Antiretroviral Therapy: Cases to Ponder
A Panel to Stump!

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Learning Objectives

After attending this presentation, learners will be able to:

• Describe HIV-1 assays used to diagnose acute and chronic HIV infection
• Apply HIV treatment guidelines on when to start antiretroviral therapy to specific clinical scenarios
• Explain the need for HIV-1 resistance testing prior to initiation of antiretroviral therapy

Diagnosis of HIV-1 Infection
In acute HIV infection which of the following tests are likely to be positive?

1. 3rd Generation EIA
2. Plasma HIV RNA
3. Rapid HIV antibody test
4. 4th Generation EIA
5. None of the above
6. B and D
7. All of the above
Treatment of Integrase Inhibitor experienced patients
Which of the following statements is true
1. Dolutegravir is active against all HIV-1 variants resistant to raltegravir and elvitegravir
2. Dolutegravir has limited activity against viruses that are resistant to raltegravir and elvitegravir
3. Dolutegravir retains full or partial activity against many HIV-1 variants that are resistant to raltegravir or elvitegravir
4. Dolutegravir once daily will be recommended for the treatment of patients with raltegravir or elvitegravir experience.

When to Start?
Is this still a question?

Case #1
- RJ is a 21-year-old Black MSM, with multiple sex partners who presents with penile discharge and gram negative cocci on gram stain
- He is diagnosed with GC but when you speak to him he has had a week of fevers and fatigue, and you note small mobile cervical nodes bilaterally and a small modestly painful ulcer on his tongue
- He is dark skinned but may have a faint rash; he has no rash on his palms or soles and no other skin, genital or perirectal lesions.
- His most recent sex was receptive and insertive anal sex 2 weeks ago with 2 partners of unknown HIV status
Case #1
In addition to an RPR, HSV PCR, throat and rectal swabs for GC and chlamydia, what additional tests would you do?

1. Standard third generation HIV EIA
2. Rapid HIV test and 4th generation EIA
3. Rapid HIV test and HIV RNA PCR
4. Something else?

Case #1
A rapid test for HIV-1 antibody is negative as is the RPR and tests for GC/Chlamydia except for urine for GC. He is sent home with appropriate treatment of GC and the next morning his 4th generation EIA is positive. Which statement is true?

1. This is a false + test and the patient is not HIV infected
2. His HIV rapid antibody test was falsely negative and this patient is chronically HIV infected
3. This patient likely has a + p24 antigen and is acutely infected
4. Something else

Assay Conversion in Acute HIV infection

Peak viremia: 10^7-10^8 gEq/mL

- HIV RNA (p24)
- HIV p24 Ag
- HIV antibody
- p24 Ag EIA
- HIV MP-RTX
- HIV 1D-RTX
- "blip" versus

- Courtesy of Cynthia Gay
4th Generation HIV Ag/Ab Assay

Solid phase: Anti-p24 Mab
* HIV-1 and HIV-2 recombinant proteins

Sample

p24 Ag
Anti-HIV Ab

Conjugates: Anti-p24 Mab
Anti-HIV Ab
HIV-1 and HIV-2 proteins

Detection

How does a 4th Generation IA (ARCHITECT® HIV Ag/Ab Combo) perform on the recent / acute infection panel?


- Detects 57 / 64 positively (89%)
  - (3rd gen detected 42%)
- Of the 29 "recently infected" specimens: 29/29 (100%)
  - (2nd gen detected 93%)
  - (Uni-gold Rapid: 76%)
- Of the 35 "acute" specimens (RNA pos, completely Ab negative: 28/35 [80%])

Sensitivity of ARCHITECT® HIV Ag/Ab Combo for antibody negative (acute) individuals:

<table>
<thead>
<tr>
<th>Viral loads of specimens NOT detected by the ARCHITECT® HIV Ag/Ab Combo: RNA copies / ml: (7 specimens)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,177</td>
</tr>
<tr>
<td>3,621</td>
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<tr>
<td>5,770</td>
</tr>
<tr>
<td>6,373</td>
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<tr>
<td>9,655</td>
</tr>
<tr>
<td>12,892</td>
</tr>
<tr>
<td>14,062</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Viral loads of acute HIV specimens detected by ARCHITECT® HIV Ag/Ab Combo: RNA copies / ml: (18 specimens)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 30,734</td>
</tr>
</tbody>
</table>

J. J. Eron, Jr, MD

June 18, 2013
Case #1
You recognize that RJ likely has acute HIV infection with a + 4th Generation EIA with a negative rapid antibody test. What is the best confirmatory test at this point?

