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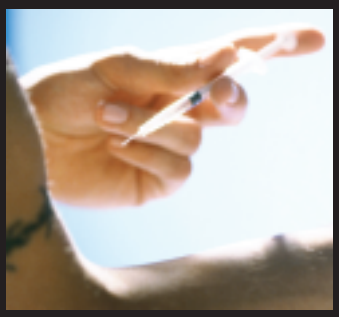

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Save The Dates

June 12, 2008
HIV Clinical Update 2008: The NJ Statewide Symposium

April 11, 2008
ANAC-NJ Day of Learning

The 2007 HIV Diagnostics Conference

CDC and APHL discuss new directions in HIV testing after 22 years

Sindy M. Paul, MD, MPH, FACPM

THE 2007 HIV Diagnostics Conference, co-sponsored by the Centers for Disease Control and Prevention (CDC) and the Association of Public Health Laboratories (APHL), was held December 5-7, 2007 in Atlanta, Georgia. HIV testing started with the development of a first generation enzyme immunoassay (EIA) in 1985 and approval of the Western blot (WB) as a supplemental confirmatory test in 1987. CDC and APHL recommended the combination of an EIA and a WB as the "gold standard" for the diagnosis of HIV infection in 1989.

Many HIV diagnostic tests have been approved for use in the United States since 1989. A single algorithm using the EIA and WB is no longer able to provide cost-effective screening, point-of-care testing (POCT) with a short turn-around time of results, and identification of acute infection. During the past five years, the Food and Drug Administration (FDA) has approved six rapid HIV tests (four of which are CLIA-waived for POCT); two third generation EIA tests that can detect HIV-1, HIV-2, and HIV-Group O; a qualitative diagnostic RNA assay; and new quantitative viral load assays. Additional HIV tests may soon be available in the United States, including a fourth generation EIA.

CDC and APHL have established two work groups to develop the new strategies and algorithms. One work group is developing the laboratory-based algorithms, while the other group is working on the POCT algorithms. New Jersey is well represented on the POCT Algorithm Work Group by Sindy M. Paul, MD, MPH, FACPM, Evan Cadoff, MD, and Eugene Martin, PhD. The Work Group has developed four draft POCT algorithms and five draft laboratory algorithms, which are available at http://www.hivtestingconference.org/hta.htm.

Several dilemmas have emerged in HIV testing that need to be addressed with the new strategies. With the September 2006 CDC recommendations to test all persons 13 to 64 years of age, more screening is being done of low prevalence populations. False positive WB results are problematic. Current supplemental confirmatory tests, such as WB, are now less sensitive than some of the screening EIA tests. Because some of the third generation EIAs can detect HIV earlier than the currently approved confirmatory tests, a screening test could accurately detect HIV infection while the confirmatory test would inaccurately indicate that the patient is not infected. These discordant results could delay access to treatment, entrance into prevention for positive programs, and inhibit access to social programs. As presented at the conference by the New Jersey Department of Health and Senior Services – Robert Wood Johnson Medical School Rapid HIV Testing Program, this delay is minimized at publicly funded counseling and testing sites in New Jersey by obtaining a specimen for Nucleic Acid Assay Testing (NAAT) when the confirmatory test specimen is obtained.[1]

(Continued on page 29)

APHL: Association of Public Health Laboratories
CDC: Centers for Disease Control and Prevention
CLIA: Clinical Laboratory Improvement Amendments of 1988, legislation assuring the accuracy of tests
EIA: Enzyme immunoassay
WB: Western blot
POCT: Point-of-care testing

CONTINUING EDUCATION INFORMATION

Role of Newly-Approved HIV Antiretroviral Agents in Treatment-Experienced Patients

Release Date: January 1, 2008 • Exp. Date: December 31, 2009 • Course Code: 09HC08-DE01

Sponsorship

Sponsored by the University of Medicine & Dentistry of New Jersey (UMDNJ), UMDNJ-Center for Continuing & 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 persons with HIV/AIDS.

Statement of Need

In NJ and other areas of high HIV/AIDS prevalence, many HIV-positive patients have taken multiple treatment regimens, and their virus has become resistant to multiple classes of HIV medications. Drug interactions and toxicity also led to the need to change from first-line and salvage therapies for HIV patients who have become "treatment-experienced" or resistant to more than one medication or class of medications.

In 2007, two new agents in two new antiretroviral classes were approved by the FDA for use with treatment-experienced HIV patients. Maraviroc is an entry inhibitor, which was FDA approved on August 6, 2007 for treatment-experienced HIV adults infected with only CCR5-tropic HIV-1 strains resistant to multiple antiretroviral agents. Raltegravir, an Integrase inhibitor, was FDA approved on October 12, 2007 for the treatment of HIV-1 infection in treatment-experienced adult patients who have HIV-1 strains that are resistant to multiple antiretroviral agents.

New antiretroviral agents can only be prescribed once there is laboratory confirmation, through genotypic tests, that the patient's HIV strain will respond to these specific treatments.

Learning Objectives

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

1. Outline the signs and test results that would document that a patient has developed toxicity and/or resistance to their current therapy.
2. Discuss the role of integrase inhibitors in treatment experienced HIV-positive patients.
3. Identify the role of entry inhibitors in treatment experienced HIV-positive patients.
4. Explain viral tropism and the role of tropism testing in the management of HIV patients.

Method of Instruction

Participants should read the learning objectives and review the activity in its entirety, review the material, and complete the self-assessment test, a series of multiple-choice and True/ False 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 form. Estimated time to complete this activity as designed is 1.25 hours.

Accreditation

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

Nurses: UMDNJ-Center for Continuing & Outreach Education is an approved provider of continuing nursing education by the New Jersey State Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.

This activity is awarded 1.25 contact hours. (60 minute CH)

Provider approved by the California Board of Registered Nursing, Provider Number CEP 13780.

Review: The activity was prepared in accordance with the ACCME Essentials. This activity was reviewed for relevance, accuracy of content, balance of presentation, and time required for participation by Patricia C. Kloser, MD, MPH, FACP. This activity was reviewed for relevance, accuracy of content, balance of presentation, and time required for participation by Bonnie Abedini, RN, MSN; Mary C. Krug, RN, MSN, APN-C; and Debbie Y. Mohammed, MS, MPH, APRN-BC, AACRN.

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Faculty Disclosure Declarations

The following have no financial relationships to disclose: authors: Amrita Kaur, DO; Sindy M. Paul, MD, MPH, FACPM; Patricia C. Kloser, MD, MPH, FACP; editor: Kimi Nakata, MSW, MPH and field testers: Bonnie Abedini, BSN, MS; Mary C.Krug, RN, MSN, APN-C, and Debbie Y. Mohammed, MS, MPH, APRN-BC, AACRN.

Off-Label Usage Disclosure

This activity does not contain information of commercial products/devices that are unlabeled for use or investigational uses of products not yet approved.

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.

Editor's note

Following the American Medical Association guideline, UMDNJ-CCOE will list trade names with capital letters but will no longer note ® and T status of medications, as the US Federal Dilution Trademark Act does not require these designations in publications.

[1] Iverson C, Christiansen S, Flanagin A, et al. AMA Manual of Style: A Guide for Authors and Editors. 10th ed. New York, NY: Oxford University Press; 2007.

Role of Newly-Approved HIV Antiretroviral Agents in Treatment-Experienced Patients

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

1. Outline the signs and test results that would document that a patient has developed toxicity and/or resistance to their current therapy.
2. Discuss the role of integrase inhibitors in treatment experienced HIV-positive patients.
3. Identify the role of entry inhibitors in treatment experienced HIV-positive patients.
4. Explain viral tropism and the role of tropism testing in the management of HIV patients.

Amrita Kaur, DO and Sindy M. Paul, MD, MPH, FACPM

INTRODUCTION

IN NEW JERSEY and other areas of high HIV/AIDS prevalence, many HIV patients have taken multiple treatment regimens, and their HIV has become resistant to multiple classes of HIV medications. Drug interactions and toxicity have also led to the need for changes from the first-line and available salvage therapies for people with HIV/AIDS who have become "treatment-experienced" or resistant to more than one medication or class of medications.

In 2007, **two new agents** in two new antiretroviral classes were approved by the FDA for use with treatment-experienced HIV patients. **Maraviroc** is an entry inhibitor, which was FDA approved on August 6, 2007 for treatment-experienced HIV adults infected with only CCR5-tropic HIV-1 strains resistant to multiple antiretroviral agents. **Raltegravir,** an integrase inhibitor, was FDA approved on October 12, 2007 for the treatment of HIV-1 infection in treatment-experienced adult patients who have HIV-1 strains that are resistant to multiple antiretroviral agents.

New antiretroviral agents can only be prescribed once there is laboratory confirmation, through genotypic/phenotypic tests, that the patient's HIV strain will respond to these specific treatments

One of the greatest challenges for clinicians providing HIV care is managing treatment-experienced patients, who have developed resistance to multiple classes of antiretroviral medications. The clinician must know the history of treatment, resistance patterns identified through testing, and when and how to use new drugs for salvage therapy. Cross-resistance within the currently available antiretroviral classes has driven the development of agents from novel drug classes. The availability of new agents for treatment-experienced patients offers options for replacing existing agents which are no longer working.

(Continued on next page)

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TREATMENT GOALS

According to the December 1, 2007, U.S. Department of Health & Human Services guidelines for antiretroviral therapy in adults, the goal of treatment for all patients, regardless of their level of treatment experience and drug resistance, is to maximally suppress the HIV-1 RNA level.[1] The International AIDS Society-US guidelines from August 2006, state that the goal of achieving HIV-1 RNA <50 copies/ml should be achievable for most patients if newer antiretroviral agents are employed.[2]

UPDATED GUIDELINES:

Management of the Treatment-Experienced Patient

PANEL'S RECOMMENDATIONS:

- In treatment-experienced patients with suppressed viremia, assess adherence frequently and simplify the regimen as much as possible. Change individual antiretroviral drugs to reduce or manage toxicity, as needed.
- Evaluation of antiretroviral treatment failure in a patient should include an assessment of the severity of HIV disease of the patient; the antiretroviral treatment history, including the duration, drugs used, antiretroviral potency, adherence history, and drug intolerance/toxicity; HIV RNA and CD4 T-cell count trends over time; and the results of prior drug resistance testing.
- Virologic failure on treatment can be defined as a confirmed HIV RNA level >400 copies/mL after 24 weeks, >50 copies/mL after 48 weeks, or a repeated detectable HIV RNA level after prior suppression of viremia.
- Drug resistance testing should be obtained while the patient is taking the failing antiretroviral regimen (or within 4 weeks of treatment discontinuation) (AI).
- The goal of treatment for patients with prior drug exposure and drug resistance is to re-establish maximal virologic suppression, HIV RNA <50 copies/mL (AI).
- Use the treatment history and the past and current resistance test results to identify fully active agents to design a new regimen (AII). A fully active agent is one that is likely to demonstrate antiretroviral activity on the basis of both the treatment history and susceptibility on drug resistance testing. Adding at least two, and preferably three, fully active agents to an optimized background antiretroviral regimen can provide significant antiretroviral activity (BII).
- Immunologic failure can be defined as a failure to achieve and maintain an adequate CD4 response despite virologic suppression.
- For immunologic failure, current medications, untreated coinfection, and serious medical conditions should be assessed.
- There is no consensus for when and how to treat immunologic failure.
- Assessing and managing a patient who has antiretroviral experience, who exhibits drug resistance, and who is experiencing treatment failure is complex and expert advice is critical.

[1] USDHSS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. December 1, 2007.

INDICATIONS FOR CHANGING ARV REGIMENS

There are generally four indications for changing the antiretroviral regimen, which are reflected in the USDHHS guidelines in the table on this page.

1. **Drug-drug toxicity** (accounts for half of all regimen changes),
2. **Virologic failure** (defined as the failure to achieve a viral load <50 copies/ml by 24 weeks after initiation of antiretroviral regimen or any sustained return of the viral load to >50copies/ml),
3. **Difficulty adhering** to the regimen, and
4. **Sub-optimal current antiretroviral regimen**.

The most common causes of virologic failure with the recommended regimens are the development of resistance and inadequate adherence. The development of resistance to the current antiretroviral regimen is documented through the use of genotypic or phenotypic tests. Commercially available resistance tests generally require a viral load of at least 1000 copies/ml. In patients who are experiencing failure of an antiretroviral (ART) regimen, the goal is to select a regimen with at least three active ART medications. Patients with resistance to an NNRTI-based regimen will usually be resistant to all NNRTIs. In contrast, it may be possible to use alternate PIs or NRTIs in patients resistant to some members of those classes.[3]

Virologic failure often leads to the impression of non-adherence. If there is actual non-adherence, the clinician must determine if the patient is ready to adhere to an antiretroviral regimen, and what barriers may have contributed to inconsistent treatment in the past.

