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Women and HIV Treatment: Recently Reported Data

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Nursing Credit for this activity will be provided through June 30, 2010.

Sponsor
Sponsored by the University of Medicine and Dentistry of New Jersey (UMDNJ), Center for Continuing and Outreach Education. This activity is supported by an educational grant from NJDHSS Division of HIV/AIDS Services through a MOA titled “Education and Training for Physicians and other Healthcare Professionals in the Diagnosis and Treatment of HIV/AIDS.”

Target Audience
This activity is designed for physicians and nurses, and for other health care professionals in New Jersey who are involved in the care of women and/or persons with HIV/AIDS.

Statement of Need
Since the beginning of the HIV/AIDS epidemic, researchers, clinicians, patients and advocates have raised concerns about whether women with HIV infection have different disease manifestations or response to treatments. Women with HIV/AIDS are now included in almost all clinical trials of HIV treatments, although there are often restrictions related to protection of women and fetuses, for women of child-bearing age. The USDHSS HIV treatment guidelines published in January 2008 included a section titled “Considerations For Antiretroviral Use In Special Patient Populations: HIV-Infected Women of Reproductive Age and Pregnant Women.”

Updated guidelines published in November 2008, referenced in this article, continue the previous specific recommendations for treatment of women.


Learning Objectives
On the completion of this activity, participants should be able to:
1) Summarize the epidemiology of HIV infection in US women
2) Identify antiretroviral drug interactions with oral contraceptives and changes in pharmacokinetics that may occur with antiretroviral dosing in pregnancy
3) Describe recent antiretroviral clinical trial results, including comparison of outcomes among men and women.

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Method of Instruction
Participants should read the learning objectives and review the activity in its entirety. After reviewing the material, complete the self-assessment test which consists of a series of multiple-choice questions. Upon completing this activity as designed and achieving a passing score of 70% or more on the self-assessment test, participants will receive a credit letter and the test answer key four (4) weeks after receipt of the self-assessment test, registration, and evaluation materials; or may complete the activity on the internet at www.umdnj.edu/ccoed. Estimated time to complete this activity is designed is 1.25 hours.

Accreditation
Physicians: UMDNJ-Center for Continuing and Outreach Education is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. UMDNJ-Center for Continuing and Outreach Education designates this educational activity for a maximum of 1.25 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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This activity is awarded 1.25 contact hours.

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Review:
This activity was peer reviewed for relevance, accuracy of content, and balance of presentation by Patricia Kloser, MD, MPH; Debbie Y. Mohammed, MS, MPH, APRN-BC, and Brenda Christian, MED, PA-C; and pilot tested for relevance and time required for participation by Kinshasa Morton, MD; Bonnie Abединi, MSN, RN; Mary C. Krug, RN, MSN, APN-C; and Kara Winslow, BSN, RN.

Faculty Disclosure Declarations
Dr. Hodder has disclosed the following: She was on the speaker's bureau of BMS, has received grant/research support from BMS, Gilead, Tibotec and Pfizer; has been a consultant on advisory boards for: BMS, Gilead, Tibotec, and Boehringer-Ingelheim; and is a shareholder of Merck. Debbie Mohammed has disclosed the following: she is on the speaker's bureaus of BMS and Gilead.

Conflicts of interest were resolved by review by Activity Director Patricia Kloser, MD, MPH.

The following have no financial relationships to disclose: Activity Director Patricia Kloser, MD, MPH; Planning committee members Sindy M. Paul, MD, MPH, FACPM; Linda Berezny, RN, BA; and Kimi Nakata, MSW, MPH (editor); content reviewer Brenda Christian, MED, PA-C; and field testers: Kinshasa Morton, MD; Bonnie Abединi, MSN, RN; Mary C. Krug, RN, MSN, APN-C; and Kara Winslow, BSN, RN.

Off-Label Usage Disclosure
This activity contains information about commercial products that are unlabeled for use or investigational uses of products not yet approved: Vicriviroc is currently in Phase II/III clinical trials. Darunavir is in FDA Pregnancy Category B, and lopinavir/ritonavir is in FDA Pregnancy Category C; each should be used only if the potential benefit justifies the potential risk.

