

JMCM

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Supplement



**HIV Treatment
Guidelines**

JMCM

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HIV TREATMENT GUIDELINES

Target Audience

This monograph is intended for medical directors, physician executives, nurse case managers and other healthcare professionals interested in HIV.

This activity is supported by an educational grant from Abbott Laboratories.

Statement of Need

The treatment of HIV is continually changing. In order to provide optimal treatment to patients, clinicians need up to date information including current treatment guidelines. The guidelines for the use of antiretroviral agents in HIV infected adults and adolescents were recently updated by the U.S. Department of Health & Human Services. In addition to new guidelines, AIDS is the leading cause of death for women and disproportionately affects women of color. Although women of all ages are at risk, younger and older women are at particular risk. There are some specific issues related to gynecology, fertility, pregnancy and complications that need to be addressed in HIV infected women across the lifespan. Unfortunately, many of the antiretroviral (ARV) medications have a significant negative impact on the lipid profile. Because HIV infection can now be managed as a chronic condition, many patients are living long enough to experience the long term effects of elevated lipids. Although changing the patient's ARV regimen may produce some reduction in lipids, many patients will require lipid-lowering therapy. The primary agents, statins, have significant interactions with ARVs which must be considered in choosing appropriate therapy.

Learning Objectives

- Discuss the U.S. Department of Health and Human Services Treatment Guidelines for HIV
- Identify contradictions in treatment regimens
- Review diagnostic, treatment and outcome concerns for women of childbearing age
- Identify the impact of over-the-counter and lipid drug interactions with antiretroviral treatment

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NAMCP designates this activity for a maximum of 1 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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The American Association of Managed Care Nurses (AAMCN) has been approved as a provider of continuing education by the Virginia Nurses Association (VNA). VNA is accredited as an approver of continuing education in nursing by the American Nurses Credential Center's Commission on Accreditation. 1.0 contact hours will be awarded to nurses who complete this activity.

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Disclosure

Dr. Dobkin serves on the speakers bureau for Abbott and Roche.

Dr. Kaminsky serves on the speakers bureau for Abbott, Boehringer-Ingelheim, Bristol Meyers-Squibb, GlaxoSmithKline, Genentech, Gilead, and Tibotec.

Dr. Smith has no financial relationships to disclose. However, Dr. Smith's live presentation contained brand names.

NAMCP's CME Committee reviewed the faculty disclosures and determined that a conflict of interest was not presented in relationship to the content of this activity.

NAMCP planning committee members have no financial relationships that result in a real or potential conflict of interest.

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To receive continuing education credits for this activity, participants must read the monograph, complete the post test and submit an activity evaluation. A passing score of 70 percent must be achieved on the post test. Certificates of credit will be sent to the address on the evaluation form within six weeks of receipt.

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Updates to the Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents

Donald L. Kaminsky, MD

Summary

The treatment of HIV is continually changing. In order to provide optimal treatment to patients, clinicians need up-to-date information, including current treatment guidelines. The guidelines for the use of antiretroviral agents in HIV infected adults and adolescents were recently updated.

Key Points

- Goal of therapy is complete virologic suppression (<50 copies/ml).
- Viral load is not included in the current guidelines as a deciding factor in starting therapy.
- Recommendations for several "preferred" and "alternative" antiretroviral components for treatment-naïve patients have been revised.
- HLA-B*5701 screening should be done if abacavir therapy is being considered.
- Coreceptor tropism assay should be performed when a CCR5 antagonist (maraviroc) is being considered.
- The guidelines currently recommend antiretroviral therapy for all patients with CD4 <350 cells/mm³ and certain others regardless of CD4.
- Long-term treatment interruption is not recommended.

THE HIV MANAGEMENT GUIDELINES WERE updated by the Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents in December 2007 and published in January 2008. Although there were not many changes to the guidelines, some of these are important changes. The HIV management guidelines are useful for practitioners to formulate a plan to care for their patients.

The guidelines address a number of issues including baseline evaluation, laboratory testing (HIV RNA, CD4 cell count, resistance), when to initiate therapy, when to change therapy, therapeutic options, adherence, and antiretroviral therapy (ART)-associated adverse effects. Additionally, the guidelines address treatment of acute HIV infection; special considerations in adolescents, pregnant women, injection drug users, and patients coinfecting with HIV and hepatitis B, hepatitis C, or tuberculosis; and prevention counseling for HIV-infected patients.

The guidelines provide goals of therapy and the tools to achieve these goals. The goals include

improved quality of life, reduction of HIV-related morbidity and mortality, restoration and/or preservation of immunologic function, maximal and durable suppression of viral load, prevention of vertical transmission, and prevention of transmission to sexual partners. The tools include selection of ARV regimen, preservation of future treatment options, maximizing adherence, and resistance testing.

Achieving and maintaining medication adherence is important to successful treatment of HIV infection. If the patient does not take the medication, then it cannot be effective. Tools for improving adherence include support and reinforcement; simplified dosing strategies; reminders, alarms, timers, and pillboxes; ongoing patient education; and trust in primary care providers. Once a day dosing trumps everything.

CD4 cell levels are used to guide therapy decisions. CD4 count is a surrogate marker that is used as the major indicator of immune function. A patient's most recent CD4 count is the best predictor of disease progression. The new guidelines have tables that stratify predictable mortality by CD4 count.

Exhibit 1: Drug Resistance Testing: Recommendations

Recommended	Comment
Acute HIV infection, regardless of whether treatment is to be started	To determine if resistant virus was transmitted; guide treatment decisions. If treatment is deferred, consider repeat testing at time of ART initiation.
Chronic HIV infection, at entry into care	Transmitted drug-resistant virus is common in some areas; is more likely to be detected earlier in the course of HIV infection. If treatment is deferred, consider repeat testing at time of ART initiation.
Virologic failure during ART	To assist in selecting active drugs for a new regimen.
Suboptimal suppression of VL after starting ART	To assist in selecting active drugs for a new regimen.
Pregnancy	Recommended before initiation of ART or prophylaxis (genotype). Recommended for all on ART with detectable HIV RNA levels.
Not Usually Recommended	Comment
After discontinuation (>4 weeks) of ARVs	Resistance mutations may become minor species in the absence of selective drug pressure
Plasma HIV RNA <1000 copies/mL	Resistance assays unreliable if HIV RNA is low.

Exhibit 2: Indications for Initiating ART: Chronic Infection

Clinical Category and/or CD4 Count	Recommendation
History of AIDS-defining illness CD4 <200 cells/mm ³ CD4 200-350 cells/mm ³ Pregnant women HIV-associated nephropathy Hepatitis B coinfection, when HBV treatment is indicated*	Initiate ART
CD4 >350 cells/mm ³ , asymptomatic, without conditions listed above	Optimal time to initiate ART is not well defined. Consider individual patient characteristics and comorbidities.

*Treat with fully suppressive drugs active against both HIV and HBV.