In patients who are experiencing failure of an antiretroviral regimen because of viral resistance, the goal is to select a regimen with preferably three, or minimally, two active antiretroviral medications.[2] Use of a single active agent usually leads to resistance to that particular drug and limits future treatment options.

Role of Newly-Approved HIV Antiretroviral Agents in Treatment-Experienced Patients

The FDA has approved use of specific medications in three classes of drugs for patients with multi-drug resistance.

FDA Approved

1. **Entry inhibitors:**
   a. Enfuvirtide (FuzeonT20)
   b. Maraviroc (Selzentry – FDA approved CCR5 co-receptor antagonist for treatment-experienced HIV adults with only CCR5-tropic HIV-1 strains resistant to multiple antiretroviral agents.
2. **Protease inhibitors:** darunavir and tipranavir
3. **Integrase inhibitors:** raltegravir (Isentress) approved by FDA for HIV treatment-experienced adult with HIV strains resistant to multiple antiretroviral agents.

There are three antiretroviral agents in development.

In Development

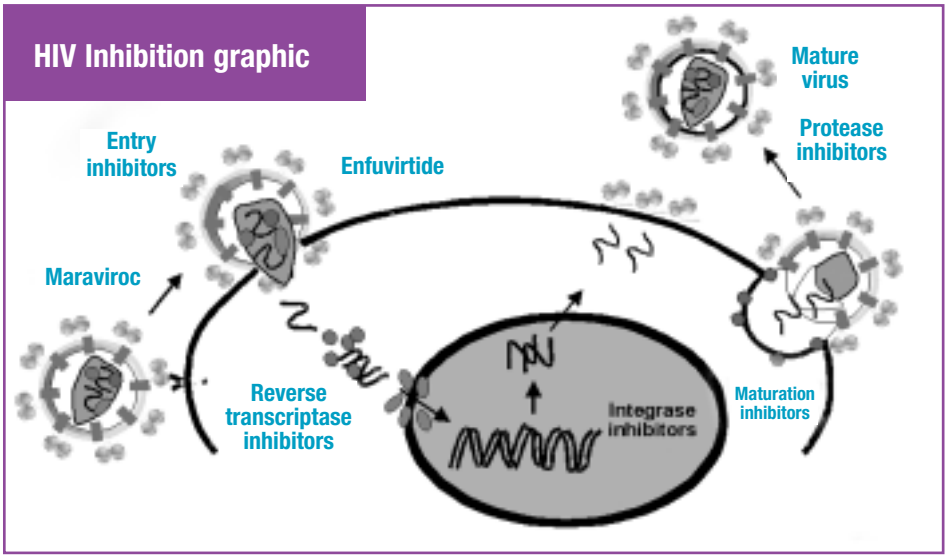
1. **Entry inhibitors** including TNX-355 and vicriviroc
2. **Integrase inhibitors,** including elvitegravir, and
3. **A novel agent** belonging to the maturation inhibitor class, bevirimat.

The two classes of target for antiretroviral therapy that will be discussed here are the entry inhibitor maraviroc and the integrase inhibitor raltegravir. The use of tropism assays including Trofile and SensiTrop will be discussed to help clinicians make decisions of when to use the CCXR5 inhibitor in treatment-experienced patients.

Mechanism of Entry

Mechanisms of HIV entry involve attachment, triggering and fusion. Entry of the virus into the CD4$^+$ cell involves binding of the viral gp120 envelope protein to the CD4 receptor on the host cell, followed by interactions with chemokine receptors, either CCR5 or CXCR4, which leads to fusion of the viral and cell membranes. (See "HIV Inhibition" figure, below.)

HIV Inhibition graphic



Graphic Source: Clinical Care Options downloadable slideset: Understanding HIV Entry and Targets for Therapy; October 2007. Available at: www.clinicaloptions.com/tropism.

HIV tropism

HIV tropism is the ability of a given HIV strain to use CCR5 and/or CXCR4 as co-receptors for entering CD4$^+$ cells.[4] When protein on the virus binds to CCR5 or CXCR4, conformational changes occur that enable it to cause membrane fusion. Drugs that prevent these steps are referred to as entry inhibitors. The virus that enters the cell using the CCR5 co-receptor is termed R5 virus. Viruses that use CXCR4 co-receptor are termed X4 viruses. Viruses that can use either co-receptor are termed R5/X4 or dual tropic viruses.[4] New HIV infections are almost always due to R5 viruses. The CCR5 antagonists have activity against R5 tropic virus only, and *cannot* be used for patients who have dual-mixed tropic (D/M) or X4 virus. In some patients, D/M and/or X4 viruses emerge years after infection. Most of the experience in clinical trials for assessing co-receptor tropism has been with one commercially developed assay, the Trofile.[5]

1) HIV RNA suppression – Phase IIb/III studies of maraviroc in treatment experienced patients and treatment-naïve patients with R5 virus have been presented. In MOTIVATE trials, triple class-resistant patients were randomized to maraviroc 150mg or 300mg daily or BID or to placebo, both combined with an optimized background regimen (OBR). At 24 weeks, twice the proportion of patients on maraviroc plus OBR vs. placebo plus OBR achieved the primary endpoint of HIV-1 RNA <400 copies/ml.[6, 7] Use of maraviroc is not recommended in patients with D/M or X4 HIV-1, as efficacy was not demonstrated in a Phase II study, nor is its safety and efficacy established in treatment-naïve adult patients or pediatric patients.[8]

2) Tropism Shifting or Switching – In an HIV-positive patient, viral tropism is not fixed at primary infection, but may evolve towards CXCR4 use over time. In some patients only a small amount of CXCR4 may be present, possibly existing below the limits of detection by current technologies. This drug associated shift or switch in the population tropism will result in a change in the tropism call, e.g., from R5 to

(Continued on next page)

HIV tropism *(Continued from previous page)*

dual/mixed or X4 tropism. It has not yet been determined whether such a co-receptor antagonist associated switch/shift has an impact on disease progression over long-term follow-up.

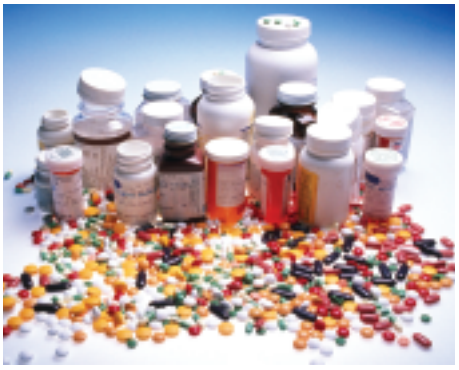
3) Unmasking caused by co-receptor antagonist exposure – treatment with a co-receptor antagonist will suppress the majority R5 population revealing the underlying CXCR4 virus.

4) Resistance – the virus may develop phenotypic resistance to the CCR5 co-receptor antagonist, and this area is being explored.[9]

Several studies have used this assay to define the prevalence of co-receptor usage in various patient populations. Data from 8 cohorts, 3 of them treatment naïve-patients, and 5 of the treatment-experienced patients revealed that dual/mixed or X4 virus appears to be less prevalent among those with earlier stages of disease.[6, 10-14] Even among treatment-naïve subjects, 12-19% of individuals had detectable D/M or X4 virus.[10,12] Therefore, it is necessary to assess each individual patient for viral tropism before the use of a CCR5 antagonist cells to alter the conformational state of the receptor. Monogram's co-receptor assay, Trofile, identifies the tropism of a patient's virus. The sensitivity to detect minority variant populations is 100% when X4 virus is 10% and is 85% when X4 virus is 5% with successful amplification and reliable results with viral load >1000 copies/ml.[8] Another challenge for the use of maraviroc will be reimbursement for the cost of the tropism assay. The FDA has approved Pathway Diagnostics for the process of SensiTrop HIV Co-receptor Tropism Assay, a second-generation molecular based diagnostic HIV tropism assay, with a projected turn around time as fast as 2-4 days compared to the cell based assay development time of two weeks or more. Pathway describes this assay as highly sensitive in detecting CXCR4-tropic HIV in patient samples that contain as little as 1% CXCR4.[10]

Entry Inhibitors

Maraviroc is an antiviral CCR5 co-receptor antagonist indicated for treatment-experienced adults infected with only CCR5-tropic HIV-1 who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. Use of this drug is not recommended in patients with dual/mixed or CXCR4 tropic HIV-1 as efficacy was not demonstrated in a Phase 2 study of this patient group and safety and efficacy have not been established in treatment-naïve adult or pediatric patients. The recommended dose differs based on concomitant medications used. Dosing may be 150 mg BID, 300 mg BID or 600 mg BID.



Maraviroc comes with a black box warning of hepatoxicity with allergic features. In such cases, discontinuation of the medication should be considered with signs and symptoms of hepatitis, or with increased liver transaminases combined with a rash. The drug should be used with caution in patients with increased cardiovascular risk, as myocardial ischemia and/or infarction were observed in patients. Immune reconstitution syndrome has been reported in patients treated with a combination antiretroviral therapy as well as increased risk of developing upper respiratory infections and herpes virus infections. There was no potential risk of malignancy due to maraviroc, but long-term follow-up is needed to assess this risk. The most common adverse events with twice daily therapy included cough, pyrexia, upper respiratory tract infections, rash, musculoskeletal symptoms, abdominal pains, and dizziness. Some of the less common side effects included *Clostridium* difficile colitis. Maraviroc is a substrate for cytochrome P4503A4 and so several antiretroviral agents have been shown to have relevant drug-drug interactions with it as shown below.[15]

Maraviroc Dosage Adjustments with Co-Administered CYP3A Inhibitors or Inducers	
➤ **Reduce dose when given** with strong CYP3A inhibitors (with or without CYP3A inducers) including PI (except tipranavir/ritonavir), delavirdine, ketoconazole, itraconazole, clarithromycin, telithromycin,	**150 mg twice daily**
➤ **Use standard dose when given** with NRTI, tipranavir/ritonavir, nevirapine, enfuvirtide and other drugs that are not strong CYP3A inhibitors or CYP3A inducers,	**300 mg twice daily**
➤ **Increase dose when given** with CYP3A inducers (without a strong CYP3A inhibitor) including efavirenz, rifampin, carbamazepine, phenobarbital, phenytoin,	**600 mg twice daily**

Administration of maraviroc with St. John's Wort is not recommended as it will decrease maraviroc concentrations and lead to loss of virologic response and possible resistance. Maraviroc should be used with caution in patients with renal impairment and in patients with pre-existing liver dysfunction, or who are co-infected with hepatitis B or C. It can be taken with or without food.

Integrase Inhibitors

Integrase enzyme is required for HIV-1 replication. It catalyzes the irreversible process of integrating the viral DNA into the host cell's DNA, called integration. The viral integrase enzyme is a target for antiviral therapy by integrase inhibitors. Raltegravir (formerly MK-0518) was recently approved by the FDA for the treatment of HIV-1 infection in treatment-experienced adult patients who have HIV-1 strains that are resistant to multiple antiretroviral agents. The safety and efficacy of raltegravir have not been established in treatment-naïve adult patients or pediatric patients. The dosage is 400mg twice daily with or without food.[16]

Caution should be used during the initial phase of treatment, when patients may develop immune reconstitution syndrome. The most common side effects reported are diarrhea, nausea, headache, and pyrexia. Cancers like Kaposi's sarcoma, lymphoma, squamous cell carcinoma, hepatocellur carcinoma, and anal cancer were reported in treatment experienced subjects, but it is unknown if these cancers were related to raltegravir use. The rates of AST and ALT abnormalities were higher in the subjects co-infected with hepatitis B and/or hepatitis C. It is metabolized by UGT1A1 glucuronidation pathway, and hence, caution should be used with rifampin or other strong inducers of UGT1A1. Less strong inducers like efavirenz, nevirapine, rifabutin, and St. John's Wort may be used with raltegravir.[15]

The mutations that resulted in raltegravir resistance included an amino acid substitution at either Q148 (changed to H, K, or R) or N155 (changed to H) plus one or more substitutions (L74M/R, E92Q, T97A, e138A/K, G140A/S, V151I, G163R, H183P, Y226D/F/H, S230R and D232N). Another pathway to raltegravir resistance was seen with amino acid substitution at Y143C/H/R.[15]

BENCHMRK 1 and 2 studies confirmed the potency of raltegravir in treatment-experienced patients.[16,17] Patients were randomized to raltegravir 400mg twice daily, or to placebo plus an OBR. At 16 weeks, 77% of patients in the raltegravir arms had HIV-1 RNA <400 copies/ml compared to 41-43% of placebo patients. $CD4^+$ cell count response was also significantly higher in the raltegravir arms (83-86 cells/mm^3) than in control as (31-40 cells/mm^3). Data from BENCHMRK studies indicate that this drug will be beneficial in treatment-experienced patients when combined with at least one other active agent. Raltegravir does not require ritonavir boosting. Twice daily dosing will be a drawback, but the drug's tolerability and lack of toxicity in studies will expand the options for sequential antiretroviral regimens.