Disclaimer
The views expressed in this activity are those of the faculty, It should not be inferred or assumed that they are expressing the views of NJDHSS-Division of HIV/AIDS Services, UMDNJ, or any manufacturer of pharmaceuticals. The drug selection and dosage information presented in this activity are believed to be accurate. However, participants are urged to consult the full prescribing information on any agent(s) presented in this activity for recommended dosage, indications, contraindications, warnings, precautions, and adverse effects before prescribing any medication. This is particularly important when a drug is new or infrequently prescribed.

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Women and HIV Treatment: Recently Reported Data

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Learning Objectives

Upon completion of this learning activity, the participant should be able to:

1. Summarize the EPIDEMIOLOGY of HIV infection in US women.
2. Identify antiretroviral DRUG INTERACTIONS with ORAL CONTRACEPTIVES and changes in PHARMACOKINETICS that may occur with antiretroviral DOSING IN PREGNANCY.
3. Describe recent ANTIRETROVIRAL CLINICAL TRIAL RESULTS, including COMPARISON of outcomes among MEN & WOMEN.

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Sally Hodder, MD, is Professor of Medicine, Vice Chair and Director of HIV Programs, Department of Medicine, New Jersey Medical School, University of Medicine and Dentistry of New Jersey. She previously served as the Vice President of U.S. Virology Medical Affairs at Bristol Myer Squibb. Dr. Hodder is a frequent contributor to Clinical Care Options webcasts and other medical education activities. She presented a poster on clinician provision of reproduction counseling to HIV-infected women at the 2008 International AIDS Conference in Mexico City.

To obtain continuing education credit, complete the quiz, registration, and evaluation on the following pages, or go to: www.umdnj.edu/ccoe/aids

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**Case No. 1**

Ms. J. is a 47-year-old Black woman who presents with fever, oral ulcers, pharyngitis, and cervical lymphadenopathy. Work-up to date is negative, though Ms. J. elected to opt out of HIV testing because she feels that she is not at risk. She states that she has never used illicit drugs of any sort and has had a monogamous sexual partner (though he never uses condoms). After further discussion, Ms. J. agrees to HIV testing and is found to have a positive rapid test and an indeterminate Western Blot.

**COMMENT:** Though Ms. J. presents with symptoms suggestive of acute retroviral syndrome, these symptoms are also consistent with a number of other diagnoses. In a prospective cohort study, Hecht et al. found that fever (Odds ratio 5.2; 95% CI 2.3-11.7) and rash (Odds ratio 4.8; 95% CI 2.4-9.8) were strongly associated, by multivariate analysis, with the presence of acute retroviral infection. The Western Blot should be repeated in several weeks, and HIV RNA testing may be helpful in defining likely presence of HIV infection.

The CDC recently estimated that:

- 56,300 HIV new infections occur annually in the U.S., a more accurate estimate than previous approximations of 40,000 annual new U.S. infections.²
- Noteworthy is that 27% of U.S. infections now occur in women,³ an increase from 20 years ago. Black women are disproportionately affected, constituting 66% of US women with HIV infection in 2005, but only 13% of the US female population.⁴ ⁵
- Many women perceive themselves to be at “low risk” for HIV infection as does Ms. J. In a survey of obstetricians and gynecologists, Gray, et al. reported that the major reason women decline HIV testing is that they reportedly believe themselves to be at low risk for HIV acquisition.⁶
- Black women without high risk behaviors may be at increased risk for HIV acquisition compared with their white counterparts.
- Hallfors, et al., in a study population of 8,706 non-Latino blacks and whites 18-26 years of age, found that in a subgroup of individuals with low risk behaviors, both Black men and women were 25 times more likely than their white counterparts to acquire a sexually transmitted infection (STI) and/or HIV infection. These data suggest that the risk of STI and HIV infection is not only associated with their behaviors but also with the risk behaviors of their partners or other unmeasured factors.⁷
Ms. L. is a 33-year-old woman who comes to your office for routine HIV follow-up. She has been aware of her HIV infection for the past year and has been followed at another clinic. She advises you that she has never had any opportunistic infections; however, she has been told that she should consider starting antiretroviral therapy. Physical examination is normal, her most recent CD4+ count is 320 cells/mm³, and her HIV RNA viral load is 110,000 copies/ml. You and she decide that it is time to start antiretroviral therapy. Which of the following do you choose?

A  Efavirenz + zidovudine/lamivudine as a fixed dose combination because current data suggest that efficacy is better than the alternatives.