Exhibit 3: Current Antiretroviral Medications

NRTI	NNRTI	PI	Entry Inhibitor	Integrase Inhibitor
Abacavir	Delavirdine	Atazanavir	Fusion Inhibitor	Raltegravir
Didanosine	Efavirenz	Darunavir	Enfuvirtide	
Emtricitabine	Nevirapine	Fosamprenavir		
Lamivudine		Indinavir	CCR5	
Stavudine		Lopinavir	Coreceptor	
Tenofovir		Nelfinavir	Antagonist	
Zidovudine		Ritonavir	Maraviroc	
		Saquinavir		
		Tipranavir		

Additionally, CD4 count is one of the most important considerations in the decision to start ART and is important in determining ART response. By the guidelines, an adequate response to ART is a CD4 increase of 100–150 cells/mm³ per year. After a baseline is established, CD4 monitoring is recommended at least every three to six months. Most clinicians would choose to monitor every three months if economically feasible for the patient. Interestingly, viral load is not included in the current guidelines as a deciding factor in starting therapy.

HIV RNA levels are also used to guide therapy decisions. HIV RNA is less important than CD4 count, but may influence the decision to start ART and determine the frequency of CD4 monitoring. These levels have not been demonstrated to determine outcome over time. HIV RNA levels are critical in determining response to ART. The goal of ART is to achieve HIV RNA below limit of detection (i.e., <40 to <80 copies/mL, depending on assay). RNA monitoring is recommended at least every three to four months in stable patients after a baseline is established. More frequent monitoring will help identify a failure of therapy faster than less frequent monitoring. It should be checked immediately before initiating therapy and at two to eight weeks after the start or change of ART.

Testing for drug resistance is recommended for all at entry to care, even if treatment is not currently planned. Overall 6 to 16 percent of HIV-infected patients will have a resistance mutation at the time of diagnosis. It is also recommended for all HIV+ pregnant women at their first prenatal visit. Identification of resistance mutations may optimize treatment outcomes. It prevents the use of medications that will not be effective. In the absence of therapy, resistance mutations may decline over time and become undetectable by current assays, but may persist and cause treatment failure when ART is started.

In patients with virologic failure, resistance testing should be performed while patient is still taking ART or within four weeks after discontinuing therapy. The mutation may disappear from the circulating virus but may still be in dormant virus. The results of resistance testing have to be interpreted in combination with history of ARV exposure and ARV adherence. Exhibit 1 summarizes the situations where resistance testing is or is not recommended.

There are some other assessments and monitoring studies that are now recommended in specific circumstances. HLA-B*5701 screening is used to predict abacavir hypersensitive reactions. Testing is recommended before starting abacavir to reduce risk of these reactions. The test is very good for predicting who will have a reaction. HLA-B*5701-positive

patients should not receive abacavir and a positive status should be recorded as an abacavir allergy. If HLA-B*5701 testing is not available, abacavir may be initiated, after counseling and with appropriate monitoring for a hypersensitivity reaction.

A coreceptor tropism assay should be performed when a CCR5 antagonist (maraviroc) is being considered. CD4 cells have receptors to which the HIV virus attaches. A CCR5 antagonist is not effective in patients who express CCR4 receptors, which the coreceptor tropism assay detects. The assay should be considered in patients with virologic failure on a CCR5 antagonist.

ART is indicated for all patients with low CD4 and/or symptoms. Earlier ART may result in better immunologic responses and better clinical outcomes. Potent ART may improve and/or preserve immune function in most patients with virologic suppression, regardless of baseline CD4. Early therapy can be recommended because the available ARV combinations produce a durable and tolerable response. For patients where there are not good available combinations (i.e., high level of resistance), the clinician may choose to wait to initiate therapy. The exact CD4 at which to initiate therapy is not known, but evidence points to starting at higher CD4 counts. The guidelines currently recommend ART for all patients with CD4 <350 cells/mm³ and certain others regardless of CD4 (Exhibit 2). Previously, therapy was recommended at CD4 < 200 cells/mm³.

The potential benefits of early therapy (CD4 >350 cells/mm³) include maintaining a higher CD4 to prevent irreversible immune system damage, decreasing risk of HIV-associated complications (e.g., tuberculosis, non-Hodgkin's lymphoma, Kaposi's sarcoma, peripheral neuropathy, human papillomavirus-associated malignancies, HIV-associated cognitive impairment), decrease risk of nonopportunistic conditions and non-AIDS associated conditions (e.g., cardiovascular, renal, and liver disease; malignancies; infections) and decreased risk of HIV transmission.

There are risks associated with early therapy. These include antiretroviral (ARV)-related side effects and toxicities; drug resistance (due to ART failure); inadequate time for the patient to learn about HIV, treatment, and adherence; increase in total time on ART which may cause long term adverse effects; greater chance of treatment fatigue; and transmission of ARV-resistant virus, if incomplete virologic suppression. Additionally, current ART may be less effective or more toxic than future therapies.

Exhibit 3 lists the available antiretroviral therapies. Components of initial ART should include preferred agents. These are agents that have clinical data that show optimal efficacy and durability, acceptable

**Exhibit 4: Initial Treatment:
Preferred Components**

NNRTI Option

Efavirenz*

OR

PI Options

Atazanavir + ritonavir
Fosamprenavir + ritonavir (BID)
Lopinavir/ritonavir (BID)

NRTI Options

Tenofovir +
emtricitabine**

Zidovudine +
lamivudine**

*Avoid in pregnant women and women with significant pregnancy potential.
**Emtricitabine can be used in place of lamivudine and vice versa.

tolerability and ease of use. Alternative agents are those which clinical trial data show efficacy but also show disadvantages in ARV activity, durability, tolerability, or ease of use (compared to “preferred” components). These may be the best option in select patients. Other possible options include agents with inferior efficacy or greater or more serious toxicities.

Exhibit 4 shows the preferred components of the initial ARV regimen. If a protease inhibitor (PI) is used, the data suggest it should be boosted with another agent, as shown in the exhibit. Alternatives are shown in Exhibit 5. The regimens outlined in Exhibit 6 are considered acceptable but inferior to preferred or alternative components. They may be used in special circumstances. Several agents or combinations are not recommended because of high rates of early virologic failure, inferior antiviral activity, high incidence of toxicity, high pill burden or dosing inconvenience, lack of initial treatment data, or no benefit over standard regimens. These are detailed in Exhibit 7.

Some regimens should not be used at any time. These include monotherapy (except possibly zidovudine used to prevent perinatal HIV transmission), dual nucleoside reverse transcriptase inhibitor (NRTI)

**Exhibit 6: Initial Treatment:
Other Possible Options**

ARV Drugs or Regimens

Rationale

Abacavir + lamivudine + zidovudine (conformulated)	Inferior virologic efficacy
Nelfinavir*	Inferior virologic efficacy
Saquinavir (ritonavir-boosted)	Inferior to lopinavir/ritonavir
Stavudine + lamivudine	Significant toxicities

These are considered acceptable but inferior to preferred or alternative components. They may be used in special circumstances.