Conclusion

As with any antiretroviral agent, the patient should be informed that neither maraviroc nor raltegravir is a cure for HIV infection, and that he or she can still develop opportunistic infections. These treatments do not lower the risk of passing HIV to other people through sexual contact or sharing needles, so they should continue to practice safer sex, and use barrier methods to lower the chance of sexual contact with any body fluids. Patients should remain under the care of a physician when using these drugs, and if they forget to take a dose, they should take the next dose of medication as soon as possible and then take their next scheduled dose at its regular time.[15]

OBR: Optimized background regimen

EAP: Expanded access programs provide new treatments that are "nearly approved" in Phase III clinical trials, to patients who have exhausted or are intolerant of approved therapies, in open studies or parallel tracks.

Maraviroc: Entry inhibitor approved for use in patients infected with HIV strains that are CCR5-tropic and resistant to multiple antiretroviral agents.

Raltegravir: Integrase inhibitor, approved for use in patients infected with HIV strains that are resistant to multiple antiretroviral agents.

Tropism assay: Test to determine whether patient has HIV that uses CCR5 and/or CXR4 as a co-receptor for entering $CD4^+$ cells.

BENCHMRK 1 and 2 studies: Multi-center, triple-blind randomized Phase III studies to evaluate safety and efficacy of oral raltegravir twice daily vs placebo, each plus OBR, in HIV-infected patients with HIV resistant to three classes of oral ART.

MOTIVATE 1 and studies: Multi-center, double-blind randomized Phase III studies to evaluate safety and efficacy of maraviroc vs. placebo, each plus OBR, in HIV-infected patients with HIV resistant to three classes of oral ART, with only R5 HIV-1 detected at screening by Trofile assay.

Clinical Trials Phases

In Phase I trials, researchers test an experimental drug or treatment in a small group to evaluate its safety in humans, determine a safe dosage range, and identify side effects.

In Phase II trials, the experimental study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety. A control group receives either a placebo or the standard treatment regimen.

In Phase III trials, the experimental study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely.

In Phase IV trials, post marketing studies delineate additional information including the drug's risks, benefits, and optimal use.

Clinicaltrials.gov, a service of the U.S. National Institutes of Health. Understanding Clinical Trials. http://www.clinicaltrials.gov/ct2/info/understand

Continuing Education: Registration, quiz, and evaluation follow case discussions, on pp. 10-12.

Online: This activity [09HC08] is posted at http://ccoe.umdnj.edu/catalog/aids where you will be able to submit your registration, quiz, and evaluation, and print your own credit letter.

Cases and Clinician Viewpoints

20 Years of Resistance and Salvage Therapy "Been There, Done That"

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UMDNJ-NJ Medical School and University Hospital, Newark

After 20 years of treating HIV patients, I greet the approval of new medications with both hope and caution. The new ones are much better than the old ones, for the most part. But we won't know right away how well they work for our patients, and we need to watch for long-term side effects and interactions. This is a lifelong disease, and we need to be cautious about starting patients on new medications or classes of medications, so that we get the longest and best possible benefit for the patient.

Many patients struggle with adherence and side effects, and develop resistance. Some have switched to "the newest medication" several times, with varying success. Once a patient is on a regimen that works – that keeps HIV either undetectable or at low levels, and lets the patient get on with his or her life without unbearable side effects or opportunistic infections – we will stick with that regimen until there is a problem. Then we identify their resistance patterns and find different medications, and are glad to have some new classes of medications that have not yet been tried for this patient.

I know and care for many long-term survivors, who have had HIV for 15 or 20 years. Some of them were very sick in the early days, and they have a lot of motivation to keep taking their medications every day because they have things they want to do besides take care of their HIV. I have several patients who just come in every 6 months for check-ins and support, and they are doing very well, whether they are on a long-established combination or a new medication.

Most of my patients who have developed resistance were not adherent early in treatment. It is seldom just the medication, side effects or interactions. If the patient does not have the motivation and is not adherent, then she is not ready to take on the challenge of the schedule and restrictions of the medication guidelines, and having a new regimen will not help.

> "Most of my patients who have developed resistance were not adherent early in treatment. It is seldom just the medication, effects and interactions."

We are now able to avoid some resistance by doing genotypic testing when a patient first comes in or is ready for treatment, so that we identify the mutations or resistance. Many of our patients in Newark already have resistant virus when we begin ARV treatment. We have run tropism tests on several patients but even if the results indicate Maraviroc might be appropriate, we are waiting to switch them until their current regimen fails. Sometimes patients refuse newer treatments.

CASE SCENARIO

C.C. was a 54-year-old Hispanic woman known to me since 1985. She was found to be HIV positive at that time by way of an experimental lab test that was all that was available to us then. She had a history of substance abuse, alcohol abuse, smoking, and a "wild lifestyle" involving dancing in clubs and on cruise ships for a living. She stopped all drugs. She reluctantly started AZT in 1987 along with Bactrim. She was found to have hepatitis B and C with mild liver enzyme elevation. In 1993 she started Combivir. Over the next 13 years, I encouraged her to add an efavirenz booster, or switch to newer medicines, but she never agreed. Her husband died of AIDS in 1993 and three years later she found a new boyfriend, who was also HIV-positive. She brought him in to the clinic. He was started on Combivir and Sustiva, and does well to this day.

In early 2006, after 13 years on her regimen, C.C. started to miss her Combivir doses and stopped it in early summer. At the beginning of August she developed jaundice and ascites. Her $CD4^+$ count dropped to 123, after years of relative stability between 200 – 400. Her viral load was never undetectable, but now it increased to 98,000, after many years between 11,000 and 23,000. Her condition worsened and she started to drink again because she became depressed. Her family became discouraged, placed her on hospice care, and she died one month later.

Discussion:

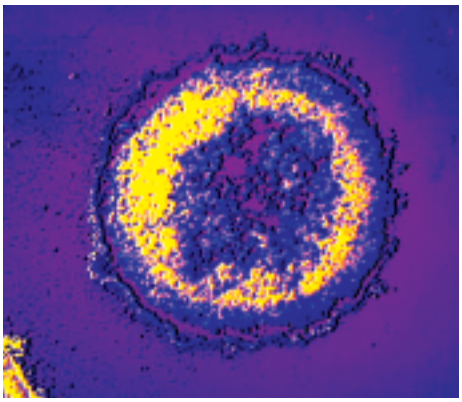
1. **Why did this woman do so well for so long on dual therapy?**
2. **Why did she develop jaundice?**
3. **What would you have done when she began to decline?**

TO COMPARE YOUR OWN ANSWERS to these questions to those provided by the clinician who presented this case, see: http://ccoe.umdnj.edu/online/AIDSLine/09HC08/

CASES AND CLINICIAN VIEWPOINTS

Multi-Drug Resistant HIV: Clinical Case Scenarios

Erin Murphy, MMS, PA-C • Peter Ho Clinic, St. Michael's Medical Center



Multi-drug resistant (MDR) HIV poses a difficult challenge to clinicians when they select a regimen. The clinician must consider many factors including adherence, patient preference, previously taken antiretroviral medications, current HIV drug resistance-associated mutations, co-morbidities, and side effects. With the increasing number of approved HIV medications and potential combinations, it is possible that a patient is starting his/her fourth or fifth regimen. The clinician also needs to consider the reasons a patient with MDR HIV has accumulated so many viral mutations. Virologic suppression starts with proper adherence to the specific dosing schedule. Adherence depends on many factors including adverse side effects, concomitant substance abuse, the number and dosing of pills, and psychiatric and other co-morbidities.

Once adherence is taken into consideration, the selection of the specific medications requires critical thinking. Sometimes the clinician may need to refer the patient to clinical trials, which can range from agents that are early in investigation to nearly approved agents. Phase II or III trials have a very limited study population that is relatively stable. Only a few medical centers in New Jersey participate in Phase II or III trials. Expanded access programs (EAP) for nearly approved agents have much less stringent restrictions. EAPs mirror usage in the actual population because the investigator selects the optimized background regimen (OBR) and there are less rigorous exclusion and inclusion criteria. Many New Jersey HIV care centers have access to EAPs.

The two most recently approved antiretroviral medications, maraviroc (Selzentry) and raltegravir (Isentress), moved from EAP to open label use upon FDA approval earlier this year. As with all new agents, there is limited long-term safety and efficacy data available. However, both are first-in-class drugs. Maraviroc is the first CCR5 inhibitor approved and raltegravir is the first integrase inhibitor approved. Their addition to the antiretroviral armamentarium offers new options for patients who are infected with MDR HIV.

The following case scenarios from the past year highlight how raltegravir and maraviroc may be used in the clinical setting. Case scenario #1 involves medication used in a clinical trial setting, and case scenario #2 involves medication used outside the clinical trial setting.

CASE SCENARIO #1:

M.B. is a 47-year-old African American male with MDR HIV who is failing his current regimen of atazanavir, fosamprenavir and ritonavir. He was previously virologically suppressed but presents with two consecutive HIV RNA levels >1000 copies/ml. Most recent labs are an HIV RNA of 31,860 copies/ml and a $CD4^+$ T cell of 1009 cells/mm^3/17%. When questioned, he reports missing approximately 1 dose a week.

What do you do next?

A. Refer to clinical trials.
B. Repeat his plasma HIV RNA level and $CD4^+$ T cell only.
C. Obtain phenotypic analysis.
D. No action.

Answer: C

This patient has at least two HIV RNA levels >1000 copies/ml, confirming virologic failure. Phenotypic analysis is crucial to guiding the next treatment choice. Referral to a clinical trial may not be necessary, but the clinician must analyze the current mutations before making that decision. It is important to note this patient is on a double boosted protease inhibitor regimen. There is little data supporting the efficacy of this regimen, however, it is occasionally selected by experienced HIV clinicians when facing extensive NRTI mutations. For M.B. it was selected after a previous failure, and despite a few PI mutations it was successful in virologic suppression. This specific regimen was chosen for the once a day dosing, offering a chance of better adherence for M.B. However, after less than a year of intermittent compliance, he was in virological failure.

Phenotypic analysis returns revealing NRTI mutations 41L, 184V, 210W, 215Y and PI mutations 10I, 13V, 32I, 33F, 46I, 53L, 62V, 63P, 71I, 73S, 77I, 82A, 84V, 90M, 93L and although there are no NNRTI mutations listed, 103N is confirmed by previous genotype. Upon discussion with M.B., he states he doesn't want to use enfuvirtide (Fuzeon) and at this point.

Cases and Clinician Viewpoints

Multi-Drug Resistant HIV: Clinical Case Scenarios

CASE SCENARIO #1:

(CONTINUED FROM PREVIOUS PAGE)

What would you do next?

A. Discuss adherence and continue current regimen.
B. No action.
C. Start a nucleoside backbone with enfuvirtide.
D. Refer to clinical trials.

Answer: D

This patient is referred to clinical trials. He is screened for the raltegravir EAP combined with the TMC-125 EAP. TMC-125 is a second generation NNRTI that has shown efficacy in patients with current cross class resistance due to 103N. After carefully reading both informed consents M.B. decides to participate in the raltegravir EAP, but declines participation in the TMC-125 protocol.

At this point what OBR would you select?

A. Lopinavir/ritonavir, enfuvirtide.
B. Truvada, darunavir, ritonavir.
C. Tipranavir, ritonavir.
D. Truvada, efavirenz.
E. Saquinavir, enfuvirtide.

Answer: B

It is important to note the OBR is entirely investigator selected and faced with multiple resistance there is more than one "right" answer. Despite the NRTI mutations present, Truvada was selected due to data that suggests even with the 184V present cytosine analogs (emtricitabine or lamivudine) offer some efficacy. Also, with the presence of 184V there is the possibility of increased susceptibility to tenofovir. When choosing a PI to combine raltegravir with there is more data from the BENCHMRK studies supporting the use of darunavir than lopinavir/ritonavir.

However, it is difficult to do a clinical trial for every possible drug combination so the clinician may have to make a decision that will later be fed by clinical data. Integrase inhibitors are likely to change the current HIV treatment paradigm of a nucleoside backbone combined with either a NNRTI or a PI and we will probably see raltegravir used earlier and earlier. Now there are more options to choose for a second line regimen, which can only be a good thing. For now we expect to see raltegravir used mostly in the heavily treatment experienced patients, but as we get more comfortable it will probably be used in many different combinations.

After starting the EAP, the patient returned for labs in 6 weeks and experienced full virologic suppression. Upon approval of raltegravir, he was referred back to the clinic, and remains virologically suppressed with no adverse side effects.

What side effects should you watch for in this patient?

