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THIS ACTIVITY HAS EXPIRED.

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The following content is provided for informational purposes only.
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 page 3)
Role of Newly-Approved HIV Antiretroviral Agents in Treatment-Experienced Patients

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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 approved 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, FACP; 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.

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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.

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. 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.

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 >50 copies/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.

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. 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.

1. **Entry inhibitors:**
   a. Enfuvirtide (Fuzeon T20)
   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.

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 CCR5 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 tropism**
HIV tropism is the ability of a given HIV strain to use CCR5 and/or CXCR4 as co-receptors for entering CD4+ cells.6 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.6 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.

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. Even among treatment-naïve subjects, 12-19% of individuals had detectable D/M or X4 virus. 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. 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.

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.

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.

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.

Maraviroc comes with a black box warning of hepatotoxicity 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.

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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, hepatocellular 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 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/mm³) than in control as (31-40 cells/mm³). 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

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 Trojan 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.


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

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

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

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/mm3/17%. 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.
### Multi-Drug Resistant HIV: Clinical Case Scenarios

#### CASE SCENARIO #1:

**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.
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/mm³/18%. 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/mm³/16%. 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/mm³/16%. He is tolerating the regimen well without adverse side effects.
Role of Newly-Approved HIV Antiretroviral Agents in Treatment-Experienced Patients

REFERENCES


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