*Should not be given to pregnant women.

**Exhibit 5: Initial Treatment:
Alternative Components**

NNRTI Option

Nevirapine*

OR

PI Options

Atazanavir**
Fosamprenavir
Fosamprenavir + ritonavir (1x/day)
Lopinavir/ritonavir (1x/day)

NRTI Options

Abacavir +
lamivudine

Didanosine +
(emtricitabine
or lamivudine)

**Nevirapine should not be initiated in women with CD4 counts >250 cells/mm³ or men with CD4 counts >400 cells/mm³

**Atazanavir must be boosted with ritonavir if used in combination with tenofovir

therapy, 3-NRTI regimen (except abacavir/lamivudine/ zidovudine and possibly lamivudine/zidovudine + tenofovir) and NRTI-sparing regimens. Additionally some combinations are not recommended for use at any time - didanosine + stavudine because of neuropathy, stavudine + zidovudine because of competition, emtricitabine + lamivudine because of identical mechanism of action, atazanavir + indinavir because of additive toxicities, or saquinavir as single unboosted PI because of likelihood of failure. Efavirenz and nelfinavir should not be used in pregnancy and in women with significant potential for pregnancy. Because of increased risk of adverse effects, nevirapine should not be initiated in women with CD4 >250 cells/mm³ or men with CD4 >400 cells/mm³.

There are some advantages to including a non-nucleoside reverse transcriptase inhibitor (NNRTI)

**Exhibit 7: ARVs Not Recommended
in Initial Treatment**

High rate of early virologic failure	Didanosine + tenofovir
Inferior antiviral activity	Delavirdine Saquinavir as sole PI (unboosted)
High incidence if toxicities	Indinavir + ritonavir (boosted) Ritonavir used as sole PI
High pill burden/ Dosing inconvenience	Indinavir (unboosted) Nelfinavir + saquinavir
Lack of data in initial treatment	Darunavir, Enfuvirtide, Tipranavir
No benefit over standard regimens	3-class regimens 3 NRTIs + NNRTI

in initial therapy. These include less dyslipidemia and fat maldistribution than in PI-based regimens and PI options are preserved for future use. These agents are especially beneficial in patients with a preexisting lipid disorder or family history of heart disease. The disadvantages on NNRTI initial therapy include a low genetic barrier to resistance, cross-resistance among NNRTIs, significant adverse effects (rash and hepatotoxicity) and the potential for liver based drug interactions (CYP450). With a single genetic mutation, this whole class is no longer effective.

Some advantages of including a PI in initial therapy include their high genetic barrier to resistance and NNRTI options are preserved for future use. The major disadvantages of this class are the metabolic complications and the potential for CYP450 drug interactions, especially with ritonavir.

Including NRTIs in initial therapy is established as the backbone of combination therapy with minimal drug interactions. There is a lot of familiarity and data with these agents. By including NRTIs, PIs and NNRTIs are preserved for future use. Some disadvantages include lactic acidosis and hepatic steatosis reported with most NRTIs. Triple NRTI regimens show inferior virologic response compared with efavirenz- and indinavir-based regimens.

In clinical studies of ART, most patients maintained virologic suppression for 3-7 years. In patients with suppressed viremia, measures to maintain adherence should be instituted. The ARV regimen should be simplified as much as possible. Older regimens can be changed but patients may be resistant.

For patients with ARV failure, they should be assessed and addressed aggressively. The reason for failure should be indentified, if possible. Causes of treatment failure include patient factors (CD4 nadir, pretreatment HIV RNA, comorbidities, etc), drug resistance, suboptimal adherence, ARV toxicity and intolerance, pharmacokinetic interactions, and sub-optimal drug potency.

ARV failure can be because of a virologic failure, immunologic failure, or clinical progression. Virologic failure is defined as sustained HIV RNA >400 copies/mL after 24 wks, >50 after 48 wks, or >400 copies/mL after viral suppression. An immunologic failure is failure to achieve and maintain adequate CD4 increases despite virologic suppression. Immunologic failure may be due to bone marrow suppression. The occurrence of HIV-related events (after three or more months on therapy) signals clinical progression.

Patients with virologic failure should be assessed for drug resistance by drug resistance testing, reviewing prior treatment history, and reviewing prior resistance test results.

Websites to access the
HIV treatment guidelines:
www.aidsetc.org and
<http://aidsinfo.nih.gov>.

Usually, drug resistance is cumulative so all previous treatment history and test results have to be considered. To manage the patient, their goals should be clarified. The aim is to reestablish maximal virologic suppression (e.g., <50 copies/ml). The clinician should evaluate remaining ARV options. Newer agents have expanded treatment options. The new regimen should be based on medication history, resistance testing, expected tolerability, adherence, and future treatment options. An effective regimen can be crafted for most patients who are experiencing a virologic failure. Treatment interruption, which may cause rapid worsening of CD4, HIV RNA, and clinical status, should be avoided.

The general principles of changing an ARV regimen include adding at least two (preferably three) fully active agents determined by ARV history and resistance testing to an optimized background ARV regimen. Potent ritonavir-boosted PIs or drugs with new mechanisms of action (e.g., fusion inhibitor, CCR5 inhibitor, integrase inhibitor) should be considered in addition to an optimized ARV background. In general, one active drug should not be added to a failing regimen because drug resistance is likely to develop quickly. This is also a good time for a consult with experts.

Conclusion

The HIV management guidelines for adults and adolescents were recently revised. The revisions reflect the most up-to-date data on the management of the HIV infected patient. The major revisions have been summarized here. **JMCM**

Donald L. Kaminsky, MD, is a member of the Gramercy Park Physicians and an attending physician in medicine and infectious diseases at Beth Israel Medical Center.

Reference

Panel on Antiretroviral Guidelines for Adult and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 29, 2008; 1-128. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed February 19, 2008.

Optimizing The Care of HIV Infected Women

Cheryl Smith, MD

Summary

AIDS is a leading cause of death for women and disproportionately affects women of color. Although women of all ages are at risk, younger and older women are at particular risk. There are some specific issues related to gynecology, fertility, pregnancy and complications which need to be addressed in HIV infected women across the lifespan.

Key Points

- AIDS is fifth leading cause of death for women.
- Women of color are disproportionately affected by HIV infection.
- Heterosexual contact is the most frequent route of HIV transmission in women.
- HIV infected women appear to be at higher risk of HPV related cervical cancer than non-infected women.
- Antiretroviral therapy during pregnancy dramatically reduces transmission to the fetus.
- The number of older women with HIV/AIDS is on the rise.

THERE IS DISPARITY IN WOMEN AFFECTED by HIV infection related to the population as a whole. Although 72 percent of the female U.S. population are white women, they account for only 17 percent of HIV infected females (Exhibit 1).¹ Black women, who are 13 percent of U.S. females, account for 66 percent of HIV infected women.