A. GI intolerance.
B. Creatine phosphokinase (cpk) elevation.
C. Malignancies.
D. All of the above.

Answer: D

Raltegravir seems to be a very well tolerated drug. It is important to remember that it has been studied mostly in heavily treatment experienced patients who tend to be sicker and lend themselves to more adverse events. However, as discussed in the previous section, the most commonly seen adverse side effect is GI intolerance, as with most HIV medications. CPK elevations have also been seen. This is something to keep an eye on in coming months and years. There have been some suggestions of increased malignancies. Again, due to the study population it is hard to delineate if this was from background instances of neoplasm. The post marketing period will be important for raltegravir, as it is for all compounds with limited clinical trial data.

Cases and Clinician Viewpoints

Multi-Drug Resistant HIV: Clinical Case Scenarios

CASE SCENARIO #2:

L.T. is a 35-year-old African American male with MDR HIV and hepatitis C. He is currently failing on atazanavir, fosamprenavir, ritonavir with an HIV RNA level of 1,025 copies/ml and a $CD4^+$ T cell of 476 cells/mm^3/18%. L.T. has been on this regimen for three years, with successful virologic suppression originally, but has had a low level viremic breakthrough for the past year. He has a previous antiretroviral history of lamivudine, didanosine, abacavir, lopinavir/ritonavir, indinavir, amprenavir, and enfuvirtide. At this time darunavir, raltegravir and maraviroc do not have EAPs available.

What would you do next?

A. No action, maintain current regimen.
B. Order a phenotype.
C. Change his regimen to Truvada/efavirenz and monitor his viral load.

Answer: B

As discussed earlier, it is necessary to obtain phenotypic analysis to guide your treatment decision.

Phenotype results show NRTI mutations 41L, 184V, 210W, 215Y, NNRTI mutations 103N and PI mutations 10F, 13V, 20M, 36M/I, 46L, 54V, 58E, 63P, 71T, 84V, 89V, 90M. L.T. is repeatedly screened for clinical trials. Unfortunately, he is not eligible due to his grade II/III liver transaminase elevations secondary to his hepatitis C status. His current regimen is maintained and after 1 year his HIV RNA level is 4680 copies/ml and $CD4^+$ T cell is 532 cells/mm^3/16%. At this time darunavir, raltegravir and maraviroc have been approved. Repeat phenotype shows no new mutations and a tropism test reveals an R5-tropic virus.

You decide to change his regimen; what would you choose?

A. Maraviroc, lopinavir/ritonavir.
B. Maraviroc, darunavir, ritonavir.
C. Raltegravir, darunavir, ritonavir, Truvada.
D. Maraviroc, atazanavir, fosamprenavir, ritonavir.
E. Maraviroc, raltegravir, darunavir, ritonavir, Truvada.

Answer: E

Truvada is selected for the same reasons listed in case scenario #1. Also, as discussed earlier, studies indicate maraviroc is successful in patient's possessing an R5-tropic virus as opposed to a dual tropic (R5X4) or an X4-tropic virus. Furthermore, it is well understood that when active agents are combined, virologic suppression is much more likely. For this reason, raltegravir and maraviroc were chosen due to the extensive level of drug resistance. Full activity was not expected from darunavir due to the presence of the 84V mutation. This mutation was selected for in this patient due to previous failure of protease inhibitor containing regimens. However, darunavir/ritonavir is added because with the absence of 32I, 47V, 50V, 54M/L, and 76V, there is the possibility of partial darunavir activity.

Four weeks after his regimen change L.T. has an HIV RNA <50copies/ml and a $CD4^+$ T cell of 481 cells/mm^3/16%. He is tolerating the regimen well without adverse side effects.

Role of Newly-Approved HIV Antiretroviral Agents in Treatment-Experienced Patients

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Information Resources

FDA MedWatch
Updated reports on medication interactions and warnings:
1-800-FDA-1088; Subscribe to e-bulletin: http://www.fda.gov/medwatch/elist.htm

Stanford resistance database
Clinical Trials datasets, Summaries of Clinical Studies, Antiretroviral drug summaries, Query function for analysis of genotype data. http://hivdb.stanford.edu

CONTINUING EDUCATION REGISTRATION

Role of Newly-Approved HIV Antiretroviral Agents in Treatment-Experienced Patients

Self-Assessment Test

Questions refer to the content of the article and the notes that follow. To receive CME/CEU credit: complete exam, registration, and evaluation forms on-line at http://ccoe.umdnj.edu/online/AIDSLine/index.htm or fill in the forms on the next two (2) pages, and mail or fax to UMDNJ-CCOE (see Registration Form).

1. **Which of the following are indications for changing the antiretroviral regimens?**
   A. Drug toxicity.
   B. Suboptimal antiretroviral regimen.
   C. Virologic failure.
   D. All of the above.

2. **According to the International AIDS Society-US, which of the following is the goal for antiretroviral therapy?**
   A. HIV-1 RNA <5 copies/ml.
   B. HIV-1 RNA <50 copies/ml.
   C. HIV-1 RNA <500 copies/ml.
   D. HIV-1 RNA <5000 copies/ml.

3. **Which of the following antiretroviral agents is recommended for inclusion in a new regimen for a patient with virologic failure due to resistance?**
   A. Delavirdine.
   B. Raltegravir.
   C. Ritonavir.
   D. Stavudine.

4. **The mechanism of action of maraviroc is:**
   A. Blocks CCR5 co-receptor.
   B. Blocks fusion of HIV-1 virus.
   C. Blocks integrase enzyme.
   D. Blocks viral protease.

5. **The mechanism of action of raltegravir is:**
   A. Blocks CCR5 co-receptor.
   B. Blocks fusion of HIV-1 virus.
   C. Blocks integrase enzyme.
   D. Blocks viral protease.

6. **With which of the following tropism testing results would it be appropriate to use maraviroc?**
   A. Dual/mixed virus.
   B. R5 virus.
   C. X4 virus.
   D. All of the above.

7. **If a patient on maraviroc develops signs and symptoms of hepatitis with increased transaminases and allergic reaction, one should:**
   A. Discontinue maraviroc.
   B. Continue maraviroc.
   C. Discontinue for one month and then restart.
   D. None of the above.

8. **The recommended dosage of maraviroc with concomitant rifampin should be:**
   A. Maraviroc 150mg BID.
   B. Maraviroc 300mg BID.
   C. Maraviroc 600mg BID.
   D. Maraviroc 600mg daily.

9. **During the initial phase of treatment a patient on raltegravir may develop:**
   A. Constipation.
   B. Immune reconstitution syndrome.
   C. Peripheral neuropathy.
   D. Vomiting.

10. **Administration of St. John's Wort is not recommended with:**
    A. Maraviroc.
    B. Raltegravir.
    C. Both.
    D. Neither.

CE Activity Code: 09HC08-DE01

CONTINUING EDUCATION REGISTRATION

Role of Newly-Approved HIV Antiretroviral Agents in Treatment-Experienced Patients

Registration Form

CCOE
Center for Continuing & Outreach Education

In order to obtain continuing education credit, participants are required to:

(1) Read the learning objectives, and review the activity, and complete the self-assessment.

(2) Complete this registration form and the activity evaluation form on the next page, and record your test answers below.

(3) Send the registration and evaluation forms to: UMDNJ-Center for Continuing and Outreach Education
• VIA MAIL: PO Box 1709, Newark, NJ 07101-1709 • VIA FAX: (973) 972-7128

(4) Retain a copy of your test answers. Your answer sheet will be graded and if you achieve a passing score of 70% or more, a credit letter awarding *1.25 AMA PRA Category 1 Credits*™ or 1.25 contact hours, or 0.125 continuing education units, and the test answer key will be mailed to you within four (4) weeks.

Individuals who fail to attain a passing score will be notified and offered the opportunity to complete the activity again. This activity will be posted online at http://ccoe.umdnj.catalog/aids

Please note: CE credit letters and long-term credit retention information will only be issued upon receipt of completed evaluation form.

SELF-ASSESSMENT TEST *Circle the best answer for each question.*					
	1. A B C D	**3.** A B C D	**5.** A B C D	**7.** A B C D	**9.** A B C D
	2. A B C D	**4.** A B C D	**6.** A B C D	**8.** A B C D	**10.** A B C D

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Nurses: I attest that I have completed the activity as designed and am claiming [up to 1.25] ____ contact hours for nurses from the NJSNA.

Physicians: I attest that I have completed the activity as designed and am claiming [up to 1.25] ____ *AMA PRA Category 1 Credits*.™

General: I attest that I have completed the activity as designed and am claiming [up to 0.25] ____ Continuing Education Units (CEUs).

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Release date: January 1, 2008 **Expiration date:** Credit for this activity will be provided through December 31, 2009.

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CONTINUING EDUCATION REGISTRATION

Role of Newly-Approved HIV Antiretroviral Agents in Treatment-Experienced Patients

Activity Evaluation Form

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The planning and execution of useful and educationally sound continuing education activities are guided in large part by input from participants. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few moments to complete this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants.

Please note: CE credit letters and long-term credit retention information will only be issued upon receipt of completed evaluation form.

PROGRAM OBJECTIVES: Having completed this activity, are you better able to:		**Strongly Agree**				**Strongly Disagree**
Objective 1:	Outline the signs and test results that would document that a patient has developed toxicity and/or resistance to their current therapy.	5	4	3	2	1
Objective 2:	Discuss the role of integrase inhibitors in treatment experienced HIV-positive patients.	5	4	3	2	1
Objective 3:	Identify the role of entry inhibitors in treatment experienced HIV-positive patients.	5	4	3	2	1
Objective 4:	Explain viral tropism and the role of tropism testing in the management of HIV disease.	5	4	3	2	1

OVERALL EVALUATION:	**Strongly Agree**				**Strongly Disagree**
The information presented increased my awareness/understanding of the subject.	5	4	3	2	1
The information presented will influence how I practice.	5	4	3	2	1
The information presented will help me improve patient care.	5	4	3	2	1
The faculty demonstrated current knowledge of the subject.	5	4	3	2	1
The program was educationally sound and scientifically balanced.	5	4	3	2	1
The program avoided commercial bias or influence.	5	4	3	2	1
Overall, the program met my expectations.	5	4	3	2	1
I would recommend this program to my colleagues.	5	4	3	2	1

If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide us with a brief description of how you plan to do so.

Please provide any additional comments pertaining to this activity (positives and negatives) and suggestions for improvement. Please list any topics that you would like to be addressed in future educational activities.

CE Activity Code: 09HC08-DE01
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CONTINUING EDUCATION REGISTRATION

Medical Implications of Injection Drug Use

Release Date: January 1, 2008 • Exp. Date: December 31, 2009 • Course Code: 09HC09-DE01

Sponsorship

Sponsored by the University of Medicine & Dentistry of New Jersey (UMDNJ), UMDNJ-Center for Continuing & 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 persons with HIV/AIDS and others at risk of infection.

Statement of Need

An estimated 424,000 persons in the United States, aged 12 or older injected heroin, cocaine, methamphetamines or other stimulants during 2005. These needles and syringes are usually shared with other injection drug users, which may result in the transmission of infectious diseases and skin and bone infections.

This article is designed to increase knowledge among healthcare professionals about the common diseases which may be acquired through injection drug use (IDU), and the screening and patient education that could reduce the transmission of disease among individuals who inject drugs.

Learning Objectives

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

1. List common routes of injection for drug use.
2. Identify diseases which can be transmitted through injection drug use (IDU).
3. Discuss the role of Staphylococcus aureus in soft tissue infections.

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 consisting of a series of multiple-choice and True/ False 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. Estimated time to complete this activity as designed is 1.0 hour.

Accreditation

Physicians: UMDNJ-Center for Continuing & Outreach Education is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. UMDNJ-Center for Continuing & Outreach Education designates this educational activity for a maximum of 1.0 *AMA PRA* Category 1 *Credits*™. Each physician should claim only credit commensurate with the extent of their participation.

Nurses: UMDNJ-Center for Continuing & Outreach Education is an approved provider of continuing nursing education by the New Jersey State Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.

This activity is awarded 1.0 contact hours. (60 minute CH)

Provider approved by the California Board of Registered Nursing, Provider Number CEP 13780.

Review: The activity was prepared in accordance with the ACCME Essentials. This activity was reviewed for relevance, accuracy of content, balance of presentation, and time required for participation by Patricia C. Kloser, MD, MPH, FACP. This activity was reviewed for relevance, accuracy of content, balance of presentation, and time required for participation by Bonnie Abedini, RN, MSN; Mary C. Krug, RN, MSN, APN-C; and Ella Shaykevich, APRN, MSN, MPA.

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Faculty Disclosure Declarations

The following have no financial relationships to disclose: authors: Debbie Y. Mohammed, MS, MPH, APRN-BC, AACRN, Patricia C. Kloser, MD, MPH, FACP; editor: Kimi Nakata, MSW, MPH and field testers: Bonnie Abedini, BSN, MS; Mary C. Krug, RN, MSN, APN-C; and Ella Shaykevich, APRN, MSN, MPA.

