

Current and Emerging Issues in HIV

Jennifer Janelle, MD
Clinical Assistant Professor
University of Florida, Gainesville
Faculty, Florida/Caribbean AETC

Disclosure of Financial Relationships

- This speaker has no significant financial relationships with commercial entities to disclose.

This slide set has been peer-reviewed to ensure that there are no conflicts of interest represented in the presentation.

Outline

- Recently approved antiretroviral drugs (ARVs) for the treatment of HIV
- Review of changes in the most recent DHHS Guidelines for the Use of Antiretroviral Agents in the Treatment of HIV-1 Infected Adults and Adolescents (January 2011)

Recent FDA Approvals



Nevirapine (Viramune XR™)

- New extended release formulation of nevirapine (NVP) approved March 25, 2011
- Class: Non-nucleoside reverse transcriptase inhibitor (NNRTI)
- Indication
 - Treatment of HIV-1 infection in adults in combination with other antiretroviral agents (ARVs)

Nevirapine (Viramune XR™)

- Dosage: 400 mg tablet once daily with other ARVs **after traditional lead in dose of 200 mg regular release NVP**
- Side effect profile remains unchanged
- Patient selection is important
 - Unless benefit outweighs the risk...
 - Do not initiate in women with CD4 greater than 250 cells/mm³
 - Do not initiate in men with CD4 greater than 400 cells/mm³
 - Due to potential for serious and life-threatening hepatotoxicity

Nevirapine (Viramune XR™)

- In a patient starting NVP
 - Start with the traditional lead in dose of nevirapine 200 mg once daily for 14 days
 - If rash persists beyond the 14-day lead-in period with immediate release nevirapine, do not begin dosing with Viramune XR™
 - An alternative regimen should be chosen if the patient is still on the lead in dose of nevirapine 200 mg daily at 28 days

Nevirapine (Viramune XR™)

- Laboratory Monitoring F/C AETC Recommendation
 - LFTs at baseline, 2 weeks then every 4 weeks for the 1st 3 months, then every 3 months
 - Optimal frequency of monitoring has not been determined

Nevirapine (Viramune XR™)

- On Day 15, the dose can be changed to Viramune XR™ 400 mg tablet once a day in absence of rash and hepatotoxicity
- Patients already stable on a regimen of nevirapine 200 mg regular release tablets BID or 2 tablets once daily can be transitioned directly to one Viramune XR™ 400 mg tablet daily.

Case

- JR is a 50 year old AA woman who has maintained an undetectable HIV viral load and CD4 count over 500 cells/mm³ for the last 5 years on emtricitabine/tenofovir (Truvada®) once daily and nevirapine (Viramune®) 200 mg 2 tablets once a day. Can you switch her to the new formulation of Viramune XR™ 400 mg one tablet daily?

Case

- BD is a 40 yo WM newly diagnosed HIV + who has a CD4 count of 300 cells/mm³ and HIV viral load of 75,000 copies/mL. Can he be started on nevirapine (Viramune XR™) 400 mg once daily + emtricitabine/tenofovir (Truvada®) and carefully monitored for evidence of rash/liver abnormalities?

Case

- RK is a 25 year old black woman who was recently diagnosed with HIV infection. Her CD4 count is 280 cells/mm³ and HIV viral load is 35,000 copies/mL. She wants a one pill, once daily regimen for treatment of her HIV. She uses only condoms for birth control despite extensive counseling regarding risks of pregnancy and offering of birth control options. What are her options?

Virologic Outcome Pooled Data: Echo and Thrive Studies

	Rilpivirine (RPV) + BR* N=686	Efavirenz (EFV)+ BR* N = 682
HIV-1 RNA < 50 copies/mL	83%	80%
Virologic Failure by Baseline Plasma Viral Load (copies/mL)		
≤ 100,000	5%	5%
>100,000 to ≤500,000	20%	11%
>500,000	29%	17%

*tenofovir/emtricitabine, zidovudine/lamivudine or abacavir/lamivudine

Reference: Table adapted from Edurant™ (package insert), Raritan, NJ: Tibotec Therapeutics/Division of Centocor Ortho Biotech Products, L.P., May 2011.