Overall, AIDS is the fifth leading cause of death for women.² For the 25–34 age group, AIDS is the leading cause of death in African American women (Exhibit 2).² Although much attention has been focused on the HIV epidemic in other parts of the world, the epidemic is still significant in the U.S. in communities of color and especially women of color. AIDS is no longer just an epidemic in New York and San Francisco. As shown in Exhibit 3, the issue is in all parts of the country.¹

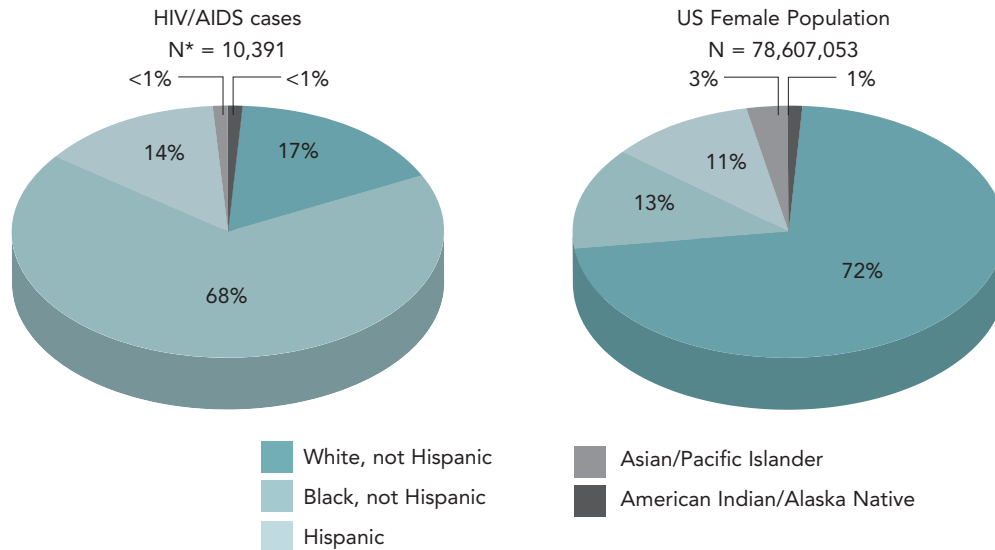
Women have a different presentation of HIV than men. They have decreased viral loads compared with men at similar stages of HIV infection. Women also have increased CD4 cell counts during HIV infection. Women have increased incidence of certain disease manifestations (toxoplasmosis, herpes simplex, and bacterial pneumonia). They have a decreased incidence of Kaposi sarcoma compared with men.

In most women the transmission of HIV is through heterosexual contact (Exhibit 4).^{1,3} Women

are more susceptible than men to contracting HIV during unprotected heterosexual intercourse (Exhibit 5).^{3,4} In addition, a number of other specific risk factors increase the risk for HIV infection in women. The presence of certain sexually transmitted diseases (STDs), such as gonorrhea, chlamydia, and syphilis, makes women two to five times more vulnerable to HIV infection.⁵ The risk for HIV infection also increases if the woman's partner has more severe HIV disease, if the frequency of intercourse is high, and if anal intercourse occurs.^{4,5} The use of an intrauterine device (IUD) for contraception also increases the risk for infection.⁶ Risk is also increased in younger minority women who are likely to begin engaging in sexual behavior at a young age and who also may be engaging in substance use.^{4,6}

Biological and social factors make adolescents vulnerable to unsafe sexual practices. Sexually active female teenagers may be biologically more susceptible to HIV acquisition than older women. High age-specific rates of both gonorrhea and chlamydia may increase the relative risk of acquiring HIV twofold to threefold in teenagers.⁷ The less mature cervix commonly has larger areas of cervical ectopy than that of a more mature woman.⁸ Additionally, age-discrepant sexual relationships increase female teenagers risks.⁹ Younger women are experimenting with older men.

Exhibit 1: Proportion of HIV/AIDS Cases and Population among Female Adults and Adolescents, by Race/Ethnicity 2004 — 33 States



Note: Data include persons with a diagnosis of HIV infection regardless of AIDS status of diagnosis. Data from 33 states with confidential name-based HIV infection reporting since at least 2000. Data have been adjusted for reporting delays. *Includes 49 female adults and adolescents of unknown race or multiple races. Reference: 1

Screening Recommendations

The CDC recommends routine, voluntary HIV screening for all persons 13 to 64.³ Women should be screened regardless of risk factors. The current screening recommendations suggest including HIV consent with general consent for care, rather have a separate consent form (opt-out screening). Extensive prevention counseling in conjunction with HIV screening in health care settings is no longer required. Counseling should be offered when requested and when patients are at high risk.

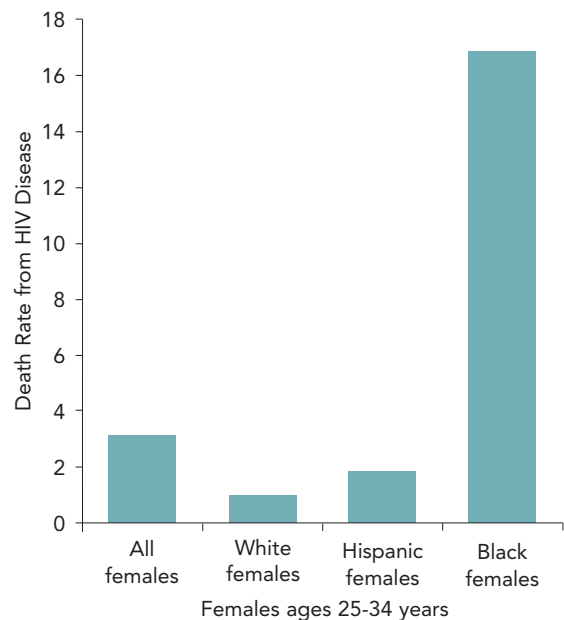
Gynecologic Considerations and Management

Women infected with HIV are more likely to be infected with oncogenic and multiple human papillomavirus (HPV) types. HIV-related immunosuppression may facilitate HPV persistence and the development of HPV-associated cervical neoplasms. The women at highest risk for oncogenic HPV infection are younger, smokers, younger at first coitus, multiple sex partners, lower CD4 counts, and higher HIV viral loads.^{10,11} It is recommended to add HPV testing to routine PAP smears in HIV positive women. Although the HPV testing is an additional cost, HIV infected women appear to be at significantly higher risk of cervical cancer.

Anal HPV cytologic screening of HIV-infected women, regardless of their history of anal sex, for the detection of abnormalities including precancerous

lesions is also recommended. A history of anal sex is not predictive of abnormal HPV-associated cytology. The HPV vaccine (Gardasil[®]) is available and indicated for the prevention of cervical cancer,

Exhibit 2: HIV Disease is the Leading Cause of Death for Black Females Ages 25-34



Reference: 2

precancerous or dysplastic cervical lesions, genital warts, and infection caused by the HPV types targeted by the vaccine (HPV 6, 11, 16, and 18). This vaccine is recommended for routine vaccination of all 11- to 12-year-old girls.¹² For those females who were not vaccinated at 11 or 12, catch-up vaccination of 13- to 26-year-old girls and women can be done.

