INFORMATION



This program has been reviewed and approved for a maximum of .5 hours of AAPA Category 1 CME credit by the Physician Assistant Review Panel. Approval is valid for 1 year from the issue date of October 2009. Participants may submit the self-assessment at any time during that period.

This program was planned in accordance with the AAPA's CME Standards for Enduring Material Programs and for the Commercial Support of Enduring Material Programs.

Successful completion of the self-assessment is required to earn Category 1 CME credit. Successful completion is defined as a cumulative score of at least 70% correct. The AAPA will issue a certificate of completion for your CME records. Keep your certificate of completion in your professional files, and be sure to list this activity on your CME Logging Form. Please see page 7 for instructions on submitting the post-test.

### DISCLOSURE POLICY

It is the policy of the American Academy of Physician Assistants to ensure balance, independence, objectivity, and scientific rigor in all of its educational activities. All faculty participating in our programs are expected to disclose any relationships they may have with commercial companies whose products or services may be mentioned so that the participants may evaluate the objectivity of the presentations. In addition, any discussion of off-label, experimental, or investigational use of drugs or devices will be disclosed by faculty.

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The Faculty for this program reported the following financial relationships with commercial interests.

**Richard A. Elion, MD**, serves as a consultant to Bristol-Myers Squibb Company, Gilead Sciences, Inc., GlaxoSmithKline, Panacos Pharmaceuticals, Inc., ThaiMed, and Tibotec Therapeutics; has received grant/research support from Bristol-Myers Squibb Company, Gilead Sciences, Inc., and Tibotec Therapeutics; and is on the speakers' bureaus of Bristol-Myers Squibb Company, Gilead Sciences, Inc., and Tibotec Therapeutics.

**Susan F. LeLacheur, DrPH, PA-C**, has no relevant financial relationships to disclose.

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Unlabeled/investigational use of commercial products is not discussed in this activity.

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test, and it has high (>99%) sensitivity, while the Western blot is highly specific. The ELISA will be positive in most patients with HIV within 3 to 12 weeks of infection. Other tests, including determination of plasma HIV RNA with reverse transcriptase polymerase chain reaction (RT-PCR), DNA PCR, and viral isolation and culturing, detect the virus itself rather than antibodies to it and can therefore identify infection during the “window period” prior to seroconversion. The sensitivities of these tests all exceed 90%, and they are highly specific.<sup>5</sup>

Overwhelmingly, both patients and providers prefer rapid HIV tests to conventional enzyme immunoassays, because they obviate the need to return for results.<sup>6</sup> These tests have high degrees of sensitivity and specificity. Like conventional immunoassays, rapid HIV tests require confirmation if reactive.

### **REVEALING POSITIVE TEST RESULTS—A DIFFICULT CONVERSATION**

HIV-negative results can be communicated over the phone, but patients at high risk for the virus should be advised of the need for periodic re-testing and offered or referred to prevention counseling. In contrast, HIV-positive results should be conveyed confidentially and in person by a clinician, nurse, counselor, or other skilled staff.<sup>3</sup> At the time a positive test result is given, patients should be provided with links to clinical care, counseling, support, and prevention services. Test results, whether positive or negative, should be documented in the patient’s confidential medical record and accessible to all health care providers who care for the patient. As with any health care information, disclosure of HIV status requires the patient’s permission.<sup>3</sup>

Telling patients that test results are positive is far from easy and may require multiple conversations. Patients should be asked open-ended questions about what they think the test results mean, whether they have known anyone with HIV or AIDS, and what they know about current therapies. It is important to reassure patients they can have a good quality of life and that treatment regimens are not as difficult as they once were. Above all, let patients know that there is hope: CDC surveillance data found that average life expectancy from time of HIV diagnosis improved from 11.2 years to 20.5 years from 1996 to 2004.<sup>7</sup>

HIV-positive patients should be strongly encouraged to disclose their status to current and previous sex partners, and to recommend that these individuals be tested for HIV. Health departments can assist with this without disclosing the patient’s identity.<sup>3</sup> Patients who test positive should be informed that they

may be contacted by health department personnel for a voluntary interview to discuss partner notification. Finally, prevention education is an essential element of managing patients who test positive for HIV.