1. HIV antibody EIA using a different assay
2. Western blot
3. Plasma HIV RNA assay
4. Wait 2 – 4 weeks and repeat the Western blot
5. Something else

Case #1
You ask that the HIV RNA assay be done as soon as possible and you also send HIV genotype – the plasma HIV RNA comes back at 3,400,000 c/mL. What do you do now?

1. Counsel the patient on risk reduction and refer to local Ryan White Clinic as he has no insurance
2. Refer to a clinical trial for patients with acute HIV infection
3. Wait for the results of the resistance test and begin ART
4. Begin ART as soon as possible
5. Something else

Case #1
There is no available clinical trial in your area. What do you do now?

1. Counsel the patient on risk reduction and refer to local Ryan White Clinic as he has no insurance
2. Wait for the results of the resistance test and begin ART
3. Begin ART as soon as possible
4. Something else
Case #1
You decide to initiate antiretroviral therapy – what regimen do you begin?
1. 2 NRTI and DRV/r or ATV/r
2. FDC TDF/FTC/EFV
3. FDC TDF/FTC/EVG/cobicistat
4. 2 NRTI and raltegravir
5. FDC TDF/FTC/rilpivirine
6. Something else

DHHS Recommendation March 2013
• ART is recommended for all persons with HIV infection and should be offered to those with acute/early HIV infection (BII); definitive data are lacking as to whether this will result in long-term virologic, immunologic, or clinical benefits.
• Genotypic drug-resistance testing should be performed before initiation of ART to guide the selection of the regimen (AII). If therapy is deferred, genotypic resistance testing should still be performed.
• ART can be initiated before drug resistance test results are available. RTV-PIs combined with NRTIs should be used in this setting (AIII).

IAS-USA 2012 Thompson et al JAMA
• ART is recommended and should be offered to persons during the acute phase of primary HIV infection, regardless of symptoms (BIII)
• Benefit may be more apparent with symptomatic acute infections
• Reasons include
  – Potential to limit immune damage
  – Reduction in HIV DNA (and by inference HIV reservoir)
  – Lower set-point in acutely treated patients who stop therapy and delayed CD4 cell decline
  – Decrease transmission risk
Very early initiation of ART limits size of reservoir, particularly in those cells which may be main barrier to cure ($T_{CM}$)

HPTN 052: HIV Transmission Reduced by 96% in Serodiscordant Couples

Single transmission in patient in immediate HAART arm believed to have occurred close to time therapy began and prior to suppression of genital tract HIV
Each percentage point increase in ART coverage among all HIV+ adults in a community associated with 1.7% decline in the hazard of HIV acquisition ($P < .001$) faced by an HIV- adult living in the same community.

Case #2: EM, a 61-year-old woman, newly diagnosed with HIV infection

- Husband died 4 years ago of “alcoholism”
  - She has not been sexually active since that time
- Asymptomatic; not coinfected with HBV or HCV but is obese, has diabetes on metformin and HTN on HCTZ
- Attended several follow-up visits and is engaged in care
- Will follow your advice regarding ART but is worried about adding additional medications if she “doesn’t need them”
- HIV-1 RNA: 1480 copies/mL
- CD4+ count: 800 cells/mm$^3$
Would you recommend ART for EM?