The USPHS/IDSA recommends women with HIV have a complete pelvic exam annually with routine STD screening.¹³ They should have a PAP smear twice during the first year after diagnosis. If

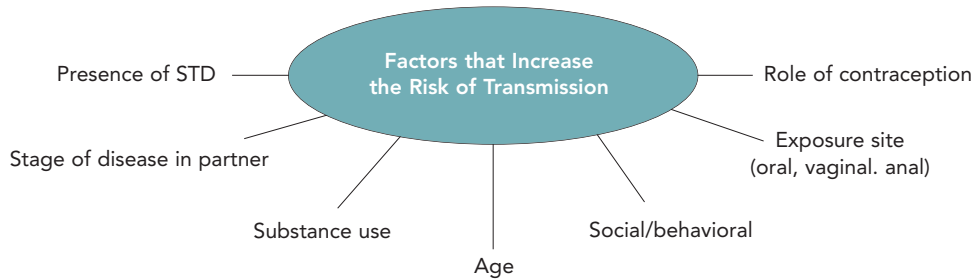
the results are normal, the PAP smear should be repeated annually. If atypical squamous cells of undetermined significance (ASCUS) are identified, the test should be repeated every four to six months for two years until three consecutive negatives. Colposcopy and possibly directed biopsy are used to treat repeat ASCUS, low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesions (HSIL). No data are available to demonstrate that these guidelines to prevent cervical disease should be modified for women on antiretroviral (ARV) therapy.

Fertility and Pregnancy

Unintended pregnancy, which threatens the health of women, is a persistent, serious problem in the United States. A significant number of pregnancies (49 percent) in the U.S. are unintended.¹⁴ Eighty-two percent of pregnancies in w

Exhibit 5: Risk Factors for HIV Transmission

Women are more susceptible than men to contract HIV through heterosexual intercourse.



Reference: 6

that there is an important failure of the interaction between health care providers and women to provide protection against unintended pregnancy.

Many of the ARV medications interact with estrogens, which may decrease their effectiveness as contraceptives. These interactions need to be considered in choosing a contraceptive medication. Alternate methods of nonhormonal contraception are recommended when a patient is taking nevirapine, indinavir, nelfinavir, amprenavir, ritonavir, lopinavir, darunavir, tipranavir, and atazanavir. There are many pros and cons of the various contraception options for women with HIV (Exhibit 6).

For women who want to become pregnant, there is no evidence that HIV+ women have more irregular periods than HIV- women once co-morbidities are excluded (substance abuse, weight loss). Decreased pregnancy rates after in vitro fertilization have been reported in HIV+ women on HAART.

Worldwide, each year, two million HIV infected women become pregnant and the majority deliver

healthy children.¹⁶ In one study, the majority of women became HIV+ before pregnancy (Exhibit 7).²⁰ Between 1/4 and 1/3 will transmit the disease to their newborns either during labor, during delivery, or while breast-feeding.¹⁶ Approximately, 2,000 HIV-infected infants are born each day worldwide.¹⁶

HIV screening recommendations in pregnant women are similar to those for non-pregnant populations.³ HIV screening should be included in the routine panel of prenatal screening tests. A second screening is done in the third trimester for women known to be at risk for HIV, living in communities with elevated HIV incidence, or living in high-prevalence health care facilities. The woman and newborn should receive a rapid HIV test with antiretroviral prophylaxis initiated based on the results.

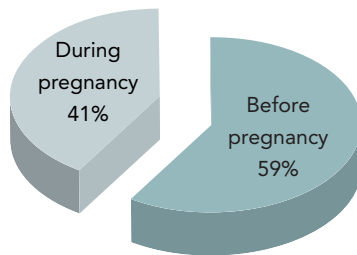
All pregnant women with HIV Infection should receive a standard HIV clinical evaluation.¹⁸ Any prior or current ARV use needs to be documented so the best choice of ARV for both the mother and child can be made. The woman needs to be informed

Exhibit 6: Pros and Cons of Contraception Options in HIV

Method	Pros	Cons
Condoms	STI/HIV protection	Requires partner cooperation and correct technique
Oral Contraceptive	Effective, less blood loss	Rx-Rx interaxns; not rec. with Pls; ↑shedding
Patch, ring, combo injectable	Effective, less blood loss	Rx-Rx interactions; lack of data; ↑shedding
Depot progesterones	Low maintenance, effective	↑ Shedding, ↑ viral set-point
IUD	Low maintenance, effective	Blood loss with Copper T, shedding with LNG-IUS; ↑ pelvic infection
Cervical barrier	Some STI protection	↑ UTI with diaphragm, requires correct technique
Sterilization	Low maintenance, effective	No future fertility; cost; invasive

Exhibit 7: Time of HIV Diagnosis in Pregnant Women

PACTG 367 n = 2,895 pregnancies
Timing of HIV Diagnosis (1998-2001)



Reference: 20

about the known or unknown risks and benefits of therapy during pregnancy. The clinician should develop a strategy for long-term evaluation and management of the mother and infant. Patients need to be monitored for potential complications of the ARVs based on what is known about the drugs the mother is receiving. Adherence monitoring and support are vital to good medication adherence. Intensive fetal monitoring should be considered for mothers on combination ARV therapy. Assessment of fetal anatomy with level II ultrasound and continued assessment of fetal growth and well being during the third trimester are recommended.

Decisions regarding the use and choice of ARV drugs during pregnancy are complex. A 3-part zidovudine regimen for reducing perinatal transmission, alone or in combination with other antiretrovirals should be offered to the pregnant woman.¹⁸ Preventable risk factors for perinatal transmission should be discussed. A patient's acceptance or refusal of antiretrovirals or zidovudine should not result in denial of care or punitive action.

There is little evidence that ARVs are associated with adverse pregnancy outcomes such as preterm delivery, low Apgar scores, or stillbirths. There is an

increased risk of very low birth weight infants [$<1500\text{g}$] with protease inhibitor use and ARVs without zidovudine.^{19,20} The late use of ARVs is associated with gestational diabetes.