### **PROGRESSION OF HIV**

In untreated disease, the primary HIV infection is characterized by high titers of virus in the blood and a steep drop in cluster of differentiation (CD)4 cells, the primary viral target. (A normal CD4 cell count is between 500 and 1500 cells/mm<sup>3</sup>.) During this initial period—often about 2 weeks after infection—up to 70% of patients experience an influenza-like illness called acute retroviral syndrome.<sup>8</sup> An adaptive immune response ensues, controlling the acute illness and, for the most part, restoring levels of CD4 cells.<sup>9</sup> An asymptomatic period follows; this may last for months or years, during which the viral load (as determined by quantification of HIV RNA in the blood) and the CD4 cell count remain in balance. However, even during this asymptomatic period, there is progressive immune system suppression, and the CD4 cell count declines at an average rate of approximately 50 cells/mm<sup>3</sup> per year.<sup>9</sup>

Opportunistic infections (OIs) and other symptoms occur more often as the CD4 cell count falls, starting at around 500 cells/mm<sup>3</sup>.<sup>3</sup> Ultimately, long-term untreated HIV infection progresses to AIDS, which is defined by an absolute CD4 cell count of less than 200 cells/mm<sup>3</sup> or by the occurrence of specific OIs or malignancies. The interval between acute HIV infection and AIDS is highly variable, with a median time of approximately 10 years.<sup>10</sup>

### **INITIATING THERAPY**

The latest guidelines from the US Department of Health and Human Services (DHHS) suggest a CD4 cell threshold of 350 cells/mm<sup>3</sup> as the set point for initiating antiretroviral (ARV) therapy. Recent data published in *The New England Journal of Medicine* showed approximately 80% reductions in mortality rates for individuals who initiated therapy when their CD4 counts were over 500.<sup>11</sup> Some debate exists on determining the optimal time to start based on these observational data; the editorial accompanying the article questioned whether the choice should be described as “Ready When You Are?”<sup>12</sup> These findings are currently being reviewed by the Guidelines Committee of the DHHS; their recommendations should help clarify the controversy.

<b>NRTIs</b>		<b>PIs</b>	
• Abacavir	ABC	• <b>Atazanavir</b>	<b>ATV</b>
• Didanosine	ddl	• <b>Darunavir</b>	<b>DRV</b>
• <b>Emtricitabine</b>	<b>FTC</b>	• <b>Fosamprenavir</b>	<b>FPV</b>
• Lamivudine	3TC	• Indinavir	IDV
• Stavudine	d4T	• <b>Lopinavir</b>	<b>LPV</b>
• <b>Tenofovir</b>	<b>TDF</b>	• Nelfinavir	NFV
• Zidovudine	ZDV	• <b>Ritonavir</b>	<b>RTV</b>
		• Saquinavir	SQV
		• Tipranavir	TPV
<b>NNRTIs</b>		<b>Fusion/Entry Inhibitors</b>	
• Delavirdine	DLV	• Enfuvirtide	T-20
• <b>Efavirenz</b>	<b>EFV</b>	• Maraviroc	MVC
• Nevirapine	NVP		
• Etravirine	ETV		
<b>Integrase Inhibitor</b>			
• Raltegravir			
<small>NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside or nucleotide reverse transcriptase inhibitor; PI = protease inhibitor. Some of these drugs are available in fixed-dose combinations. Agents in bold font are appropriate for use in a newly diagnosed patient without antiretroviral resistance. Ritonavir is used to boost the other PIs.</small>			