B  Efavirenz/tenofovir/emtricitabine as a fixed dose combination because recent data indicate that time to virologic failure is longer with this combination compared with alternatives.

C  Lopinavir/ritonavir (fixed dose combination) + abacavir/lamivudine because the incidence of lipoatrophy is less than with efavirenz-based regimens.

D  Darunavir + ritonavir + tenofovir/emtricitabine because recent 96-week trial data in antiretroviral naive patients demonstrate superiority to lopinavir/ritonavir-based therapy.

E  Further discussion with the patient to determine her toxicity concerns regarding antiretroviral therapy as well as her reproductive needs.

Efavirenz (EFV), a component of regimens in answers A and B, is classified as an FDA Pregnancy Category Class D drug; animal data show an increased risk of central nervous system (CNS) defects and there have been several retrospective reports of CNS defects in infants exposed to efavirenz.10 As the neural tube forms in the first month of pregnancy, EFV should not be used in women of child-bearing potential unless a barrier form of contraception as well as another method of contraception (e.g., hormonal contraception) are consistently used. In addition, a negative pregnancy test result should always be documented before initiation of EFV. Tenofovir/emtricitabine combined with efavirenz has been demonstrated to have superior durability of virologic control as well as an improved safety profile compared with zidovudine/lamivudine combined with efavirenz,11 and less lipoatrophy has been reported with lopinavir/ritonavir-containing regimens when compared to efavirenz regimens.12 Noteworthy, is that the November 3, 2008 Department of Health and Human Services (DHHS) Guidelines continue to recommend tenofovir with either lamivudine or emtricitabine as the preferred nucleoside reverse transcriptase inhibitor (NRTI) backbone.13

The combination of Abacavir + lamivudine was recently moved from preferred to alternative NRTI status in the DHHS guidelines for two reasons:

1) IN ACTG (AIDS Clinical Trials Group) 5202, a large randomized study in treatment naïve persons comparing tenofovir/emtricitabine to abacavir/lamivudine when used in combination with either efavirenz or with atazanavir/ritonavir, the Data Safety Monitoring Board (DSMB) recommended termination of the study in participants with starting viral loads ≥100,000 copies/ml, as data demonstrated a shorter time to virologic failure if they had been randomized to abacavir/lamivudine (ABC/3TC) compared to individuals randomized to tenofovir/emtricitabine (TDF/FTC).14 Participants with starting viral loads <100,000 copies/ml remain on study. It is noteworthy that 96-week data from a smaller study (the HEAT Study) comparing ABC/3TC to TDF/FTC, each in combination with lopinavir/ritonavir, did not demonstrate significant differences in the proportion of virologically suppressed patients with starting viral loads ≥100,000 copies/ml among participants randomized to the two arms.15

2) TWO STUDIES have indicated an increased incidence of myocardial infarction among patients currently (or within six months) of taking abacavir.16,17 Though a pooled analysis of clinical trials involving 9,639 patients taking abacavir (compared with 5,044 participants not taking abacavir) did not reveal an elevated risk of myocardial infarction,18 the guidelines committee concluded that ABC/3TC should be used with caution in patients with HIV RNA viral loads >100,000 copies/ml or with increased cardiovascular risk.19 Ritonavir boosted darunavir with tenofovir/emtricitabine has been shown to be superior to lopinavir/ritonavir + tenofovir/emtricitabine.19 However, there are scant data on use of darunavir in pregnant women. It is noteworthy that ritonavir-boosted darunavir was designated as a “preferred” protease inhibitor in the most recent DHHS guidelines.13

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Multiple presentations at recent conferences have addressed issues of women living with HIV. The Women Living Positive survey, an anonymous phone interview of 700 HIV-infected women (43% Black, 29% Latino, and 29% Caucasian) who had lived with HIV infection a mean of 10.6 years (8.1 years on antiretroviral therapy), found that nearly half (48%) of the survey respondents were never asked by their health care provider about their current or future childbearing plans. Clearly, HIV care providers are missing important opportunities to discuss contraception and preconceptional care, particularly as relates to antiretroviral treatment. As highlighted in the above case presentation, an important factor in antiretroviral agent selection is the reproductive intention of the patient.

Antiretroviral agents may have a wide range of effects on oral contraceptive hormone levels.