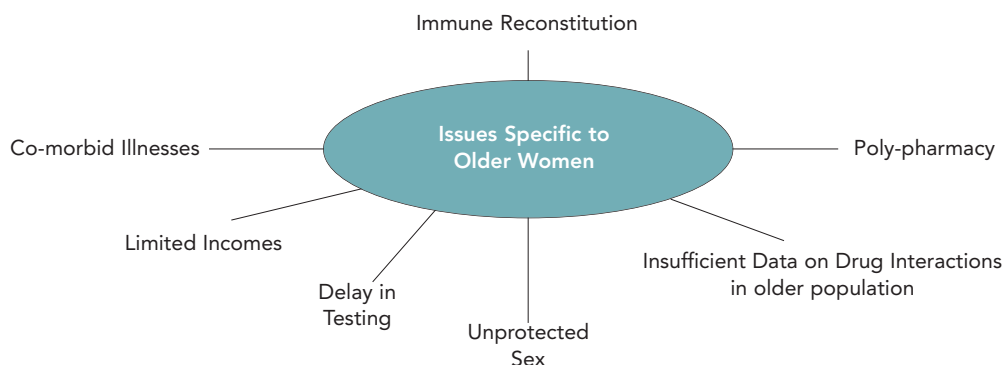
Manufacturers of ARV agents maintain a registry of birth defects associated with these agents.²¹ As a whole, the rate of birth defects from first trimester exposure are approximately equivalent to the background rate of birth defects. Efavirenz (Sustiva), nelfinavir (Viracept), and the combination of didanosine and stavudine should be avoided in women. Use of nelfinavir should be avoided because of the ethyl methanesulfonate (EMS) levels, a teratogen, within the current formulation.²²

Without ARV drugs during pregnancy, mother-to-child transmission has ranged from 16 percent to 25 percent in North America and Europe.¹⁸ There was a 21 percent transmission rate in the U.S. in 1994 before the standard zidovudine recommendation during pregnancy. With the change in practice, transmission decreased to 11 percent in 1995.¹⁸ Today, risk of perinatal transmission can be reduced to less than 2 percent with effective antiretroviral therapy, elective cesarean section as appropriate, and formula feeding.

Older Women

The number of older women with HIV/AIDS is on the rise. It has been estimated that in the US 78,000 people over the age of 50 are living with HIV/AIDS, and approximately 20 percent of them are women.²³ A number of issues regarding HIV prevention and treatment are specific to older women (Exhibit 8). Older women are likely to be postmenopausal and thus not concerned about getting pregnant. As a result, they may be less likely to use a condom.²³ Older women may also mistake HIV symptoms for normal problems of aging, thus delaying testing and treatment. They are likely to have limited incomes, which may limit access to treatment. They are also less likely than younger women to get support from peer groups.

Exhibit 8: Older Women



Many older adults do not perceive themselves to be at risk for HIV infection but may be newly single and sexually active. They lack of awareness of HIV risk factors. The use of erectile dysfunction medications has contributed to increased sexual activity in older adults.

Vaginal dryness due to estrogen depletion can increase a women's risk of acquiring HIV. Lastly, there is a lack of HIV prevention education targeting older adults.

There is conflicting data whether earlier menopause occurs in HIV+ women. Although it is appropriate to consider hormone replacement therapy (HRT) in older women with HIV infection, data are still insufficient on interactions between HRT and ARVs.²⁴

Immune reconstitution may be limited in older people receiving ARVs, and they may develop AIDS more rapidly than younger patients.²⁵ Co-morbid illnesses (e.g., diabetes, hypertension, obesity, hyperlipidemia) may complicate treatment as a result of drug interactions between ARVs and other required medications.

Complications

Depression is one complication of HIV infection which can have a significant impact on women. In one study, HIV infected women with chronic symptoms of depression were 2.3 times more likely to die than those with no symptoms.²⁶ Depression is associated with significantly more rapid decline in CD4+ T-cell counts and a 150 percent increase in mortality relative to women without depression. Patients with depression are also less likely to be adherent with their ARV therapy.²⁷

Another potential complication is myocardial infarction. In a Kaiser Permanente Northern California Surveillance Cohort, hospitalizations for myocardial infarction were significantly higher among HIV+ patients compared with HIV- health plan members. HIV+ women had almost a fourfold relative risk of MI hospitalization.²⁸

Recent studies show that differences in rates of progression to AIDS or death are not different between men and women.²⁹ Women have been shown in various studies to enter treatment with lower median viral loads and higher CD4 cell counts than men. However, adjusting for these differences, the response to treatment for women and men is statistically similar in several large-scale longitudinal cohorts. No difference in disease progression was found between women and men in recent medication studies.^{30,31}

Early studies in women with HIV being treated with antiretroviral agents showed that adverse events might be more prevalent than in men. Adverse events

HIV Resources:

General	www.hivatis.org
www.acog.org	www.medscape.com
www.apregistry.com	www.thebody.com
www.cdc.gov	www.unaids.org
www.cdc.gov/MMWR	www.worldaids.org
www.clinicaltrials.gov	www.4woman.gov
Peer Support	
www.women-alive.org	www.womenhiv.org

may also impact women's adherence to HAART, causing higher rates of discontinuation. These reports were produced prior to the availability of more-tolerable antiretroviral agents; however, they point out the need to consider the special needs of women with HIV disease with regard to adverse events.^{33,34}

There are some female specific issues with ARV medications. As discussed previously, certain medications are contraindicated in pregnancy. Nevirapine is not recommended for women with CD4 counts >250 cells/mm³ due to risk of severe hepatotoxicity. A specific genetic phenotype (HLA-DRB 0101) appears to be associated with nevirapine hypersensitivity, especially at higher CD4 counts. There are also higher incidence of hepatotoxicity and rash among women when compared with men.^{34,35} Women receiving nevirapine have an overall 12-fold higher risk of severe hepatotoxicity than men. Women have a sevenfold increase in risk for severe rash (adjusted for CD4 cell count) and are 3.5 times more likely to discontinue due to rash. Rash does not appear to be associated with viral load, age, race, or other medications.

Conclusion

Unlike at the beginning of the HIV/AIDS epidemic, women are now significantly affected by this infection. Gender specific differences are being identified and need to be considered when caring for HIV infected women. **JMCM**

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Pharmacokinetic Interactions in Managing HIV-related Hyperlipidemia

Jay Dobkin, MD

Summary

Unfortunately, many of the antiretroviral (ARV) medications have a significant negative impact on the lipid profile. Because HIV infection can now be managed as a chronic condition, many patients are living long enough to experience the long term effects of elevated lipids. Although changing around the patient's ARV regimen may produce some reduction in lipids, many patients will require lipid-lowering therapy. The primary agents, statins, have significant interactions with ARVs, which must be considered in choosing appropriate therapy.

Key Points

- Antiretroviral therapy can lead to lipid abnormalities.
- Changing agents can have some benefit in reversing lipid abnormalities.
- Most patients are going to require lipid-lowering therapy to achieve appropriate goals.
- Simvastatin and lovastatin have the most interactions with HIV medications and should be avoided.
- Pravastatin has the least interactions but is less potent than low dose atorvastatin or rosuvastatin.

METABOLIC DERANGEMENTS ARE A common issue in the treatment of patients with HIV infection. Lipid abnormalities have been identified in these patients from the beginning. In the pre-highly active antiretroviral therapy (HAART) era, lipid abnormalities included decreased high-density lipoprotein (HDL) and total cholesterol, increased very low-density lipoprotein (VLDL) and increased triglycerides (TG). With the advent of HAART, lipid effects of the antiretroviral (ARV) agents are a common issue in managing patients. Some of the HAART agents cause hyperinsulinemia and insulin resistance. This leads to significantly increased LDL, total cholesterol, and triglycerides. Typically there are no changes in HDL related to HAART.