### SELECTION OF INITIAL THERAPY: KEY CONSIDERATIONS

Although CD4 cell count often drives the decision to initiate ARV therapy, there is usually time to select a regimen that is right for the particular patient. Factors such as the likelihood of adherence, pregnancy, and cost all play a role in the choice of therapy. The presence of co-morbidities such as tuberculosis, liver disease, psychiatric disease, cardiovascular disease, and chemical dependency must be considered. Dosing and administration issues like pill burden, dosing frequency, and food requirements may make one drug a better fit for a patient than another. The potential for adverse events and drug interactions also plays a role. No less important are the characteristics of the viral disease itself—particularly the genotypic ARV resistance test results.<sup>12</sup> The necessity for strict adherence to a long-term regimen needs to be discussed in depth, and potential barriers to adherence identified and dealt with before treatment is begun.<sup>13</sup>

Antiretroviral medications fall into several classes, including nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion and entry inhibitors and integrase inhibitors. Because these classes of drugs inhibit the replication cycle of HIV at different stages, they are usually used in combination; some of these agents are available in fixed-dose combinations. *Table 1* lists all current ARV medications; those that are bolded are appropriate for use in a newly diagnosed patient in the absence of antiretroviral resistance.

In treatment-naïve patients, an ARV regimen usually comprises an NNRTI + 2 NRTIs; or either a PI boosted with ritonavir (preferred) or a single PI plus 2 NRTIs. *Table 2* lists the antiretroviral components recommended by the DHHS Guidelines for treatment-naïve patients. In HIV-positive pregnant patients, the clinician should refer to “Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal Transmission in the United States,” at <http://aidsinfo.nih.gov/guidelines/>.

A number of considerations exist when choosing whether to use an NNRTI or a PI regimen. The NNRTIs are very effective, have the lowest pill burden, and when taken regularly, a low rate of resistance. This class is relatively well-tolerated with limited toxicity. Efavirenz is not recommended for use in the first trimester of pregnancy or in sexually active women of childbearing potential who are not using effective contraception. In addi-

When making the decision of whether to initiate ARV therapy in patients with a higher CD4 count, the presence of co-morbidities, age, patient readiness, potential impact on quality of life, and potential for adherence should all be taken into consideration.<sup>13</sup>

Patients with higher CD4 cell counts who should automatically receive ARV therapy include those with a history of an AIDS-defining illness, pregnant women, and individuals with HIV-associated nephropathy. Patients who are co-infected with hepatitis B virus (HBV) should receive ARV therapy if and when HBV treatment is indicated.<sup>13</sup>

### RESISTANCE TESTING

To determine optimal therapy and to prevent transmission of resistant HIV strains, resistance testing is recommended prior to treatment initiation by all the major guidelines. It is also recommended by all guidelines in the face of treatment failure and in pregnant patients. However, among treatment-naïve patients with chronic infection, only the DHHS guidelines suggest resistance testing, while the International AIDS Society (IAS)-USA and European guidelines recommend considering such testing.<sup>13-15</sup>

**Table 2. Antiretroviral Components Recommended for Treatment of HIV-1 Infection in Treatment-Naïve Patients**

To Construct an Antiretroviral Regimen, Select 1 Component from Column A + 1 from Column B					
Column A (NNRTI or PI Options — in alphabetical order)			Column B (Dual-NRTI Options — in alphabetical order)		
Preferred Components	NNRTI-efavirenz <sup>1</sup>	or	PI — atazanavir + ritonavir (1x day) darunavir + ritonavir (1x/day) fosamprenavir + ritonavir (2x day) lopinavir/ritonavir <sup>2</sup> (1x or 2x/day) (co-formulated)	+	Preferred Components tenofovir/emtricitabine <sup>3</sup> (co-formulated)
Alternative to Preferred Components	NNRTI-nevirapine <sup>4</sup>	or	PI — atazanavir (1x day) <sup>5</sup> fosamprenavir (2x day) fosamprenavir + ritonavir (1x day) saquinavir/ritonavir (1x day)		Alternative to Preferred Components abacavir/lamivudine <sup>3</sup> (co-formulated) didanosine + (emtricitabine or lamivudine) zidovudine/lamivudine <sup>3</sup> (co-formulated)