A study of the interaction of oral contraceptives agents with vicriviroc or SCH-D (a new CCR5 antagonist in development) demonstrated no significant interaction per se with vicriviroc.21 Another recently reported study of women given oral contraceptives and efavirenz, presented at the 2008 ICAAC/IDSA conference in Washington DC, demonstrated that ethinyl estradiol levels were not altered, however, norelgestromin, a metabolite of progestin as well as levonorgestrel (an active component of some oral contraceptive agents) were decreased.22 Therefore, a barrier contraceptive is recommended in addition to oral contraceptive agents in women taking efavirenz to assure effective contraception as well as effective protection against HIV transmission. Studies of protease inhibitors’ effects on levels of oral contraceptives have demonstrated decreased ethinyl estradiol levels with ritonavir23 and lopinavir/ritonavir,24 but increased levels with atazanavir.24

By and large, levels of antiretroviral agents are in most cases unaffected by the presence of oral contraceptive agents. There is one prominent exception; amprrenavir levels, and probably fosamprenavir levels, are decreased, leading to a recommendation in the package insert that alternative methods of non-hormonal contraception should be used when taking fosamprenavir.25 One note of caution with progesterone only contraception was recently reported at the Mexico City IAC meeting. Investigators of the Women’s Interagency HIV Study (WHIS), a cohort of HIV infected and uninfected women, found that use of progestin-only contraception was associated with reduced HDL levels and increased insulin resistance.26

Several recently presented studies have addressed the issue of antiretroviral use in pregnancy.

Many physiologic changes occur during pregnancy; therefore, pharmacokinetic study results of several drugs have recently been reported. An interim analysis of pregnant women receiving atazanavir (300 mg daily) boosted with ritonavir (100 mg daily) together with zidovudine/lamivudine (300/150 mg twice daily) found that atazanavir exposure expressed as AUC and the Cmin levels were decreased 40% and 21% respectively for women in the third trimester of pregnancy compared with historical controls.27 Based on these findings, the investigators recommended increasing the atazanavir dose for HIV-infected women in the third trimester of pregnancy. At four weeks postpartum, the atazanavir drug levels were higher than historical controls, suggesting that pharmacokinetics revert to the non-pregnant state soon after delivery. Lower drug levels have also been demonstrated during the third trimester of pregnancy in women taking lopinavir/ritonavir (LPV/r),28 and a recent study suggests that LPV/RTV (600/150 mg twice daily) be considered for use in the third trimester of pregnancy to assure appropriate LPV exposure.29 However, when emtricitabine, a nucleoside reverse transcriptase inhibitor, pharmacokinetics were assessed in pregnancy, AUC decreased just 12%, precluding need for dose adjustment.29

Questions regarding birth defects in infants born to women on antiretroviral agents, however, remain.

The Antiretroviral Pregnancy Registry (APR) was established in 1989 to prospectively collect data on birth outcomes following antiretroviral exposure during pregnancy. Though this is an international registry, most of the reported data have, in fact, come from the U.S. The APR recently reported on birth defects rates from 987 women who took LPV/r during pregnancy, noting that this sample size was sufficient to detect a 2.4-fold increase in the risk of birth defects. The reported birth defect rate in this study of LPV/r exposed pregnancies was 2.4%, similar to the rate of 2.67% observed in the Metropolitan Atlanta Congenital Defects Program (MACDP) which was the control population.30 The prevalence of birth defects following first trimester LPV/r exposure was 1.9%, again similar to the 2.09% first trimester early diagnosis rate of birth defects in the control population.30 These results are the first adequately powered reported results for risk of birth defects in infants exposed to antiretroviral agents in utero. The Pregnancy Registry is an important available resource that assesses pregnancy outcomes. Health-care providers are asked to prospectively (before outcome of pregnancy is known) register women exposed to antiretroviral agents during pregnancy. Further information on the antiretroviral pregnancy registry is available at www.apregistry.com.