Exhibit 1 illustrates relative lipid changes with certain agents. There are variable increases which each agent. Full dose ritonavir, which is no longer used, is the worst offender. Low dose ritonavir is frequently used as a booster agent and still has a significant negative effect on lipids.

The cardiovascular risk associated with HIV is a controversial subject. The data on the level of cardiovascular events and the association with particular medications are debatable but there is clear evidence of increased risk. In one large study looking at cardiovascular risk factors in patients with HIV,

51.5 percent were smokers, 22.2 percent had increased total cholesterol, and 25.7 percent had low HDL cholesterol.¹ Metabolic syndrome (increased cholesterol, insulin resistance, abdominal obesity) is frequently present in these patients. This syndrome dramatically increases risk of cardiovascular disease and events. Cardiovascular risk is especially an issue with an aging HIV infected population.

Cardiovascular risk reduction is important in patients with HIV. Lifestyle changes including dietary changes, exercise, and smoking cessation need to be implemented for many patients.

Recently, there has been a lot of focus on treatment switching to help manage lipid abnormalities. Unfortunately, a lot of this focus has been commercially motivated (i.e., pharmaceutical companies) and there may be some tradeoff in efficacy when switches are made.

Options for improving a patient's lipid profile include switching from thymidine analogues (AZT, stavudine) to other nucleoside reverse transcriptase inhibitor (NRTI) or from a protease inhibitor (PI) to a non-nucleoside reverse transcriptase inhibitor (NNRTI). Other options are changing an older PI, such as nelfinavir, to atazanavir or amprenavir or changing lopinavir/ritonavir (Kaletra) to saquinavir/ritonavir or darunavir/ritonavir. In one

Exhibit 1:

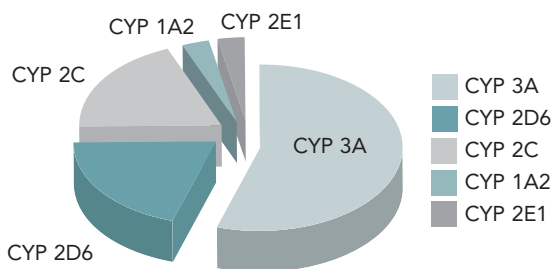
Drug	Total Cholesterol	LDL Cholesterol	Triglyceride
Ritonavir	3+ Increase	3+ Increase	4+ Increase
Indinavir	2+ Increase	2+ Increase	No change
Atazanavir Amprenavir	0-1+ Increase	0-1+ Increase	No change
Lopinavir/ Ritonavir	2+ Increase	2+ increase	4+ increase
Efavirenz	0-2+ Increase	0-2+ Increase	No change

study of switching from nelfinavir to atazanavir, total cholesterol decreased 16 percent, LDL, 20 percent, and triglycerides, 25 percent.² Although a significant change, this does not compare with decreases that can be obtained with lipid-lowering agents. Exhibit 2 includes data from one of the studies illustrating a lack of effect with a switch from fosamprenavir/ritonavir to lopinavir/ritonavir.³ There was very little change with the switch. The addition of ritonavir for boosting purposes may erase the benefits of the more “lipid friendly” protease inhibitors. Switching may be worth a try but if the patient has significant lipid abnormalities, pharmacotherapy with lipid-lowering therapy will be necessary.

Rather than switch medications, many clinicians will choose the most potent ARV regimen and manage the hyperlipidemia with lipid-lowering therapy. A less active regimen with lower lipid impact may put the patient at risk for HIV resistance.

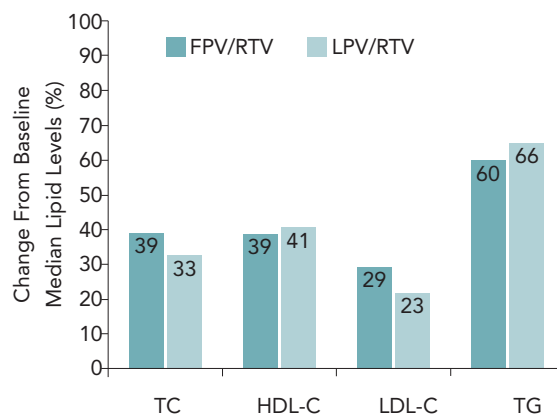
Statins have a dramatic effect on hyperlipidemia, cardiovascular pathology, and mortality. They can reduce LDL 18-55 percent and TG 7-30 percent and raise HDL 5-15 percent. The major side effects of myopathy and increased liver enzymes are well known. The major contraindications to these agents are liver disease

Exhibit 3: Proportion of Drugs Metabolized by CYP450 Enzymes



Reference: 4

**Exhibit 2: KLEAN Study:
Lipid Changes at Week 48
With FPV/RTV vs LPV/RTV**



Reference: 3

(absolute) and use with certain medications (relative).

Many of the ARV agents have major pharmacokinetic drug interactions. The statins are one class with which many of these agents interact. Some ARVs cause changes in liver metabolism through enzyme induction or inhibition. Others cause alterations in drug absorption, drug displacement from binding sites, or additive/synergistic toxicity. The focus of the remaining discussion will be on liver enzyme induction or inhibition, which leads to the most significant interactions.

The cytochrome system of the liver is responsible for a large part of medication metabolism. Of the isoforms of the cytochrome P450 system, CYP 3A4 is responsible for the bulk of drug metabolism (Exhibit 3).⁴ This is the isoenzyme that metabolizes four major classes used in HIV treatment: PIs, NNRTIs, azole antifungals, and macrolides. Many of these medications are also inducers, inhibitors or both. Therefore, the drug interactions may be complex and difficult to predict.

Exhibit 4 lists the common inducers and inhibitors of CYP 3A4 metabolism. As an example, rifampin can increase the metabolism of PIs so dramatically that it nullifies the impact of the ARV medication. Because of this, rifampin is not used in combination with PIs. There is growing evidence that rifampin can be given with efavirenz. This is important because there are lots of patients who are infected with both tuberculosis and HIV. Rifabutin is a less potent inducer and can be used with PIs.

Inhibition of CYP 3A4 by ritonavir is an example of a successful drug interaction. Ritonavir is designed to inhibit its own metabolism. It also inhibits the metabolism of many of the heavily metabolized PIs and low doses are used to “boost” levels of these agents.

In choosing a lipid-lowering agent, drug interactions with the patients ARV regimen must be considered.