Off-Label Usage Disclosure

This activity does not contain information of commercial products/ devices that are unlabeled for use or investigational uses of products not yet approved.

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.

Editor's note

Following the American Medical Association guideline, UMDNJ-CCOE will list trade names with capital letters but will no longer note ® and T status of medications, as the US Federal Dilution Trademark Act does not require these designations in publications.

[1] Iverson C, Christiansen S, Flanagin A, et al. *AMA Manual of Style: A Guide for Authors and Editors.* 10th ed. New York, NY: Oxford University Press; 2007.

Medical Implications of Injection Drug Use

Debbie Y. Mohammed, MS, MPH, APRN-BC, AACRN, and Patricia C. Kloser, MD, MPH, FACP

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

1. List common routes of injection for illicit drug use.
2. Identify diseases which can be transmitted through injection drug use (IDU).
3. Discuss the role of *Staphylococcus aureus* in soft tissue infections.

INTRODUCTION: INJECTION USE IN THE UNITED STATES

An estimated 424,000 persons in the United States, aged 12 or older, injected heroin, cocaine, methamphetamines or other stimulants during 2005.[1] These needles and syringes are usually shared with other injection drug users, which may result in the transmission of infectious diseases and skin and bone infections.

This article is designed to increase knowledge among healthcare professionals about the common diseases which may be acquired through injection drug use (IDU), and the screening and patient education that could reduce the transmission of disease among individuals who inject drugs.

(Continued on next page)

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Resources

Harm Reduction Coalition
The Harm Reduction Coalition is a national advocacy organization that "promotes the health and dignity of individuals and communities impacted by drug use. HRC advances policies and programs that help people address the adverse effects of drug use including overdose, HIV, hepatitis C, addiction, and incarceration."
http://www.harmreduction.org

Drug Policy Alliance
The Drug Policy Alliance (DPA) is a national organization that advocates for "drug policies based on science, compassion, health and human rights."

http://www.drugpolicy.org
Drug Policy Alliance New Jersey
609-396-8613
nj@drugpolicy.org

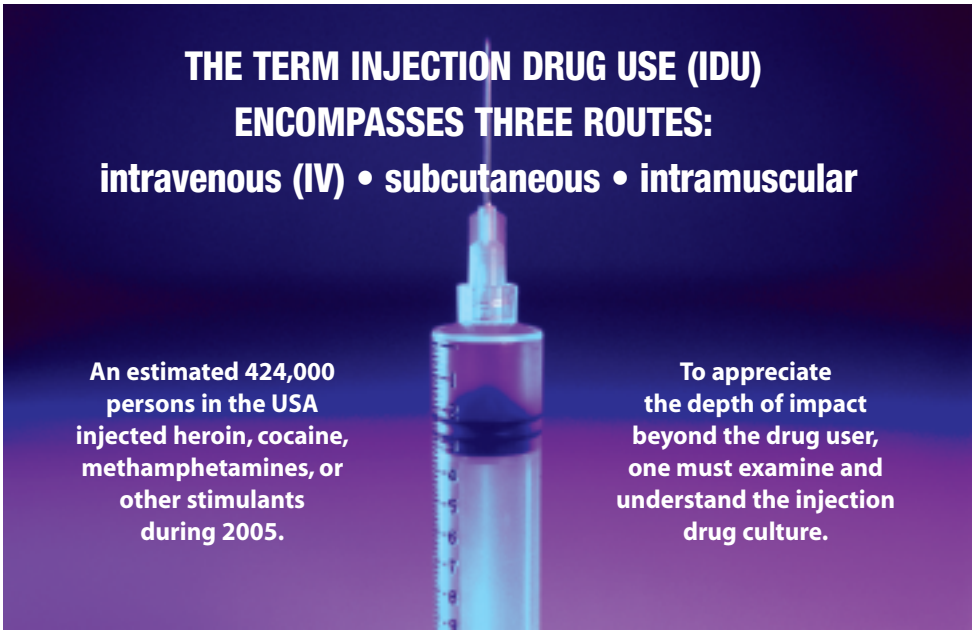
Substance Abuse Treatment
New Jersey: NJDHSS-Division of Addiction Services
http://www.state.nj.us/humanservices/das

Addictions Hotline of New Jersey
http://www.njdrughotline.org

National:

National Institute on Drug Abuse (NIDA)
http://www.nida.nih.gov

Substance Abuse and Mental Health Administration (SAMHSA)
http://www.findtreatment.samhsa.gov



Injection Drug Use

In an era when disease prevention is an integral part of primary care medicine, a significant, but often overlooked concept is the epidemiologic impact of injection drug use on the spread of deadly diseases. Morbidity and mortality among injection drug users results either from infection introduced through the process of injection, from contaminants added to the drug mixture, from sequelae of the drug usage itself, from drug overdose, or from violence associated with drug use.

To appreciate the depth of impact beyond the drug user, one must examine and understand the injection drug culture. For the IDU, the daily focus is the acquisition and use of their drug of choice. Although illicit drugs may be introduced into the body orally or nasally, for many persons the preferred method is injection. The term injection drug use (IDU) encompasses three routes: intravenous (IV), subcutaneous and intramuscular.

The intravenous route ("mainlining") is often preferred, because this is the fastest way to achieve the desired response from the drug. The IV route is most popular because when a bolus of drug is introduced into the vein, the user experiences a rapid and powerful euphoria. On the average, the desired response can be achieved within 15-30 seconds, compared to intranasal use, which produces the desired effects within 3-5 minutes.[2]

When injecting, if the vein is missed or if the vein cannot be penetrated because of excessive venous destruction, the drug may be injected under the skin, or subcutaneously ("skin popping"), or inside the muscle, or intramuscularly ("muscling"). Injection drug users may inject themselves or have someone else inject them. As needle possession is illegal in most states, and clean syringes are not available legally to those without medical prescriptions, there is a high probability that users will share equipment. This substantially increases the transmission of infectious diseases and skin and bone infections.[3]

An estimated 424,000 persons in the United States aged 12 or older injected heroin, cocaine, methamphetamines, or other stimulants during 2005.[1] Unfortunately, the injecting drug user may transmit Infectious diseases through syringe/needle sharing or sexual transmission. Pregnant women can transmit HIV and other infectious diseases through perinatal transmission. Preventing both the acquisition and transmission of diseases becomes paramount in providing medical care for this patient population.

Medical Implications of Injection Drug Use

Infectious Disease: HIV, hepatitis C and B

Injection drug use greatly enhances the introduction of pathogens and various other contaminants into the body through needle sharing or lack of sterile preparation and injection techniques. Skin infection, bone infections, systemic bacterial infections and hepatitis B and C are just a few of the diseases caused or transmitted by IDU.

Injection drug use has been clearly demonstrated to have a strong association, through the sharing of syringes and needles, with transmission of the Human Immunodeficiency Virus (HIV) which leads to Acquired Immune Deficiency Syndrome (AIDS). Data published by the Centers for Disease Control note that 24.6% of 478,488 persons living with HIV/AIDS in 2005 in the United States were identified as having a transmission risk of IDU.[4] In New Jersey, 30% of 33,623 persons living with HIV/AIDS in 2006 were identified as IDU. An additional 1,748 persons were infected with HIV/AIDS by an IDU partner. This included approximately 1,350 women who could potentially transmit the HIV to an unborn child.[5]

Hepatitis B is a serious liver infection caused by the hepatitis B virus (HBV). For some people, the infection becomes chronic, leading to liver failure, liver cancer, or cirrhosis, a condition that causes permanent scarring of the liver[11] and can be transmitted via used syringes/needles. In 2005, a total of 5,494 confirmed acute cases of hepatitis B were identified, and 15% of the patients reported IDU as a risk factor. After accounting for asymptomatic infection and underreporting, approximately 51,000 new infections of hepatitis B occurred in the United States.[6] It is estimated that 1.25 million persons in the United States are chronically infected with hepatitis B, and approximately 5,000 persons have died because of chronic liver disease related to hepatitis B.[8]

Hepatitis C is transmitted via used syringes/needles which contain the virus. This virus attacks the liver, and patients may have no symptoms. The hepatitis C virus (HCV) causes the liver to become inflamed, which interferes with its ability to function. Over time, hepatitis C infection can lead to liver cancer, liver failure or cirrhosis.[6] In 2005, a total of 671 confirmed acute cases of hepatitis C were identified in the United States. The risk factor for this disease was IDU in 50% of the cases. However, after accounting for asymptomatic infection and underreporting, approximately 20,000 new infections may have actually occurred.[7] Overall, the prevalence of hepatitis C in the United States is 1.6% (95% CI, 1.3% to 1.9%), equating to an estimated 4.1 million (CI, 3.4 million to 4.9 million) hepatitis C positive persons nationwide. A total of 48.4% of hepatitis C-positive persons between 20 and 59 years of age reported a history of injection drug use, the strongest risk factor for HCV infection.[8] An estimated 8,000-10,000 deaths have occurred because of chronic liver disease related to hepatitis C.[9] Of note, concurrent infection with hepatitis C and HIV is common in the United States, affecting 15% to 30% of HIV-infected individuals, and resulting in an accelerated sequelae of cirrhosis of the liver and end stage liver disease.[10]

Other Infections

Skin and soft tissue infections are common infections among injecting drug users, with *Staphylococcus aureus (S. aureus),* the most common bacterial pathogen for these patients.[12] This organism can cause severe infections such as endocarditis and bacteremia. *S. aureus* is carried in the nose and on the body, and is associated with an increased risk of subsequent *S. aureus* infections. Patients who are active IDUs have a higher rate of colonization with *S. aureus* than the general population.[15] In a community sample of urban poor residents of San Francisco, 22.8% were colonized with *S. aureus,* and 12% of the samples were community-acquired methicillin-resistant *Staphylococcus aureu* (MRSA). The main risk factor for having MRSA was attributed to IDU, with samples from these patients about ten times more likely to have MRSA than non-IDU.[14] A cross-sectional study among IDU in San Francisco found that 32% of patients had an abscess or cellulitis[15] when they were examined.

Musculoskeletal infections occur in IDU patients as the organism may travel in the blood and be 'seeded' in bone, causing osteomyelitis, and septic arthritis. The only symptom may be pain in uncommon places such as the sacroiliac or sternoclavicular joint, and the vertebral spine or knee.[16]

Injection technique and infections

Patients may become infected with a bacterial organism for the following reasons:

- Inexperience in accessing a vein
- Skin popping – the drug is injected subcutaneously or intramuscularly[15]
- Speed-balling- injecting mixtures of heroin and cocaine at the same time and injecting more frequently[17]
- Failing to clean the skin before injection[18]
- Sharing drug paraphernalia[19]
- Reuse of drug paraphernalia
- Booting – repeatedly flushing and pulling back the syringe during injection[20]

Harm Reduction Interventions in the Medical Setting

In instances where someone is unwilling or unable to stop injecting drugs, the harm reduction approach is recommended. In harm reduction, the focus is on identifying harms which affect the patient and others, and the patient's motivation to reduce that harm, which usually requires behavior changes. When an active drug user presents in an emergency department or clinic, the first priority is to address urgent medical needs, without requiring sobriety or agreement to addiction treatment.

> "The recommendation for hepatitis screening and vaccination is especially important for injection drug users."

Clinicians may work with patients to identify and address current and future medical risks including infections, toxic reactions, and cardiac and pulmonary effects of street drugs. The clinician should also assess the patient for the effects of injected or inhaled drugs on the cardiac and pulmonary systems, as well as complications in care for existing conditions including pregnancy and chronic illnesses. Many long-term opiate users have developed decreased tolerance for pain, and clinicians need to conduct pain assessments, and prescribe and monitor analgesic treatment that is sufficient to alleviate the pain. Substance use does not negate the difficulty of functioning with pain.[3]

In the Healthy People 2010 report, the USDHHS recommended hepatitis B screening for all adults, and hepatitis A and B vaccination for individuals who test HBV-negative. Five years into the 10-year plan, the USDHHS reported that "While infant and childhood immunization programs for hepatitis B have been successful in dramatically lowering infection rates among children less than 19 years of age, hepatitis B vaccine coverage is lowest for adults with behavioral risks. Barriers to hepatitis B vaccination in adults include the cost of vaccine, some providers' time constraints and/or lack of awareness, and patient non-adherence to the three-dose schedule."[21]

The recommendation for hepatitis screening and vaccination is especially important for injection drug users. Patients with a history of injection drug use should be screened for both hepatitis B and C, and if either test is positive, they should have further testing for liver function, hepatitis viral load and phenotype, and be referred to a specialist for evaluation and management if there is a detectable viral load. Harm reduction for patients with either hepatitis B or C includes advice to abstain from alcohol, and avoid acetaminophen (Tylenol), both of which can contribute to the development of cirrhosis of the liver. They can also reduce the impact of hepatitis by increasing liquid intake, having a healthy diet, and exercising.