- ### Rilpivirine (Edurant™)
- Patients with virologic failure during treatment with rilpivirine had...
 - Higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz
 - Higher risk of lamivudine (3TC)/emtricitabine (FTC)-associated resistance compared to EFV

Rilpivirine (Edurant™)Resistance Mutations After Virologic Failure: Pooled Data Echo + Thrive

	Rilpivirine	Efavirenz
Evaluable Post-Baseline Resistance Data	75	37
Emergent NNRTI Substitutions in Virologic Failures		
V90I	12% (9/75)	0
K101E/P/T	19% (14/75)	3% (1/37)
K103N	0	32% (1/37)
E138K/G	35% (27/75)	0
E138K+M184I	27% (20/75)	0
Y181C/I	9% (7/75)	0
Emergent NRTI Substitutions in Virologic Failures		
M184I or V	53% (40/75)	22% (8/37)
K65R/N	9% (7/75)	5% (2/37)

Reference: Table adapted from Edurant™ (package insert), Raritan, NJ: Tibotec Therapeutics/Division of Centocor Ortho Biotech Products, L.P., May 2011.

Rilpivirine (Edurant™) Drug Interactions

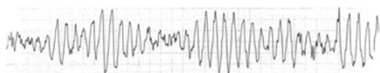
- Metabolism by CYP3A enzyme
- Drugs contraindicated with RPV
 - Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin
 - Antimycobacterials: rifabutin, rifampin, rifapentine
 - Glucocorticoid systemic dexamethasone (more than a single dose)
 - St. John's wort (*Hypericum perforatum*)

Rilpivirine (Edurant™) Drug Interactions


- Requires low gastric pH for absorption
 - **Proton pump inhibitors are contraindicated**
 - Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
 - H2-Receptor Antagonists should be administered at least 12 hours before or at least 4 hours after rilpivirine
 - Antacids should be taken at least 2 hours before or 4 hours after rilpivirine

Rilpivirine (Edurant™) Drug Interactions

- Prolongation of QT interval
 - Supratherapeutic doses of RPV have been shown to prolong the QTc interval of the electrocardiogram
 - Use with caution when co-administering with other drugs known to cause Torsade de Pointes



Rilpivirine (Edurant™)



- Use in women capable of pregnancy
 - Pregnancy category B
 - Use in pregnancy only if the potential benefit justifies potential risk
 - No known teratogenic risk at this time¹

¹Desmidt M, et al. Absence of a teratogenic potential from a novel next generation NNRTI, TMC278. 12th European AIDS Conference, Cologne, Germany, Nov 11-14, 2009. Abstract PE7.14.

Rilpivirine (Edurant™)

Impact on Lipids-Mean Change from Baseline at Week 48 (Fasted) Pooled Data from Echo and Thrive*

	RPV + BR				EFV + BR			
	N	Baseline		Week 48	N	Baseline		Week 48
Mean (95% CI)	Mean (mg/dL)	Mean (mg/dL)	Mean Change (mg/dL)		Mean (mg/dL)	Mean (mg/dL)	Mean Change (mg/dL)	
T Chol	584	161	163	2	549	160	187	27
HDL-Chol	582	41	45	4	548	40	50	10
LDL-Chol	580	96	95	-1	547	95	109	15
Triglycerides	584	121	115	-6	549	131	140	9

The clinical significance of these changes has not been determined.
 *Excludes subjects receiving lipid lowering agents during the treatment period.
 Reference: Table adapted from Edurant™ (package insert), Raritan, NJ: Tibotec Therapeutics/Division of Centocor Ortho Biotech Products, L.P., May 2011.

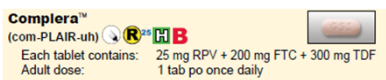
Treatment Related Adverse Effects (ADR)

	RPV	EFV
Drug discontinuation due to ADR	2%	4%
Clinical ADRs of at least moderate intensity		
Rash	3%	11%
Depressive disorders	4%	3%
Insomnia	3%	3%
Dizziness	1%	2%

Reference: Table adapted from Edurant™ (package insert), Raritan, NJ: Tibotec Therapeutics/Division of Centocor Ortho Biotech Products, L.P., May 2011.