1. Yes – I would begin once her genotype was available
2. Yes – but I would wait several months – follow her viral load, blood pressure and HgbA1C
3. No – I would wait until there was clear progression given that she is likely a very slow progressor
4. Not sure

IAS-USA 2012 Thompson JAMA

- ART should be offered regardless of CD4 cell count (AIa-CIII). The strength of the recommendation increases as CD4 cell count decreases
  - For CD4 cell count of 500/μL and below: AIa
  - For CD4 cell count above 500/μL: BIII
- Pregnancy: AIa
- HBV co-infection: AIa
- HCV co-infection: CIII (however, co-infection with CD4 cell count 500/μL may delay ART until after completion of HCV treatment)
- Age older than 60 years: BIIa
- HIV-associated nephropathy: AIa

When to Start: DHHS Guidelines 2/13/2013

ART recommended for all HIV+ individuals. Strength of recommendation varies based on CD4 count:

<table>
<thead>
<tr>
<th>Clinical Condition and/or CD4 Count</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 ≤ 350</td>
<td>AI</td>
</tr>
<tr>
<td>CD4 350-500</td>
<td>AI</td>
</tr>
<tr>
<td>CD4 &gt;500</td>
<td>BIII</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>AI</td>
</tr>
<tr>
<td>History of AIDS-defining illness</td>
<td>AI</td>
</tr>
<tr>
<td>HIV-associated nephropathy</td>
<td>AI</td>
</tr>
<tr>
<td>HBV co-infection</td>
<td>AI</td>
</tr>
<tr>
<td>Risk of sexual transmission</td>
<td>AI</td>
</tr>
<tr>
<td>- heterosexual</td>
<td>AI</td>
</tr>
<tr>
<td>- other risk groups</td>
<td>AI</td>
</tr>
<tr>
<td>Acute and Early Infection</td>
<td>BII</td>
</tr>
</tbody>
</table>
Patients Starting ART at Higher CD4+ Cell Counts Overall, but Disparities Remain

- CD4+ cell count at start of ART (cells/mm³), 2009[1]

- In San Francisco study, overall trends of starting ART at higher CD4+ counts, but pts initiating ART at CD4+ counts > 350 cells/mm³ significantly more likely to be white, older, MSM, nonpoor, and diagnosed by private provider[2]


WIHS: Black HIV+ Women Twice as Likely to Die of AIDS Than White HIV+ Women

- N = 1471 women on continuous HAART

- Other significant predictors of AIDS death: depression, peak HIV-1 RNA, nadir CD4+ cell count, HCV coinfection, illegal drug use, < 95% adherence to ART

- Black race, depression predicted reduced adherence to HAART, but black race remained associated with AIDS death after adjusting for adherence


Case #2: EM, a 61-year-old woman, newly diagnosed with HIV infection

Her BMI = 36.8, cr = 0.87, AST/ALT are normal, HgbA1C is 7.6 on metformin and her U P/cr = 0.330

Her HIV genotype is wild type

Fasting Lipid = TG 157, Chol 188, HDL 36, LDL = 120. She is not on a statin

Would you get a bone density scan prior to starting therapy (61 yo black woman – G4P3 plus 6 grandchildren)?

- Yes
- No
- Not sure

47% 1. Yes
46% 2. No
8% 3. Not sure
Case #2: EM, 61-year-old woman, new HIV
Her hip and lumbar T score on dxa are -1.2 and -1.8 (osteopenia) and no secondary causes of osteopenia or osteomalacia are found. You decide to start therapy (recall CD4 800 and VL = 1480, cr = 0.87 – CrCl 80 by MDRD, WT virus). HLA B5701 negative.
Which NRTI combination would you choose?

1. TDF/FTC
2. ABC/3TC
3. ZDV/3TC
4. You would not choose an NRTI

Case #2: EM, 61-year-old woman, new HIV
You choose TDF/FTC. What would you combine it with?