Patients may also be concerned about their physical safety related to drug use including violence, toxicity of drugs and contaminants, and injection-related injuries and infections. The clinician can teach patients the risks associated with sharing equipment, and methods to clean the skin area before injecting. Patients can also be taught methods of overdose prevention, signs of overdose, and when to go for emergency care. Many harm reduction programs explicitly teach specific injection techniques, and offer clean syringes as part of comprehensive healthcare programs.

Syringe exchange, or needle exchange, which is usually part of more comprehensive harm reduction programs, has been demonstrated to be an effective intervention to lower the risk of HIV transmission between injecting drug users, in programs in England, Switzerland, Australia, and in Connecticut and New York as well as many other areas of the United States. In December 2006, New Jersey became the last state to strike down legislation forbidding syringe exchange. (See news article.)

Some harm reduction groups focus on reducing deaths due to drug overdoses, and train injection drug users to identify and reduce the causes of overdose. They also teach drug users to identify the signs and some provide and train in the use of naloxone, which is commonly used in emergency departments, to revive other drug users who have overdosed on heroin or other opiates. A pilot project in New York City has enlisted substance abuse treatment agencies and primary care providers to begin prescribing naloxone with directions for overdose prevention and intervention.[22]

Conclusion

Preventing disease and disability which may be attributable to the sharing and re-use of syringes and needles among injecting drug users requires interventions at multiple levels. An ounce of prevention is worth more than a pound of cure, and it is undoubtedly best to never start injection of drugs. On the other hand, when patients present to the healthcare system with disease, then access to quality health care and rehabilitation is necessary to minimize the medical and financial cost to the patients, their families, and society.

Continuing Education

Please read the case material that follows, and then complete the registration, quiz, and evaluation on pp. 23-26.

Online: Register at http://ccoe.umdnj.edu/catalog/aids to complete credit requirements for this activity [09HC09] is posted at where you may submit your registration, quiz, and evaluation, and print your own credit letter.

Medical Implications of Injection Drug Use

CASE SCENARIO #1

From the Emergency Department

John is a 46-year-old African male who presented to the Emergency Department with a history of a swelling on his left upper thigh for the past 5 days. He has been homeless and sleeps at a shelter. He has a history of intravenous drug use for the past 20 years, however, he has had difficulty injecting drugs recently as his veins are 'bad.'

On physical exam John has a temperature of 103°F. The surgeon in the Emergency Department incises and drains an abscess to his left upper thigh. He will be admitted to the hospital for IV antibiotic therapy.

1. **Diagnostic testing which may be done at this time includes:**
   A. Blood cultures.
   B. Blood work for HIV, hepatitis B, hepatitis C.
   C. Wound cultures.
   D. All of the above.

The physician orders blood and wound cultures, and Rapid HIV testing, hepatitis B, and hepatitis C antibody tests.

2. **It is most likely that John injected drugs to his left upper thigh:**
   A. By main lining.
   B. By skin popping.
   C. Intramuscularly.
   D. None of the above.

3. **John's wound and blood cultures are positive for Staphylococcus aureus. He complains of pain in his lower back which is getting worse every day. Other diseases which he may have at this time include:**
   A. Osteomyelitis.
   B. Osteoarthritis.
   C. Osteoporosis.
   D. Osteomalacia.

John may have developed osteomyelitis secondary to *Staphylococcus aureus* infection. He is unwilling to give information about his method of injection.

4. **One week later, John states that he is not ready to stop using drugs at this time. The medical provider will:**
   A. Discharge John back to the shelter.
   B. Send John for drug counseling.
   C. Teach John to use the femoral (groin) vein for injection.
   D. Discuss harm reduction, including snorting drug rather than using a needle to get drugs in his body.

The medical provider discusses the concept of harm reduction with John, including the risks of new infections due to injection or skin-popping, and alternate methods of drug use that will be lower-risk for acquiring infectious diseases. However, John says that he is not willing to stop injecting because he has not been able to get enough of the drug through snorting. The provider then shows John how to clean his skin before injecting, and discusses the need to monitor his skin carefully for any swelling or other indications of infection, and to return for care whenever he is feverish or has swelling or ulcers at injection sites.

CASE SCENARIO #2

Treatment of an IVU patient, from the hospital to the clinic

C.R. is a 27-year-old female Caucasian homeless drug addict. She was admitted to University Hospital with pneumonia and was known to be HIV-positive. She took no medications and had no HIV care. Her four children are "down South" being raised by family. She is a commercial sex worker and was disorganized and depressed.

Family was found and her mother offered to help her. She was very short of breath due to PCP and weighed 82 lbs. due to her street life and oral esophageal candida. She was found to be pregnant with a live fetus at 7 weeks. Her initial decision was to have an abortion.

The patient recovered and kept her Outpatient Dept. appointment, deciding to carry the pregnancy to term. Her mother comes to the clinic with her and her $CD4^+$ count has increased from 7 to 32, with an undetectable viral load.

1. **What HIV medications would you avoid? Why?**
2. **What ARV would you use?**
3. **What other medication would you prescribe?**
4. **What was the single most important event in this case that allowed the patient to adhere to care and treatment?**

TO COMPARE YOUR OWN ANSWERS to these questions to those provided by the clinician who presented this case, see: http://ccoe.umdnj.edu/online/AIDSLine/09HC09/

Medical Implications of Injection Drug Use

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CONTINUING EDUCATION REGISTRATION

Medical Implications of Injection Drug Use

Self-Assessment Test *(page 1 of 2)*

Questions refer to the content of the article and the notes that follow. To receive CME/CE/CEU credit: complete exam, registration, and evaluation forms on-line at http://ccoe.umdnj.edu/online/AIDSLine/index.htm or fill in the forms on the next two (2) pages, and mail or fax to UMDNJ-CCOE (see Registration Form).

Questions 1 through 5 are based on the following case:

C.O. IS A 37-YEAR-OLD Newark man with a long history of drug use, including intravenous heroin and nasal ingestion of cocaine (snorting). He presented to the Emergency Department with fever, shortness of breath, and an altered mental status. He has AIDS, with a $CD4^+$ of 132. He is not on any HIV medications or medical care as he has a chaotic lifestyle.

The patient was found to have MRSA endocarditis with septic emboli to the lungs, and was placed in the MICU on a ventilator. His hospitalization was long and "stormy." At 5'7", he weighs 119 lbs. and is underweight, with a BMI of 18.6. He continues to complain of a dry cough which has not responded to any medications, and generalized aches and pains which he rates at 9 out of 10.

He is homeless and is now getting ready for discharge after 6 weeks of IV antibiotics. He refuses nursing home care and prefers to go to a shelter. He does not like methadone and does not want to pay for it. He has CDC-defined AIDS and needs care and treatment. He agrees to come to see you in the clinic if you will give him the medications he believes will make him able to manage being out of the hospital: Boost, Percocet, and Tussinex.

1. What will you do on the first outpatient visit?

A. Prescribe antiretroviral medication, based on $CD4^+$ count obtained in hospitalization.
B. Order extensive laboratory tests: $CD4^+$, viral load, genotype, hepatitis B and C, PPD, and urine toxicology.
C. Arrange for admission into a residential addiction treatment program, to provide stability and medical monitoring as well as addiction treatment.
D. Explain that you cannot provide Percocet and Tussinex because he is actively using illegal drugs.

2. What is your treatment priority?

A. Get him on antiretroviral medication.
B. Obtain full documentation of his medical and mental health status.
C. Address his substance use.
D. Provide prophylaxis for PCP (Pneumocystis jiroveci pneumonia), since his $CD4^+$ is under 200 and he is at elevated risk for this opportunistic infection.

3. What intervention can you make at this first visit that will get the patient to return for a second visit?

A. Provide a 2-week prescription for Boost, and for Tussinex to address his immediate complaint of cough, and provide pain management according to World Health Organization recommendations.
B. Refer to the nutritionist and nurse to work him up for possible wasting or nutritional deficiencies, to document the need for oral nutritional supplements.
C. Refer to onsite mental health/ substance abuse counselor evaluation.
D. Arrange for transportation vouchers for today and the next visit, through the clinic case manager.

4. When will you start antiretroviral treatment?

A. On the first clinic visit: his hospital labs showed $CD4^+$ of 132, and he needs to begin ARV treatment immediately.
B. As soon as his full lab workup has been reported, including viral load and genotype.
C. After discussion with the patient of his medical condition and treatment options, when he states that he is ready to commit to taking ARV medication daily as prescribed.
D. As soon as his full lab workup has been reported, including viral load, genotype, and hepatitis panel, so that his ARV regimen can include coverage for hepatitis B if needed.

5. Which harm reduction intervention would be most effective in reducing the likelihood of the patient needing hospitalization again very soon, due to a critical medical condition?

A. Discuss safer injection practices.
B. Refer to rapid detoxification to avoid relapse.
C. Provide education on risks associated with heroin and cocaine, focusing on medical complications of injection and the effects of cocaine on cardiovascular and central nervous systems.
D. Advise patient not to resume use of any recreational drugs upon release from the hospital.

CE Activity Code: 09HC09-DE01

CONTINUING EDUCATION REGISTRATION

Medical Implications of Injection Drug Use

Self-Assessment Test (page 2 of 2)

Questions refer to the content of the article and the notes that follow. To receive CME/CE/CEU credit: complete exam, registration, and evaluation forms on-line at http://ccoe.umdnj.edu/online/AIDSLine/index.htm or fill in the forms on the next two (2) pages, and mail or fax to UMDNJ-CCOE (see Registration Form).

Questions 6 through 10 are based on the following case:

B.J. IS A 38-YEAR-OLD CAUCASIAN FEMALE who has returned to an infectious disease clinic for medical care after a year of absence. She contracted HIV disease through injection drug use. Her $CD4^+$ count is 720 and antiretroviral medications are not currently indicated. She was recently discharged from jail and is in an outpatient substance use treatment counseling program. Initial labwork showed that BJ was positive for hepatitis C infection with a viral load of 6 million copies. Her liver biopsy showed chronic hepatitis which was minimally active. She was successfully treated with interferon and ribavirin, through adherence to the treatment plan, and has maintained a non detectable hepatitis C viral load 3 years later.

6. The proportion of patients who acquired HIV disease by injection drug use in New Jersey compared to the rest of the United States is:

A. About the same.
B. Lower.
C. Greater.
D. Not known.

7. Compared to HIV negative patients, hepatitis C disease progression in HIV infected patients is:

A. Slower.
B. Faster.
C. About the same.
D. Dependent on the HCV genotype.

8. BJ came for a routine visit to the infectious disease clinic, two years after conclusion of successful treatment for hepatitis C. She denied having any complaints. Upon physical examination she was noted to have an abscess on the back of her left hand. She denied current injection drug use, and stated that she had argued with her brother and struck a car window the previous week. She was referred to the ED for incision and drainage of the abscess. BJ did not go to the Emergency Department as instructed. If the infection is left untreated, and the organism travels in her blood, other parts of the body may develop infections, which can include:

A. MRSA Endocarditis.
B. Septic Arthritis.
C. Bacteremia.
D. All of the above.

9. The following week, BJ was later admitted to another hospital and treated for bacteremia. Three months later she returned to the infectious disease clinic, complaining of back pain. She underwent an MRI of the thoracic spine which showed T9-T10 osteomyelitis and discitis with no involvement of the epidural space. This is most likely the sequelae of the bacteremia. What kind of follow-up will BJ need following her antibiotic course?

A. She should have a brief course of physical therapy for rehabilitation.
B. She may experience chronic disabling pain, and should return frequently to be sure her pain treatment plan is working.
C. Her CD4+ count is likely to decrease, and she will need to start antiretroviral medication because of the infection's effect on her immune system.
D. She should remain on antibiotics to prevent recurrence of infection.

10. Although BJ denies current or recent drug use, you are concerned about the cause of her abscess. To explore her drug use further, you:

A. Tell her that you understand that she may relapse into drug use from time to time, and explain safer injection techniques to her.
B. Refer her to an intensive hospital-based inpatient substance abuse treatment program where she can receive ongoing medical care and be monitored more closely for drug use.
C. Ask her what drugs she is using now.
D. Conduct a substance use assessment and urine drug screening, and if either is positive for current use, ask permission to consult with her counselor.

CE Activity Code: 09HC09-DE01

CONTINUING EDUCATION REGISTRATION

Medical Implications of Injection Drug Use

Registration Form

CCOE
Center for Continuing & Outreach Education

In order to obtain continuing education credit, participants are required to:

(1) Read the learning objectives, and review the activity, and complete the self-assessment.