Exhibit 4: CYP3A4 Inducers and Inhibitors

Inducers

Rifamycins – rifampin, rifapentine, rifabutin
NNRTIs – nevirapine, efavirenz
Anticonvulsants – phenobarbital, carbamazepine, phenytoin
Herbs – St. John's Wort (Hypericum), garlic, milk thistle

Inhibitors

Grapefruit juice
Azoles – ketoconazole, itraconazole, voriconazole, fluconazole, terbinafine
Macrolides – erythromycin, clarithromycin, azithromycin
Protease Inhibitors – ritonavir > indinavir /nelfinavir/ tipranavir/ atazanavir/ lopinavir > saquinavir
NNRTI – Efavirenz can give mixture of induction and inhibition

Some PIs interact with statins. Ritonovir and nelfinavir inhibit statin metabolism.⁵ These two agents significantly increase the serum concentration of simvastatin which can cause significant toxicity. Simvastatin should not be used in patients who are on a boosted PI regimen. Atorvastatin metabolism is also significantly affected but to a lesser degree. If atorvastatin is used in combination with ritonavir or nelfinavir, a low dose should be used. Pravastatin and rosuvastatin have the least interaction with PIs. Exhibit 5 lists those lipid-lowering agents which are low risk to use with PIs.⁵⁻⁸ There is a trade off in choosing between pravastatin and rosuvastatin. Pravastatin is less potent but rosuvastatin is newer and there are less data on using it in combination with ARVs.

Efavirenz can be both an inducer or inhibitor. It gives a net induction of P450 for simvastatin, atorvastatin, and pravastatin. The dose of these statins will most likely need to be increased when used in combination with efavirenz.

The Infectious Diseases Society of America published recommendations on approaching hyperlipidemia treatment in the HIV patient.⁹ If LDL or non-HDL cholesterol (total cholesterol minus HDL) is elevated and TGs are less than 500 mg/dL, these guidelines recommend starting pravastatin 20 mg daily. If the patient's goal is not met, the dose can be increased to 40 mg daily. If the goal is still not met on 40 mg daily, the patient can be switched to low dose atorvastatin (10mg). Rosuvastatin may be useful from an interactions standpoint but can cause proteinuria. Because patients with HIV are already at risk for HIV induced nephropathy, drug-induced proteinuria is a problem. If lipid goals cannot be reached with statin monotherapy, ezetimibe (Zetia), a

Exhibit 5: Which Lipid-lowering Drugs are best for HIV-infected persons on PIs?

Low Risk	Uncertain Risk	Contraindicated
Fibrates Pravastatin Fluvastatin Rosuvastatin	Fibrate + Statin Atorvastatin	Simvastatin Lovastatin

cholesterol absorption inhibitor, can be added. When TGs are greater than 500 mg/dL, the patient should be started on a fibrate. If the patient does not reach goal on a fibrate alone, combination therapy with a statin can be considered but the patient should be monitored closely for liver dysfunction and myopathy.

Simvastatin and lovastatin are contraindicated with ARV therapy. Patients started on any lipid-lowering agent should be monitored for adverse effects. HIV can be associated with myositis, which can make identifying statin induced myositis difficult. Caution should be exhibited when combining statins and fibrates.

Conclusion

Many patients with HIV infection are going to require lipid-lowering therapy. The ARV regimen the patient is receiving needs to be considered when choosing a lipid-lowering therapy. Because many ARVs interact with the statins, the agent with the least interactions, pravastatin, is typically chosen as first line therapy. **JMCM**

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The release date of this activity is May 1, 2008. CME/CEU Credit is available through May 1, 2009. Post tests post marked after May 1, 2009 will not be considered for continuing education credits.

1. The current DHHS guidelines recommend antiretroviral therapy for all patients with CD4 counts of:

- a. < 350 cells/mm³
- b. < 500 cells/mm³
- c. 250 cells/mm³
- d. 100 cells/mm³

2. Which of the following tests should be considered before abacavir is prescribed?

- a. Coreceptor tropism assay
- b. HLA-B*5701 screening
- c. P450 3A4 polymorphism
- d. Vitamin B12 levels

3. Which of the following is the primary goal of antiretroviral therapy for HIV infection?

- a. Eradication of the virus
- b. 75 percent decrease in viral load
- c. Less than 25 percent of total viral load resistant to medication
- d. Complete virologic suppression (<50 copies/ml)

4. Which of the following is NOT a reason for resistance testing?

- a. Suboptimal suppression of viral load after starting antiretroviral therapy
- b. Virologic failure during antiretroviral therapy
- c. Possible HIV exposure in a health care professional
- d. Chronic HIV infection, at entry into care

5. Which of the following statins has the fewest drug interactions with antiretroviral therapy?

- a. Atorvastatin
- b. Lovastatin
- c. Simvastatin
- d. Pravastatin

6. Which of the following antiretroviral agents is used because it interacts with cytochrome P450 and thus increases levels of other antiretroviral agents?

- a. Lopinovir
- b. Saquinavir
- c. Ritonovir
- d. Nelfinavir

7. Which of the following does NOT make women more susceptible than men to contracting HIV through heterosexual intercourse?

- a. Presence of other sexually transmitted disease
- b. Substance abuse
- c. Stage of disease in partner
- d. Use of oral contraceptives

8. Which of the following groups of women are disproportionately infected with HIV?

- a. Whites
- b. Hispanics
- c. Blacks
- d. Asians

9. Which of the following factors increase risk for oncogenic HPV infection in HIV infected women?

- a. older age
- b. high HIV viral loads
- c. high CD4 counts
- d. non-smoker

10. Which of the following antiretroviral agents should be avoided during pregnancy?

- a. efavirenz
- b. nelfinavir
- c. didanosine/stavudine
- d. All of the above

ANSWER SHEET for HIV TREATMENT GUIDELINES

There is only one correct answer per question.

Circle your answer clearly.

1. a b c d
2. a b c d
3. a b c d
4. a b c d

5. a b c d
6. a b c d
7. a b c d
8. a b c d
9. a b c d
10. a b c d

EVALUATION

Credit will not be issued without a completed evaluation form.

Please rank the following. Circle your answer.

(1=strongly disagree, 4=strongly agree)

1. As a result of my participation I am better able to:

- | | |
|---|---------------|
| Discuss the US Department of Health and Human Services Treatment Guidelines for HIV | 1 2 3 4 |
| Identify contradictions in treatment regimens | 1 2 3 4 |
| Review diagnostic, treatment and outcome concerns for women of childbearing age | 1 2 3 4 |
| Identify the impact of over the counter and lipid drug interactions with antiretroviral treatment | 1 2 3 4 |

2. The content was:

- | | |
|--|---------------|
| Current and relevant | 1 2 3 4 |
| Well-organized and effectively written | 1 2 3 4 |
| Free of commercial bias | 1 2 3 4 |
| Useful in improving patient care | 1 2 3 4 |

3. This method of learning is very beneficial to me.

1 2 3 4

4. As a result I will change my behavior/practice patterns by:

- Having all providers review the HHS Guidelines for HIV.
- Educating providers on appropriate treatment for certain populations.
- Educating members who are at high risk for HIV.
- I will not change.

5. What other topics are of interest to you?

Continuing education implies quality improvement/change in behavior. As part of our quality improvement process, NAMCP will contact you six months from your post test submission to determine the impact of this activity on practice patterns.

First Name _____

Last Name _____

MD DO RN Other

Title _____

Company _____

Mailing Address _____

Phone: _____

Fax: _____

E-mail _____

Send my certificate by:

U.S. Mail E-mail