Complera™ (RPV+TDF+FTC)

- Once daily combination pill for treatment-naïve HIV infected patients
 - FDA approval August 10, 2011



New DHHS Recommendations for NNRTI Use

- EFV remains the preferred NNRTI (AI)
- RPV is now classified as an alternative NNRTI (BI)
- NVP remains an acceptable NNRTI in women with CD4 counts < 250 cells/mm³ and in men with CD4 counts < 400 cells/mm³ (CI)

Reference: DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents Recommendation for NNRTI use in Antiretroviral Treatment-Naïve Patients with HIV-1 Infection. August 16, 2011. Accessed from http://aidsinfo.nih.gov/contentfiles/NNRTI_One_Page_Info-RPV.pdf August 17, 2011.

Quad Pill

Elvitegravir (EVG)/Cobicistat (COBI)/FTC/TDF

- Once daily combination pill in Phase III studies
- Elvitegravir
 - HIV-1 strand-transfer integrase inhibitor
 - Metabolized by cytochrome P450 3A4
- Cobicistat (Formerly GS 9350)
 - Investigational pharmacoenhancer boosts systemic levels of EVG
 - No HIV activity

Laboratory Monitoring

- CD4 cell count monitoring can be done every 6-12 months in patients with the following:
 - Consistently suppressed HIV viral load
 - CD4 count well above the threshold for opportunistic infections
 - No change in patient’s clinical condition
 - No new HIV associated symptoms
 - No addition of immunosuppressive agents

Case

- BA is a 30 year old man with HIV who has been followed in your clinic for 5 years. His CD4 count has been above 500 with an undetectable HIV viral load for the last 3 years. On his last visit, his HIV viral load was 120. Is he experiencing virologic failure?

Laboratory Monitoring

- HIV viral load as indicator of virologic failure
 - Optimal viral load suppression is less than the limit of detection depending on the assay used
 - Isolated low level HIV viremia can occur in successfully treated patients without indicating failure
 - Virologic failure is defined as a confirmed HIV viral load greater than 200 copies/mL
 - There is no consensus regarding management of patients with HIV RNA levels between 48 and 200 copies/mL

Resistance Testing

- Standard genotypic resistance testing detects mutations in reverse transcriptase or protease genes
- Additional testing for resistance to integrase strand transfer inhibitor (INSTI) genes should be done in treatment-naïve patients if there is a concern for resistance to this class of drugs (CIII)

Resistance Testing

- Genotypic resistance testing including testing for INSTI resistance should be considered in those failing INSTI based regimens (CIII)

Coreceptor tropism assay

- Should be considered prior to initiating treatment with CCR5 antagonists and also if virologic failure occurs in patients treated with these agents.
 - Phenotype assay (Trofile) for coreceptor tropism is recommended over genotypic assays by the DHHS Guidelines panel.

Laboratory Monitoring

- Urinalysis should be done every 6 months if on tenofovir (TDF)
 - More frequent monitoring could be considered in those with increased risk of renal insufficiency
- Fasting lipid profile should be considered 4-8 weeks after starting new ART

Prevention of Mother to Child Transmission

- Combination ARV therapy is indicated for all HIV-infected pregnant women regardless of whether the mother otherwise meets criteria for ARV treatment
- A fully suppressive ARV regimen does not have to be changed to include zidovudine (ZDV) in the event of pregnancy (AIII)
- After delivery, considerations regarding continuation of ARV treatment for the mother are the same as for other nonpregnant individuals

Initial Treatment: Choosing Regimens

- 3 main categories:
 - 1 NNRTI + 2 NRTIs
 - 1 PI + 2 NRTIs
 - 1 II + 2 NRTIs
- Combination of NNRTI, PI, or II + 2 NRTIs preferred for most patients
- Fusion inhibitor, CCR5 antagonist not recommended in initial ART
- Few clinical end points to guide choices
- Advantages and disadvantages to each type of regimen
- Individualize regimen choice

Initial Treatment: Preferred

NNRTI based	▪ EFV/TDF/FTC ^{1,2}
PI based	▪ ATV/r + TDF/FTC ² ▪ DRV/r (QD) + TDF/FTC ²
II based	▪ RAL + TDF/FTC ²
Pregnant women	▪ LPV/r (BID) + ZDV/3TC ²