(2) Complete this registration form and the activity evaluation form on the next page, and record your test answers below.

(3) Send the registration and evaluation forms to: UMDNJ-Center for Continuing and Outreach Education
• VIA MAIL: PO Box 1709, Newark, NJ 07101-1709 • VIA FAX: (973) 972-7128

(4) Retain a copy of your test answers. Your answer sheet will be graded and if you achieve a passing score of 70% or more, a credit letter awarding 1 *AMA PRA Category 1 Credit*™ or 1.0 contact hours or 0.1 continuing eduction units, and the test answer key will be mailed to you within four (4) weeks.

Individuals who fail to attain a passing score will be notified and offered the opportunity to complete the activity again.

Online option: This activity will be posted at http://ccoe.umdnj.edu/catalog/aids where you will be able to submit your registration, quiz, and evaluation, and print your own credit letter.

Please note: CE credit letters and long-term credit retention information will only be issued upon receipt of completed evaluation form.

SELF-ASSESSMENT TEST *Circle the best answer for each question.*					
	1. A B C D	**3.** A B C D	**5.** A B C D	**7.** A B C D	**9.** A B C D
	2. A B C D	**4.** A B C D	**6.** A B C D	**8.** A B C D	**10.** A B C D

– PLEASE PRINT –

First Name M.I. Last Name Degree

Daytime Phone # Evening Phone #

Fax # E-mail

Preferred Mailing Address: ☐ Home ☐ Business

Address

City State Zip Code

Affiliation/Specialty

Nurses: I attest that I have completed the activity as designed and am claiming [up to 1.0] _____ contact hours for nurses from the NJSNA.

Physicians: I attest that I have completed the activity as designed and am claiming [up to 1.0] _____ *AMA PRA Category 1 Credit*.™

General: I attest that I have completed the activity as designed and am claiming [up to 0.10] _____ Continuing Education Units (CEUs).

Signature _____ Date _____

Release date: January 1, 2008 **Expiration date:** Credit for this activity will be provided through December 31, 2009.

UMDNJ-Center for Continuing & Outreach Education
PO Box 1709, Newark, New Jersey 07101-1709
Phone: 973-972-4267 or 1-800-227-4852 • Fax: 973-972-7128

CE Activity Code: 09HC09-DE01
This form may be photocopied.

CONTINUING EDUCATION REGISTRATION

Medical Implications of Injection Drug Use

Activity Evaluation Form

The planning and execution of useful and educationally sound continuing education activities are guided in large part by input from participants. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few moments to complete this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants.

CCOE
Center for Continuing & Outreach Education

Please note: CE credit letters and long-term credit retention information will only be issued upon receipt of completed evaluation form.

PROGRAM OBJECTIVES: Having completed this activity, are you better able to:	**Strongly Agree**				**Strongly Disagree**
Objective 1: List common routes of injection for illicit drug use.	5	4	3	2	1
Objective 2: Identify diseases which can be transmitted through injection drug use (IDU).	5	4	3	2	1
Objective 3: Discuss the role of *Staphylococcus aureus* in soft tissue infections.	5	4	3	2	1

OVERALL EVALUATION:	**Strongly Agree**				**Strongly Disagree**
The information presented increased my awareness/understanding of the subject.	5	4	3	2	1
The information presented will influence how I practice.	5	4	3	2	1
The information presented will help me improve patient care.	5	4	3	2	1
The faculty demonstrated current knowledge of the subject.	5	4	3	2	1
The program was educationally sound and scientifically balanced.	5	4	3	2	1
The program avoided commercial bias or influence.	5	4	3	2	1
Overall, the program met my expectations.	5	4	3	2	1
I would recommend this program to my colleagues.	5	4	3	2	1

If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide us with a brief description of how you plan to do so.

Please provide any additional comments pertaining to this activity (positives and negatives) and suggestions for improvement. Please list any topics that you would like to be addressed in future educational activities:

CE Activity Code: 09HC09- DE01
This form may be photocopied.

Syringe exchange legalized in New Jersey

ON December 19, 2006, the New Jersey State Legislature enacted the "Bloodborne Disease Harm Reduction Act," which established a demonstration program to permit operation of sterile syringe access programs in up to six cities. The Act also provided for the establishment of regional substance abuse treatment services, and appropriated $10 million of funding for inpatient and outpatient addiction treatment. There was no funding allocated to the operation of the syringe exchanges. HIV/AIDS and public health advocates and professionals had conducted educational and lobbying efforts to legalize syringe exchange for many years, citing rates of injection drug use-related HIV infection at double the national average, and research findings on the success of syringe exchange programs throughout the country and the world over the past two decades. The Act includes a service and evaluation component. It requires that staff have extensive training in infection control, as well as HIV and hepatitis C prevention and screening, and health and social service referrals, and that pilot sites gather and report data on program activities and participants. Mandated areas of reporting include participant drug use patterns, referrals to health care and substance abuse treatment, and the impact on needle stick injuries, appropriate disposal of needles, and local crime statistics. Participants will also be surveyed for their assessment of the value and impact of the program. Programs in the designated cities will provide syringe exchange and referral services for individuals who are age 18 or older.

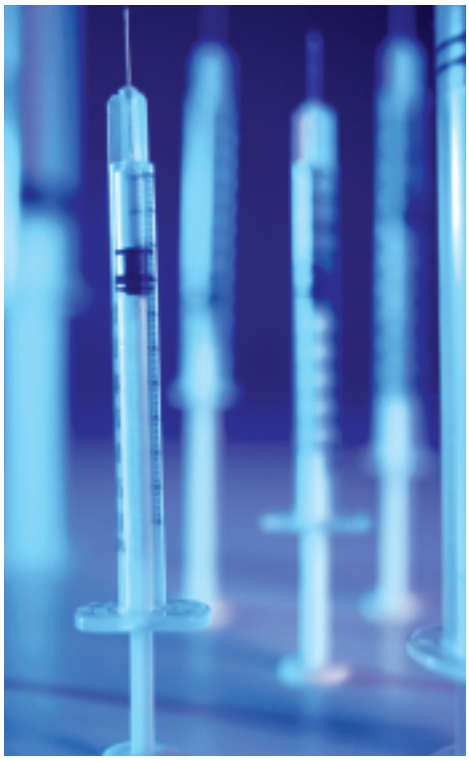
The New Jersey Department of Human Services-Division of Addiction Services (NJDHS-DAS) released a "Request for Proposals" in the spring of 2007, and accepted applications from agencies to provide substance abuse "treatment on demand" for those substance abusers referred from syringe exchange programs. Funding would provide mobile units, treatment slots, and other outreach methods to reach active drug users. The program would link substance users to medical care as well as addiction treatment. Applications were only accepted from "any municipality in which the governing body has authorized the operation of sterile syringe access programs within that municipality by ordinance." (PL 2006, Chapter 99, Bloodborne Disease Harm Reduction Act).

Four cities have been approved as pilot syringe exchange sites

Four cities, Atlantic City, Camden, Newark, and Paterson, applied to the State of New Jersey for authorization to serve as sites for pilot sterile syringe exchange programs. Each city was required to demonstrate working relationships with the legal, health, and social service components of its local program. All four cities received authorization from the NJDHSS and began working on implementing projects to begin by December 1, 2007. They were each able to secure funding to support these projects, which has come primarily from the Comer Foundation, the Drug Policy Alliance, and the Tides Foundation.

November 2007: Pilot program begins in Atlantic City

Atlantic City began the state's first legal syringe exchange program on November 27, 2007, as a collaboration between the authorizing entity, the Atlantic City Department of Health, and its partner agency, the South Jersey AIDS Alliance (SJAA). Twenty people participated in the syringe exchange program on the first day of operations at the Oasis Drop-In Center, operated by the SJAA. By early January, six weeks later, the program had enrolled 127 participants, many of whom had previously used services of the Oasis Drop-In Center



including free HIV counseling and testing, case management, and meals. Program counselors provide referrals to medical care, case management, and drug-treatment. The program operates three days per week: Tuesdays and Thursdays from 10 AM to 2 PM and Wednesdays from 7:30 AM to 11 AM.

Atlantic City was the first New Jersey municipality to state its support for legalization of needle exchange, as a response to the HIV/AIDS epidemic in this community. Atlantic City passed an ordinance in June 2004 approving a needle-exchange program, although the ordinance was struck down in the court. "For years, the best evidence from around the world has told us this is what we should be doing to prevent the spread of HIV/AIDS, but our hands were tied," said Ronald Cash, Director of Health for Atlantic City. "This year we truly have something to celebrate in New Jersey for World AIDS Day."[1]

(Continued on next page)

"Atlantic City began the state's first legal syringe exchange program on November 27, 2007, as a collaboration between the authorizing entity, the Atlantic City Department of Health, and its partner agency, the South Jersey AIDS Alliance (SJAA)."

Syringe exchange legalized in New Jersey

(Continued from page 27)

January 2008: Camden, Newark, and Paterson

Camden: The City of Camden is coordinating the provision of its syringe exchange program with two local HIV providers, the Camden Area Health Education Center (Camden AHEC),and Dooley House. The Camden program, called Lifeworks, began operations on January 15. Lifeworks operates only on Tuesdays from 1:30 to 4:30 PM. Services are provided through a mobile unit that goes to several sites in Camden.

Newark: The syringe exchange program in Newark is being developed by the City of Newark, Department of Child and Family Well-Being, who will be working collaboratively with a local HIV provider, the North Jersey Community Research Initiative (NJCRI). NJCRI will provide services through a fixed site on Central Avenue and at several other sites through a mobile unit. Program operations are projected to begin by mid-February.

Paterson: The City of Paterson has authorized the Bergen-Passaic HIV Planning Council to oversee the implementation of Paterson's syringe exchange program. As such, the Council has authorized the local drug treatment agency, the Paterson Counseling Center, to be the lead agency in developing the program. Syringe exchange services will be provided at the Well of Hope Drop-in Center, beginning on January 30. The program will operate three days a week: Mondays, Wednesdays, and Fridays, from 10 AM to 2 PM.

Program evaluation, as stipulated by the legislation, will determine the number of syringe exchange participants, disposal of participants' needles,enrollment in drug treatment programs, outcomes of referrals, and the impact of the syringe exchange program on rates of HIV, hepatitis B and C, and needlestick injuries.

Program evaluation: demonstrating the pilot program's effectiveness

The program also has an evaluation component, as stipulated by the legislation, to determine the number of syringe exchange participants, disposal of participants' needles, enrollment in drug treatment programs, outcomes of referrals, and the impact of the syringe exchange program on rates of HIV, hepatitis B and C, and needlestick injuries. Each participant in the syringe exchange program will be assigned an identification number to maintain confidentiality. Registered participants will turn in or exchange used needles for 10 clean needles plus one additional clean needle for every used needle they turn in. A sample of participants will be asked to provide information every six months about their drug and needle use, and whether they have sought drug addiction treatment.

The evaluation team, from the University of Medicine and Dentistry of New Jersey – School of Public Health, is working with the NJDHSS-DHAS staff to develop and implement training for all program staff and volunteers, covering environmental health and safety issues as well as preparing them to interview participants and enter data from mobile units and drop-in centers.

Expanded substance abuse treatment

The legislation provides funding for inpatient and outpatient drug treatment slots and outreach. The intent is to reduce or eliminate the waiting time for entering addiction services and provide drug treatment on demand.

Note: syringe exchange will be covered in more detail in the next issue of *NJ AIDSLine.*

New Jersey "Codey Law" to Make HIV Testing Routine for Pregnant Women, Newborns

On December 26, 2007, Acting Gov. Richard J. Codey signed a bill which he sponsored while Senate president, which requires that pregnant women will be tested for HIV as part of routine prenatal care in the first and third trimesters of pregnancy, unless they opt-out. Women who present in labor and delivery with unknown HIV status will be tested at that time unless they opt-out. Newborn infants will be tested for HIV if the mother is positive or if her status was unknown at delivery. The Codey bill requires that medical providers follow the recommendations of the Centers for Disease Control (CDC) for HIV testing of pregnant women. The law will take effect in six months.

Note: prenatal HIV testing and perinatal transmission will be covered in more detail in the next issue of *NJ AIDSLine.*

The 2007 HIV Diagnostics Conference

(Continued from page 1)

The conference started with information relevant to laboratory testing. Highlights of the presentations are provided below.

- An HIV-2 supplemental test needs to be FDA approved. (Currently, no HIV-2 supplemental test is FDA approved for use in the United States.)
- The role of acute infection testing needs to be defined.
- The acute infection algorithm includes options for pooled or individual NAAT testing.
- Laboratory turn-around time and notification of persons with acute infection needs to be done as quickly as possible to minimize the risk of transmission from these extremely viremic persons.
- CDC does not currently recommend the use of routine acute infection screening. CDC is currently concentrating on routine antibody screening.
- The best EIA tests to detect HIV as early as possible are not available in the United States. These fourth generation EIA tests can detect HIV three to five days sooner than the third generation EIA tests that are currently available in the United States.
- CDC presented data showing that a dual test laboratory strategy using the Bio Rad HIV-1/HIV-2 Plus O test followed by Multispot has a sensitivity of 100% and a specificity of 100%. This strategy does not include a WB.
- Other effective laboratory-based strategies that did not include a WB were also presented.
- The most sensitive test should be the first test used.