DHHS Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. November 3, 2008.  
Available at: <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed September 2, 2009.  
<sup>1</sup>Efavirenz is not recommended for use in the first trimester of pregnancy or in sexually active women with childbearing potential who are not using effective contraception.  
<sup>2</sup>The pivotal study that led to the recommendation of lopinavir/ritonavir as a preferred PI component was based on twice-daily dosing. A smaller study has demonstrated similar efficacy with once-daily dosing but also showed a higher incidence of moderate to severe diarrhea with the once-daily regimen (16% vs. 5%).  
<sup>3</sup>In patients testing negative for HLA-B\*5701. Emtricitabine may be used in place of lamivudine and vice versa.  
<sup>4</sup>Nevirapine should not be initiated in women with CD4<sup>+</sup> T-cell count >250 cells/mm<sup>3</sup> or in men with CD4<sup>+</sup> T-cell count >400 cells/mm<sup>3</sup> because of increased risk of symptomatic hepatic events in these patients.  
<sup>5</sup>Atazanavir must be boosted with ritonavir if used in combination with tenofovir.

tion, the agent can cause CNS side effects, particularly sleep disturbances and vivid dreams. Nevirapine should not be initiated in women (including pregnant women) with CD4 cell counts greater than 250 cells/mm<sup>3</sup> or in men with CD4 cell counts greater than 400 cells/mm<sup>3</sup> because of the increased risk for symptomatic hepatic events in these patients. Only one viral mutation is required to develop resistance to NNRTIs, so more scrupulous adherence is required than with the PIs.

The PIs are also very effective, but the regimens still require at least 3 pills per day. In contrast to the NNRTIs, the PIs have a high genetic barrier to resistance. They are relatively well-tolerated with the exception of gastrointestinal effects. Fat accumulation and lipid problems may be more prevalent with the use of these medications.<sup>16</sup>

The NRTIs, which are generally used in all antiretroviral regimens, may cause problems with lipoatrophy, liver damage, and lactic acidosis.<sup>13</sup>

All PIs and NNRTIs are metabolized in the liver by the cytochrome P450 (CYP) system, particularly by the CYP3A4 isoenzyme. The list of drugs that may have significant interactions with either drug class is extensive and continuously

expanding. Some examples include medications that are commonly prescribed for other conditions in HIV patients, such as lipid-lowering agents, benzodiazepines, calcium channel blockers, immunosuppressants (such as cyclosporine and tacrolimus), neuroleptics, sildenafil, ergotamine, rifamycins, azole antifungals, macrolides, oral contraceptives, St. John's Wort, fluticasone, and methadone.<sup>13</sup>

It is important that all patients receiving therapy be assessed for disease progression, efficacy of treatment, and the development of resistance. HIV disease status and HAART efficacy should be monitored every 3 to 4 months by measuring CD4 cell count and HIV RNA to gauge immune function and disease stage. Adverse effects should be assessed every 3 to 6 months, including a complete blood count to check for anemia, metabolic panel assessing liver and kidney function, and fasting blood glucose as well as fasting lipids.

Primary care clinicians should not treat patients who have or are at high risk for serious co-morbidities, resistance to therapy, or who require second-line therapies. It is important that the clinician be familiar with infectious disease specialists in his or her area so that referrals may be made as necessary.

### IMPROVING ADHERENCE

Over time, non-adherence to an HIV treatment regimen, defined as less than 95% compliance, is associated with a higher risk for mortality.<sup>17</sup> Nonadherence is unfortunately common, and clinicians often overestimate their patients' compliance.<sup>18</sup> Barriers to adherence must be identified and constructive responses to circumvent them applied. For patients who fear disclosure, there should be social support; for substance abusers, drug treatment; for forgetfulness, reminder devices; for suspicion about the effects of treatment, education; complicated regimens should be simplified. Symptom management and social support can improve adherence in patients with side-effect issues, poor quality of life, or depression.

Regimens with once- or twice-daily dosing as well as fixed-dose combinations may reduce adherence difficulties associated with pill burden. Most currently available agents have relatively low pill counts, and several HAART agents may be taken on a once-daily basis.