1. TDF/FTC/EFV – fixed-dose combination (FDC)
2. TDF/FTC + ATV/RTV
3. TDF/FTC + DRV/RTV
4. TDF/FTC + RAL BID
5. TDF/FTC/rilpivirine FDC
6. TDF/FTC/elvitegravir/cobicistat FDC
7. Wait for dolutegravir
8. Something else
DHHS Guidelines, February 2013
Preferred Regimens

Preferred regimens: Optimal and durable efficacy, favorable tolerability and toxicity profile, and ease of use
(Arranged in order of duration of clinical experience of third agent)

- Boosted PI based
  - ATV/RTV + TDF/FTC
  - DRV/RTV + TDF/FTC

- INSTI based
  - RAL + TDF/FTC

An alternative to EFV should be considered in women considering pregnancy
Atazanavir should be avoided in patients on > 20 mg omeprazole daily (or equivalent)
TDF should be used with caution in patients with renal insufficiency

DHHS Guidelines for Antiretroviral Therapy in Adults and Adolescents. Feb 2013.

DHHS Guidelines, March 2013:
Alternative Regimens

Effective and tolerable but have potential disadvantages compared with preferred regimens. May be the preferred regimen for some patients.

- Boosted PI based
  - ATV/RTV + ABC/3TC
  - DRV/RTV + ABC/3TC
  - FPV/RTV (QD or BID) + ABC/3TC or TDF/FTC
  - LPV/RTV (QD or BID) + ABC/3TC or TDF/FTC

ABC should not be used in HLA B5701 positive patients and with caution in patients with VL > 100,000 c/mL or cardiovascular disease
RPV is not recommended in patients with VL > 100,000 c/mL and is contraindicated with PPI
ELV/COBI/TDF/FTC should not be started in patients with est. CrCl < 70 mL/min

DHHS Guidelines for Antiretroviral Therapy in Adults and Adolescents. Feb 2013.

IAS-USA 2012 Thompson et al JAMA

<table>
<thead>
<tr>
<th>Included in the table</th>
<th>Alternative Regimen (2013)</th>
<th>Notes</th>
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<tbody>
<tr>
<td>NNRTI based</td>
<td>efavirenz + rilpivirine + tenofovir disoproxil fumarate</td>
<td>None</td>
</tr>
<tr>
<td>boosted PI based</td>
<td>atazanavir + raltegravir + tenofovir disoproxil fumarate</td>
<td>None</td>
</tr>
<tr>
<td>boosted PI based</td>
<td>darunavir + raltegravir + tenofovir disoproxil fumarate</td>
<td>None</td>
</tr>
<tr>
<td>boosted PI based</td>
<td>lopinavir + ritonavir + tenofovir disoproxil fumarate</td>
<td>None</td>
</tr>
</tbody>
</table>
ECHO/THRIVE: RPV + TDF/FTC vs EFV + TDF/FTC—96-Wk Efficacy


ECHO and THRIVE (Combined Data)

<table>
<thead>
<tr>
<th>All</th>
<th>RPV (n = 686)</th>
<th>EFV (n = 682)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL &lt; 50 c/mL (ITT-TLOVR)</td>
<td>84</td>
<td>82</td>
<td>2.0 (-2.0 to 6.0)</td>
</tr>
<tr>
<td>VF</td>
<td>9</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>DC AE/Death</td>
<td>2</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>DC Other</td>
<td>5</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 100K to ≤ 500 K</td>
<td>RPV (n = 249)</td>
<td>EFV (n = 270)</td>
<td>-3.1 (-9.8 to 3.7)</td>
</tr>
<tr>
<td>VL &lt; 50 c/mL (ITT-TLOVR)</td>
<td>80</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>VF</td>
<td>13</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>DC AE/Death</td>
<td>2</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>DC Other</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>&gt; 500,000 c/mL</td>
<td>RPV (n = 69)</td>
<td>EFV (n = 82)</td>
<td>-6.0 (-20.4 to 8.3)</td>
</tr>
<tr>
<td>VL &lt; 50 c/mL (ITT-TLOVR)</td>
<td>70</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>VF</td>
<td>22</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>DC AE/Death</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>DC Other</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