1. EFV should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.
2. 3TC can be used in place of FTC and vice versa.

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Initial Treatment: Alternatives

NNRTI based	▪ EFV ¹ + (ABC/3TC) ^{2,3} or (ZDV/3TC) ² ▪ NVP ⁴ + ZDV/3TC ²
PI based	▪ ATV/r + (ABC/3TC) ^{2,3} or (ZDV/3TC) ² ▪ FPV/r (once daily or BID) + (ABC/3TC) ^{2,3} or (ZDV/3TC) ² or (TDF/FTC) ² ▪ LPV/r (once daily or BID) ⁵ + (ABC/3TC) ^{2,3} or (ZDV/3TC) ² or (TDF/FTC) ²

1. EFV should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.
2. 3TC can be used in place of FTC and vice versa.
3. ABC should not be used in patients who test positive for HLA B*5701; caution if HIV RNA >100,000 copies/mL, or if high risk of cardiovascular disease.
4. NVP should not be started if pre-ARV CD4 >250 in women or >400 in men.
5. QD LPV/r is not recommended in pregnant women.

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Initial Treatment: Acceptable

NNRTI based	▪ EFV ¹ + ddI + (3TC or FTC)
PI based	▪ ATV ⁴ + (ABC/3TC) ^{2,3} or (ZDV/3TC) ²
CCR5 Antagonist based	▪ MVC ⁵ + ZDV/3TC ²

1. EFV should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.
2. 3TC can be used in place of FTC and vice versa.
3. ABC should not be used in patients who test positive for HLA-B*5701; caution if HIV RNA >100,000 copies/mL, or if high risk of cardiovascular disease.
4. ATV/r generally preferred over ATV; consider unboosted ATV if RTV boosting not possible.
5. Tropism testing required before treatment with MVC; use only if CCR5-tropic virus is present.

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**Initial Treatment: May Be Acceptable
but More Definitive Data Needed**

PI based	▪ DRV/r + (ABC/3TC) ^{1,2} or (ZDV/3TC) ²
II based	▪ RAL + (ABC/3TC) ^{1,2} or (ZDV/3TC) ²
CCR5 Antagonist based	▪ MVC ³ + TDF/FTC ² or ABC/3TC ^{1,2}

1. 3TC can be used in place of FTC and vice versa.
2. ABC should not be used in patients who test positive for HLA-B*5701; caution if HIV RNA >100,000 copies/mL, or if high risk of cardiovascular disease.
3. Test tropism before treatment with MVC, use MVC only in those with exclusively CCR5-tropic virus.

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**Initial Treatment: Use with
Caution (1)**

NNRTI based	▪ NVP + ABC/3TC ^{1,2,3,4}
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1. 3TC can be used in place of FTC and vice versa.
2. ABC should not be used in patients who test positive for HLA-B*5701; caution if HIV RNA >100,000 copies/mL, or if high risk of cardiovascular disease.
3. NVP and ABC both can cause hypersensitivity reaction in first few weeks of treatment.
4. NVP should not be started if pre-ARV CD4 >250 in women or >400 in men.

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**Initial Treatment: Use with
Caution (2)**

PI based	<ul style="list-style-type: none"> ▪ FPV + (ABC/3TC) or (ZDV/3TC) or TDF/FTC^{1,2,3,4} ▪ SQV/r + TDF/FTC^{2,4} ▪ SQV/r + ABC/3TC or ZDV/3TC^{2,3,4}
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1. FPV/r generally preferred over unboosted FPV. Virologic failure may select mutations that confer cross-resistance to DRV.
2. 3TC can be used in place of FTC and vice versa.
3. ABC should not be used in patients who test positive for HLA-B*5701; caution if HIV RNA >100,000 copies/mL, or if high risk of cardiovascular disease.
4. SQV/r associated with PR and QT prolongation. Do baseline ECG; avoid SQV/r if risks prolonged QT or risk factors for PR and QT prolongation or AV block.