HIV testing is rapidly evolving. The CDC recommendations are likely to change markedly in the future from a single algorithm to a series of strategies with multiple algorithms for laboratory-based and POCT. FDA approval of new tests such as a combination fourth generation EIA with p24 antigen, currently in use outside the United States, would shorten the time between infection and detection with diagnostic tests.

References

1. Martin E, Salaru G, Paul SM, Berezny L, Wolski M, Vega I, and Cadoff E. At the Laboratory Interface: HIV Discordant Follow-up. 2007 HIV Diagnostics Conference, Atlanta, Georgia, December 6, 2007.
2. Cadoff E, Cadoff A, Salaru G., Paul SM, and Martin E. Retrospective Application of the Proposed CDC/APHL Rapid Testing Algorithm in New Jersey 2004-7. 2007 HIV Diagnostics Conference, Atlanta, Georgia, December 6, 2007.
3. Gallagher K, Patel, P, Kowalski A, Klinger E, Gombel K, Sullivan T, Parker M, and Blank S. Implementation of Acute HIV Infection Screening in STD Clinics Using Rapid HIV Antibody Testing, New York City, 2007. 2007 HIV Diagnostics Conference, Atlanta, Georgia, December 6, 2007.
4. Simmons P, Bennett SB, Liberti T, Patel T, and Lalota M. Acute HIV Infection Screening and Prevention, Study Implementation Challenges. 2007 HIV Diagnostics Conference, Atlanta, Georgia, December 6, 2007.

New Jersey Community Nursing Leader Honored

THE National Nursing Spectrum/Nurse Week Excellence Awards were presented at their national conference in Chicago on October 9, 2007. They recognized six exceptional nurses in the categories of Mentoring, Advancing and Leading the Profession, Clinical Care, Community Service, Management, and Teaching.

Robert Skeist, RN, MS, ACRN, who is a Geriatric AIDS Nurse at the Family Treatment Center of Newark Beth Israel Medical Center in Newark, NJ, was honored with the Community Service Award. "You have accomplished at least three lifetimes worth of work in the community, particularly with the programs that serve older adults with HIV/AIDS and with initiatives that focus on prevention. You see nursing as 'a force for healing communities as well as healing individuals.' Your strength and wisdom shine like a beacon."

Retrieved from www.nurse.com on November 4, 2007.

Mr. Skeist is well-known to HIV service providers as founder of the New Jersey Association on HIV Over Fifty (NJAHOF), an affiliate of the National Association on HIV Over Fifty (NAHOF). NAHOF can be contacted at www.hivoverfifty.org. He was also lead author of *Prevention & Treatment of HIV Infection in Persons 50 & Over* in *New Jersey AIDSLine,* June 2007. *Congratulations, Rob!*

New HIV Treatment Guidelines published on December 1, 2007

Panel on Antiretroviral Guidelines for Adult and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents.

Available on the web at: http://aidsinfo.nih.gov/contentfiles/adultandadolescentgl.pdf

CDC Updates PEP Recommendations

The CDC released updated recommendations for Postexposure Prophylaxis (PEP) for Occupational HIV Exposures on December 14, 2007, identifying two significant patient safety concerns related to changes in antiretroviral use.

First, the recommendation for use of Kaletra (lopinavar/ ritonavir) must be revised due to reformulation of the medication as a twice-daily two-pill regimen rather than the earlier twice-daily three-pill regimen.

Second, the FDA recommends that pregnant women limit exposure to ethyl methane mesylat (EMS), which has been found in European-manufactured Viracept (nelfinavir), because of concerns about potential carcinogenic or teratogenic effects. As a precaution, PEP regimens for female health care personnel of child-bearing age should avoid nelfinavir.

Information and guidance re: management of specific exposures: National Clinicians' Post-Exposure Prophylaxis Hotline (888-448-4911) or http://www.ucsf.edu/hivcntr.
MMWR. December 14, 2007 / 56(49);1291-1292 Available at:
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5649a4.htm?s_cid=mm5649a4_e
Accessed December 18, 2007.

HIV Vaccine Trials Stopped; Increased Risk Found

Researchers at the HIV Vaccine Trials Network meeting reported on November 7, 2007 that clinical trial participants who received an experimental Merck & Co. HIV vaccine might be at increased risk of HIV infection compared to those who received a placebo. There were elevated numbers of HIV infections among vaccine recipients who had pre-existing immunity to adenovirus type 5, a common cold virus that was modified and used as the vector for three synthetic HIV genes.

Among trial participants, there were 49 infections among those vaccinated and 33 infections among those who received a placebo. However, the divergence was greater among 778 males with pre-existing adenovirus immunity: 21 vaccine recipients later became infected, compared with nine infections among the placebo group. Researchers said it is difficult to define statistical significance for that difference, since the trial has been stopped. For those with low pre-existing adenovirus immunity, the difference in infections between vaccinated subjects and the placebo group were not statistically significant.

Researchers emphasized that the vaccine itself could not have caused infection and that the findings on infection risk could be a statistical fluke. They are investigating both biological factors, primarily adenovirus immunity, and non-biological factors such as participant circumcision rates and sexual practices. One theory suggests that the adenovirus vector may have activated the immune system and made recipients more susceptible to HIV infection upon subsequent exposure. Women accounted for 35-40 percent of volunteers, but just one woman later acquired HIV. The reasons for the gender difference are unknown, but the case was removed from statistical analysis.

In late September, the trial involving 3,000 volunteers in nine countries was stopped when preliminary analyses found the vaccine neither blocked HIV infection nor curtailed HIV levels in the blood of those who contracted the virus.

Abridged from: CDC HIV/Hepatitis/STD/TB Prevention News Update, November 8, 2007. http://www.cdcnpin.org/scripts.

HIV/AIDS TREATMENT INFORMATION RESOURCES

National Resources

Centers for Disease Control (CDC) – Division of HIV/AIDS Prevention
HIV/AIDS research, surveillance reports, funding announcements, research and reporting software, epidemiology slide sets.
http://www.cdc.gov/hiv/hivinfo.htm#WWW

Rapid Testing:
http://www.cdc.gov/hiv/rapid_testing

MMWR [Morbidity & Mortality Weekly reports]:
http://www.cdc.gov/hiv/pubs/mmwr.htm

CDC National Prevention Information Network (NPIN)
HIV, STD, and TB news, funding announcements, materials, conference and satellite broadcast announcements.
http://www.cdcnpin.org

US Dept. of Health & Human Services
www.aidsinfo.nih.gov
1-800-HIV-0440 (1-800-448-0440)
HIV/AIDS treatment guidelines; prevention, treatment, and research. National Institutes of Health-sponsored searchable clinical trials database: http://clinicaltrials.gov

National HIV/AIDS Clinicians' Consultation Center
http://www.ucsf.edu/hivcntr
Consultation on antiretroviral therapy, drug resistance, opportunistic infection prophylaxis and treatment, laboratory evaluation; occupational exposure, perinatal intervention.
Warmline: 800-933-3413

National Clinicians' Post-Exposure Prophylaxis Hotline
(PEPline): 888-448-4911 (888-HIV-4911)

National Perinatal HIV Consultation and Referral Service:
888-448-8765 (888-HIV-8765)

AIDS Education and Training Centers (AETC)
National Resource Center www.aids-etc.org
HIV treatment guidelines, training materials/ curricula, evaluation tools, Daily HIV/AIDS Treatment News; clinical resources including PDA tools.

FDA MedWatch
Updated reports on medication interactions and warnings: 1-800-FDA-1088;
Subscribe to e-bulletin:
http://www.fda.gov/medwatch/elist.htm

New Jersey and Regional Resources

New Jersey Department of Health & Senior Services
Division of HIV/AIDS Services (NJDHSS-DHAS)
www.state.nj.us/health/aids/aidsprv

New Jersey Department of Health & Senior Services
Division of HIV/AIDS Services (DHAS)
www.state.nj.us/health/aids/aidsprv

NJ HIV/AIDS Semi-annual Newsletter (statistical report); policies, and guidelines for HIV/AIDS care and services in New Jersey
New Jersey rapid testing site: www.state.nj.us/health/aids/rapidtesting
New Jersey HIV (Testing) Helpline: 1-866-HIV-CHEC (448-2432)

New Jersey AIDS/STD Hotline: (800) 624-2377
• 24-hour professionally-staffed service • Consultation, testing referrals, free materials

HIV/AIDS TRAINING & EDUCATION

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HIV/AIDS Medical Update Series

FREE On-site Training
To schedule a free 1-hour HIV medical education program at your health care site on any of these topics, contact Michelle Thompson at (973) 972-1293 or ccthomps@umdnj.edu

- Diagnosis and Initial Management of HIV/AIDS: What the Primary Care Physician Should Know
- HIV in Pregnancy – Preventing Perinatal Transmission
- HIV/AIDS and Hepatitis C Co-Infection
- Immunizations for HIV Positive Adults
- Non-Occupational Post-Exposure Prophylaxis
- Prevention and Prophylaxis for Occupational Exposure to HIV and Other Blood Borne Pathogens
- Prophylaxis and Treatment of Opportunistic Infections in Patients with HIV Disease
- Rapid Diagnostic HIV Testing

University of Medicine & Dentistry of NJ
Center for Continuing and Outreach Education
Division of AIDS Education
www.umdnj.edu/ccoe/aids
Conferences, training for HIV/AIDS health and social service professionals.

Division of AIDS Education Programs include:

New Jersey Department of Health and Senior Services, Division of HIV/AIDS Services
• Prevention & Education • Care and Treatment

NY/NJ AIDS Education And Training Centers (AETC)
Local Performance Site, training clinicians in medical, nursing, oral health, pharmacy, dentistry; and the health care team.

Ryan White Part A, Newark EMA
Case management training and quality management programs

On the web: http://ccoe.umdnj.edu/aids

Free online CME/CE – topics include:

- HIV and Hepatitis C Virus Co-Infection
- Recommendations to Reduce Occupational HIV Transmission
- Hepatitis B and HIV Co-Infection
- Beyond HIV: Lesbian, Gay Bisexual and Transgender Health
- Immunization for HIV Infected Children and Adolescents
- Reducing Vertical HIV Transmission in NJ
- Prevention & Treatment of HIV Infection in Persons 50 & Over
- Role of Newly Approved HIV Antiretroviral Agents in Treatment-Experienced Patients
- Medical Implications of Injection Drug Use

New!

Treating Adolescents with HIV: Tools for Building Skills in Cultural Competence, Clinical Care, and Support

Five modules:

- Fundamentals of Adolescent Care & Cultural Competence
- Psychosocial Issues
- Antiretroviral Therapy and Adherence
- Transitioning Care
- Prevention with Positives

This multi-media educational activity is funded by the USDHSS-HRSA-HIV/AIDS Bureau. Continuing education credit for physicians, nurses, psychologists, social workers.

http://ccoe.umdnj.edu/aids or www.hivcareforyouth.org

Regional Resources

- **NY/NJ AIDS Education And Training Centers (AETC)**
  New York/New Jersey regional training calendar, resource directory, clinician support tools and references including training slide sets, wall charts: http://www.nynjaetc.org
- **Northeast Addiction Technology Transfer Center (NEATTC)**
  Addiction training, treatment news: http://www.neattc.org
- **Title X Family Planning Regional Training Center (RTC)**
  [DHHS/OPA funded]: training www.cicatelli.org/titlex/home
- **STD/HIV Prevention Training Centers (PTC)**
  Medical: www.nyc.gov/html/doh/html/std/ptc.shtml
  Behavioral: www.urmc.rochester.edu/chbt

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AIDS Line

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Division of AIDS Education

with

New Jersey Department of Health and Senior Services, Division of HIV/AIDS Services

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SAVE THE DATES

Thursday • June 12, 2008
HIV Clinical Update 2008
Sheraton at Woodbridge, NJ

This conference is sponsored by UMDNJ and the New Jersey Department of Health and Senior Services, Division of HIV/AIDS Services.

FOR MORE INFORMATION: See website for updates and registration at http://ccoe.umdnj.edu/catalog/aids or call (973) 972-3690.

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ANAC-NJ Day of Learning

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FOR MORE INFORMATION: Dominick Varsalone, (973) 941-9686 or http://www.nursesinaidscare.org/i4a/pages/Index.cfm?pageID=3718

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- ☐ **STOP:** Please take me off the list. (include label section, or write name & address)

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