STaR: Efficacy of Rilpivirine/TDF/FTC vs EFV/TDF/FTC at Wk 48

RPV/TDF/FTC noninferior to EFV/TDF/FTC in overall population and in pts with BL HIV-1 RNA > 100,000 c/mL
- RPV/TDF/FTC superior to EFV/TDF/FTC in pts with BL HIV-1 RNA ≤ 100,000 c/mL

**STaR vs ECHO/THRIVE: Virologic Failure by Wk 48**

- **STaR**:
  - RPV/TDF/FTC
  - EFV/TDF/FTC
- **ECHO/THRIVE (TDF/FTC subsets)**:
  - RPV + TDF/FTC
  - EFV + TDF/FTC

<table>
<thead>
<tr>
<th>BL HIV-1 RNA (c/mL)</th>
<th>Overall</th>
<th>≤ 100K</th>
<th>&gt; 100-500K</th>
<th>&gt; 500K</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STaR</strong></td>
<td>5</td>
<td>13</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td><strong>ECHO/THRIVE</strong></td>
<td>20</td>
<td>11</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td><strong>RPV/TDF/FTC</strong></td>
<td>20</td>
<td>11</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td><strong>EFV/TDF/FTC</strong></td>
<td>20</td>
<td>11</td>
<td>6</td>
<td>20</td>
</tr>
</tbody>
</table>


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**STaR: Wk-48 Resistance With Rilpivirine/TDF/FTC vs EFV/TDF/FTC**

<table>
<thead>
<tr>
<th>Pts With Resistance Outcome, %</th>
<th>Stall</th>
<th>ECHO/THRIVE (TDF/FTC subsets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance analysis data available</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Detected resistance</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>
  - BL VL ≤ 100,000 c/mL        | 2     | 1                              |
  - BL VL > 100,000-500,000 c/mL | 1     | 1                              |
  - BL VL > 500,000 c/mL        | 19    | 4                              |
| Primary NNRTI resistance      | 4     | 1                              |
  - K101E                        | 1     | 1                              |
  - K103N                        | 0.3   | 1                              |
  - E138K/Q                      | 2     | 1                              |
  - Y181C/I                      | 2     | 1                              |
| Primary NRTI resistance        | 4     | 0.3                           |
  - K65R/N                       | 1     | 1                              |
  - M184V/I                      | 4     | 0.3                           |
  - K219E                        | 4     | 0.3                           |
  - M264V/I                      | 4     | 0.3                           |


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**Case #3: To PrEP or not to PrEP**

- Your patient is a 35 yo man who was diagnosed with PML in 9/2012 and has responded well to antiretroviral therapy. He is on TDF/FTC and RAL twice daily and now has a CD4 cell count above 300 and VL < 40 c/mL detected.
- He has a wife and 3 children ages 6, 8 and 11. She is HIV negative and was just recently tested again.
- They have not had sex since his diagnosis but want to discuss this with you.
- They have never used condoms and they plan only to have vaginal and oral sex.
- She is otherwise healthy and is on no medications except birth control pills.
Case #3: To PrEP or not to PrEP

What advice would you give to this couple? – they do not have any plans to have more children

1. Resume having sex using condoms for vaginal sex but not oral sex
2. Resume having sex using condoms/barriers for oral and vaginal sex
3. Do not have sex until his HIV RNA is < 40 c/mL and undetectable
4. Resume sex, use condoms to the best of their ability but first have the uninfected woman begin TDF/FTC
5. Something else

Partners PrEP: Both PrEP Strategies Significantly Reduce HIV Acquisition

<table>
<thead>
<tr>
<th>Primary Efficacy Outcome, mITT Analysis</th>
<th>TDF (n = 1584)</th>
<th>TDF/FTC (n = 1579)</th>
<th>Placebo (n = 1584)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV acquisitions, n</td>
<td>17</td>
<td>13</td>
<td>52</td>
</tr>
<tr>
<td>HIV incidence/100 PY</td>
<td>0.85</td>
<td>0.50</td>
<td>1.99</td>
</tr>
<tr>
<td>Efficacy vs placebo, % (95% CI)</td>
<td>67 (44-81)</td>
<td>75 (50-81)</td>
<td>--</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; .0001</td>
<td>&lt; .0001</td>
<td>--</td>
</tr>
</tbody>
</table>