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ARVs Not Recommended in Initial Treatment

High rate of early virologic failure	<ul style="list-style-type: none"> • ddl + TDF
Inferior virologic efficacy	<ul style="list-style-type: none"> • ABC + 3TC + ZDV as 3-NRTI regimen • ABC + 3TC + ZDV + TDF as 4-NRTI regimen • DLV • NFV • SQV as sole PI (unboosted) • TPV/r
High incidence of toxicities	<ul style="list-style-type: none"> • d4T + 3TC • ddl + TDF • IDV/r • RTV as sole PI

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ARVs Not Recommended in Initial Treatment (2)

High pill burden/ Dosing inconvenience	<ul style="list-style-type: none"> • IDV (unboosted)
Lack of data in initial treatment	<ul style="list-style-type: none"> • ABC+ TDF • ABC + ddl • DRV (unboosted) • ENF (T-20) • ETR
No benefit over standard regimens	<ul style="list-style-type: none"> • 3-class regimens • 3 NRTIs + NNRTI

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ARV Medications: Should Not Be Offered at Any Time

- ARV regimens not recommended:
 - Monotherapy with NRTI*
 - Dual-NRTI therapy
 - 3-NRTI regimen (except ABC + 3TC + ZDV or possibly TDF + 3TC + ZDV, when other regimens are not desirable)

* If ZDV monotherapy is being considered for prevention of mother-to-child transmission, see Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States.

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Antiretroviral Combinations NOT Recommended

- Didanosine (DDI) + Tenofovir (TDF)
 - Combination leads to higher DDI drug levels and increased incidence of DDI related toxicities
 - Higher risk for immunologic nonresponse
 - Higher rate of early virologic failure
 - Rapid development of resistance
 - Clinicians with patients on this regimen should consider changing to an alternate NRTI backbone

Hepatitis B (HBV)/HIV Coinfection

- If HIV or HBV treatment is needed, include the following as part of a fully suppressive ARV regimen
 - FTC + TDF or TDF + 3TC
 - If TDF cannot be safely used, the recommended alternative regimen is:
 - Entecavir + a fully suppressive ARV regimen

HBV/HIV Coinfection

- Other treatment options for HIV/HBV
 - Peginterferon alfa monotherapy (if non-cirrhotic)
 - Adefovir in combination with 3TC or FTC or telbivudine in addition to a fully suppressive ART
- If a patient has HBV suppression, but develops HIV virologic failure, drugs active against HBV should be continued in combination with other ARVs suitable to achieve HIV suppression

Case

- HK has HIV/HBV coinfection and has been treated with TDF/FTC/EFV (Atripla®). He had full suppression of his HIV viral load and his HBV DNA PCR for 2 years. On his last 2 sets of labs, his HIV RNA was over 2000 copies/mL with continued HBV suppression. A genotype shows a mutation at K103N and no other major mutations.

Case

- Which of the following would be a reasonable option for treatment now?
- A) Continue Atripla® and add ritonavir boosted darunavir (rDRV)
- B) Stop Atripla® and start ZDV/3TC (Combivir®) + ritonavir boosted atazanavir (rATV)
- C) Stop Atripla® and start TDF/FTC (Truvada®) + DRV/r
- D) Continue Atripla®

Mycobacterium tuberculosis (TB)/HIV Coinfection

- All HIV-infected people diagnosed with active TB should be started on TB treatment immediately
- Antiretroviral initiation is recommended based on time since initiation of TB therapy as follows:

CD4 Count (cells/mm ³)	Time since initiation of TB therapy
< 200	Within 2-4 weeks (AI)
200-500	Within 2-4 weeks, at least by 8 weeks (AIII)
> 500	Within 8 weeks (BIII)

Reference: Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents. DHHS. January 10, 2011.; 1-166.

Mycobacterium tuberculosis (TB)/HIV Coinfection

- Coadministration of protease inhibitors (PIs) and Rifampin is not recommended
 - Use rifabutin in this situation*
- Immune reconstitution inflammatory syndrome (IRIS) might occur after ART initiation
 - Manage IRIS while continuing ART and TB therapy

*Other drug interactions are possible, so please refer to DHHS guidelines as well as other resources to evaluate potential drug interactions

Summary

- Recent FDA approved antiretrovirals
 - Virmune XR™
 - Rilpivirine™
- Drug on horizon: Quad Pill
 - EVG/COBI/FTC/TDF
- DHHS Adult and Adolescent Treatment Guideline Update

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