### CONCLUSIONS

HIV incidence continues to increase, with positive patients unaware of their status accounting disproportionately for new infections. Universal opt-out testing is an important way to help stem the tide of this epidemic and is now recommended by the CDC as part of routine medical care for all individuals between 13 and 64 years of age. Patients who test positive should be informed confidentially and in person. It is essential they understand that HIV infection is not a death sentence but a chronic, treatable condition, and that new treatments and regimens can extend their lives while allowing them good quality of life. Equally important, HAART can reduce viral transmission by reducing viral load.

The guidelines currently suggest starting therapy in all patients with a CD4 of 350 or fewer cells/mm<sup>3</sup>. Initiating therapy in patients with a CD4 count of greater than 350 cells/mm<sup>3</sup> is not recommended at the present time, though it may be recommended in the near future in light of recent data showing a reduced risk for mortality in patients who are treated early. Furthermore, it may be currently appropriate for some patients,

such as pregnant women and those with certain co-morbidities.

All patients should receive counseling on strategies to prevent HIV transmission, as well as links to clinical and support services as warranted. Those who receive antiretroviral therapy should be educated on the importance of near-perfect adherence to the treatment regimen to prevent treatment failure and the development of resistant viral strains. Barriers to adherence should be identified and addressed early in the course of treatment.

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# IMPROVING PATIENT OUTCOMES IN HIV/AIDS

The Role of the Primary Care Clinician

## CME/CE POST-TEST

AAPA members should submit the post-test on the AAPA web site by going to [www.aapa.org](http://www.aapa.org) and searching for keyword "Online Post-Tests." PAs who are not members of AAPA may submit the test online at no charge by going to [www.mycme.com/hivoctaapa](http://www.mycme.com/hivoctaapa). To obtain credit, you must receive a score of 70% or better. Both web sites issue your CME certificate immediately.

- 1. The Centers for Disease Control and Prevention (CDC) recommends that HIV screening should be done for all patients who:**
  - a. Are at high risk for HIV
  - b. Are aged 13 to 64 years, regardless of health care setting
  - c. Ask to be tested privately
  - d. Agree to prevention counseling
- 2. Which individuals are at high risk for contracting HIV?**
  - a. Men who have sex with other men and are not monogamous
  - b. Those with sexually transmitted infections
  - c. Men and women with multiple sexual partners
  - d. All of the above
- 3. Which test will be positive in most patients with HIV within 3 to 12 weeks of infection?**
  - a. ELISA
  - b. Western blot
  - c. Viral isolation and culture
  - d. DNA polymerase chain reaction (PCR)
- 4. In 2004, what was the average life expectancy from time of HIV diagnosis?**
  - a. 10.5 years
  - b. 15 years
  - c. 20.5 years
  - d. 25 years
- 5. A feature of acute retroviral syndrome is that it:**
  - a. Occurs at least 1-2 months after initial infection
  - b. Restores levels of CD4 cells
  - c. Affects only about 10%-15% of patients
  - d. Is associated with opportunistic infections
- 6. Patients with HIV should automatically receive antiretroviral (ARV) therapy if they:**
  - a. Are of childbearing age
  - b. Are intravenous drug abusers
  - c. Have CD4 counts  $<1000$  cells/mm<sup>3</sup>
  - d. Have a history of an AIDS-defining illness
- 7. Which agent is appropriate for use in a newly diagnosed patient in the absence of ARV resistance?**
  - a. Abacavir
  - b. Stavudine
  - c. Atazanavir
  - d. Indinavir
- 8. Which medication is not recommended for use in the first trimester of pregnancy?**
  - a. Efavirenz
  - b. Raltegravir
  - c. Didanosine
  - d. Etravirine
- 9. Nevirapine is associated with an increased risk for:**
  - a. Gastrointestinal side effects
  - b. Symptomatic hepatic events
  - c. Fat accumulation
  - d. Lactic acidosis
- 10. There is significant interaction of the protease inhibitors and nonnucleoside reverse transcriptase inhibitors with a number of other agents, including:**
  - a.  $\beta$ -blockers
  - b. Selective serotonin reuptake inhibitors
  - c. Neuroleptics
  - d. Quinolones



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