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In recent years, women have participated in trials of new antiretroviral agents in sufficient numbers to permit assessment of outcomes based on sex, and such data from several trials were presented at the IAC meeting in Mexico City. The CASTLE study was a prospective, open-label randomized trial in treatment naive persons comparing atazanavir/ritonavir (ATV/r) with lopinavir/ritonavir (LPV/r), both with tenofovir/ritonavir as the NRTI backbone. Overall in the Intention to Treat (ITT) analysis, the proportion of participants with HIV-1 RNA <50 copies/ml at week 48 (the primary endpoint) was 78% in the ATV/r arm and 76% in the LPV/r arm. Women constituted 31% of the CASTLE study population and evaluation of virologic outcomes in men and women did not demonstrate any significant differences; 76% of women and 79% of men in the ATV/r arm compared with 73% of women and 78% of men in the LPV/r arms achieved HIV RNA <50 copies/ml. CD4+ count increases at 48 weeks were also similar; 199 cells/mm³ and 205 cells/mm³ in women and men respectively in the ATV/r arm compared with 221 cells/mm³ and 219 cells/mm³ in women and men respectively in the LPV/r arm. Side effects were generally similar among men and women with the exception that women were more likely to experience nausea in both arms of the study (7% and 3% in women and men respectively receiving ATV/r: 14% and 5% for women and men respectively receiving LPV/r), though women in the LPV/r arm were less likely than men to experience diarrhea (9% and 12% respectively).

Trial results were also analyzed by sex in the ARTEMIS Trial, a prospective, multicenter, randomized trial comparing once daily darunavir/ritonavir (DRV/r) at 800 mg/100 mg with LPV/r each in combination with tenofovir/emtricitabine in antiretroviral-naive patients. Overall, at 96 weeks, 79% of participants in the DRV/r arm had <50 copies/ml compared with 71% of participants in the LPV/r arm, thereby establishing superiority of DRV/r compared with LPV/r (p for superiority, <0.012). Women constituted approximately 30% of ARTEMIS participants, and an analysis of 48-week outcomes by sex was recently presented. Eighty-four percent of both men and women in the DRV/r arm attained an HIV-1 RNA viral load <50 copies/ml at 48 weeks. Women in the ARTEMIS trial were more likely to experience vomiting (11%) compared with men (4%). A sex-based analysis of the 96 week data has not been presented.

Finally, sex-specific outcomes data were also presented for the M05-730 trial, a multicenter, prospective, randomized trial in antiretroviral naïve patients comparing once daily LPV/r with twice daily LPV/r, each in combination with tenofovir/emtricitabine. The week 48 primary efficacy endpoint demonstrated that approximately 77% of participants in the once daily arm and 76% in the twice daily arm attained virologic suppression (HIV RNA <50 copies/ml). Seventy-two percent of women and 78% of men achieved HIV-1 RNA <50 copies/ml at week 48, a difference that was not statistically significant. Immunologic recovery was similar in men and women with the exception that for those individuals with baseline CD4+ counts <50 cells/mm³, mean CD4+ increase in women was 237 cells/mm³, while in men it was 167 cells/mm³ (p=0.007). Adverse events were similar among men and women, however, grade 3 and grade 4 triglyceride abnormalities were less frequent in women than men (0.7% vs. 5.6% respectively; p=0.011).

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Women and HIV Treatment:Recently Reported Data

IN CONCLUSION, a great deal of data has been presented at recent meetings addressing efficacy, safety and tolerability of antiretroviral agents, and recent DHHS guidelines updated on November 3, 2008 have reflected findings from some of the recently presented data.

There are EMERGING DATA on pharmacokinetics of specific antiretroviral agents during pregnancy suggesting that dose modifications may be required for at least some protease inhibitors, and data on birth defect rates after in utero antiretroviral exposures are starting to emerge and, at least with lopinavir/ritonavir, are reassuring.

TO DATE, sex based significant differences in virologic and immunologic responses to antiretroviral therapy have not been seen with the exception of better CD4⁺ count responses in women with baseline CD4⁺ counts <50 cells/mm³ in the M05-730 trial.

Finally, HIV care providers MUST TAKE THE INITIATIVE WITH ALL PATIENTS to discuss expectations and fears regarding antiretroviral therapy toxicity, assure clarity in regard to prevention of HIV transmission, and take the opportunity to discuss contraception and preconceptive care, particularly as relates to antiretroviral treatment and prevention of HIV transmission.

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REFERENCES

REFERENCES


34. Gathe J, da Silva BA, Loutfy M, et al. Study MO5-730 Primary Efficacy Results at Week 48: Phase 3 randomized, open-label study of lopinavir/ritonavir (LPV/r) tablets once daily (QD) versus twice daily (BID), co-administered with tenofovir DF (TDF) + emtricitabine (FTC) in antiretroviral-naive HIV-1 infected subjects. 15th Conference on Retroviruses and Opportunistic Infections (CROI); February 3-6, 2008. Boston, USA.