- Both PrEP strategies associated with significant reduction in HIV acquisition vs placebo in both men and women
  - TDF efficacy: 71% in women, 63% in men
  - TDF/FTC efficacy: 66% in women, 84% in men

FEMPrEP: Low Adherence Rates in Oral TDF/FTC Pre-Exposure Prophylaxis Trial

- FEM-PrEP: Phase III study of oral TDF/FTC planned for 3900 high-risk women in Africa (2120 randomized)
  - Announced April 18, 2011, that study was ended early because of lack of efficacy
  - 35 vs 33 new HIV infections in the placebo and FTC/TDF arms
  - TFV blood levels indicated that use was too low (< 40%) to assess efficacy
  - 4 vs 1 patient with M184V/I in the TDF/FTC and placebo arms

VOICE: Lack of Detectable TFV in Plasma; High Rate of Infection in Younger Women

- Despite high self-reported adherence, < 40% of women had detectable plasma TFV at first study visit
- TFV detected in mean of ≤ 30% of samples in each arm
  - ≤ 50% of women in each arm had no TFV detected in any sample
- TFV detection less likely if unmarried, younger than 25 yrs, partner younger than 28 yrs
- Highest rate of HIV acquisition in unmarried, younger than 25 yrs

Efficacy of HIV Prevention Strategies From Randomized Clinical Trials

- ART for prevention, HPTN 052, Africa, Asia, Americas
- PrEP for discordant couples, Partners PrEP, Kenya
- PrEP for heterosexual men and women, TDF, Botswana
- Medical male circumcision, Uganda, Kenya, South Africa
- Sexually transmitted diseases treatment, Tanzania
- Microbicide, CAPRISA 004, South Africa
- HIV vaccine, RV144, Thailand

Case #4

- 34 yo AA man with newly diagnosed HIV. He has a long-term HIV+ partner. 4 months ago he had a severe “viral illness.” Of note his partner who had been suppressed on therapy for years stopped therapy when he moved to NC and did not enter ADAP
- Partner’s previous history: ZDV/3TC plus EFV -> TDF/FTC/EFV
- Our patient has CD4 cell count of 590 cells (confirmed on repeat) and HIV RNA 165,000. He is HCV, HBV negative, has a cr of 0.8 and ALT of 28.
- He desires antiretroviral therapy
Case #4
What resistance test(s) do you want?

1. Standard RT/pro genotype
2. Genotype and phenotype (RT/pro)
3. Tropism testing
4. Integrase resistance testing
5. 1 and 3
6. 1 and 4
7. Something else

Case #4
His RT/pro genotype has a K103N, plus a 215D mutation both in RT.
What therapy would you begin?

1. FDC EFV/TDF/FTC
2. FDC RPV/TDF/FTC
3. DRV/r plus TDF/FTC
4. DRV/r plus ABC/3TC
5. ATV/r plus TDF/FTC
6. FDC ELV/cobicistat/TDF/FTC
7. RAL BID plus 2 NRTI
8. Something else

Transmitted Drug Resistance in US:
Newly Diagnosed

- 2007 CDC surveillance for transmitted drug resistance (TDR)
  - 10,496 with new HIV Dx
  - 2,480 with genotype
- TDR detected in 16% of patients with new HIV diagnosis
  - Most common: NNRTI
  - 83% had single mutation
- No demographic risk factors identified

Transmitted Drug Resistance in North Carolina

Prevalence of Transmitted Drug Resistance

<table>
<thead>
<tr>
<th>Year</th>
<th>AHI</th>
<th>CHI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>2011</td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td>2012</td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td>2013</td>
<td>8%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Yanik EL, et al. JAIDS [Epub ahead of print].

# TDR (%)

- AHI
- CHI

PR Transmitted Drug Resistance for AHI
2.44; 95% CI 1.30; 4.59; p = 0.006

Treatment Response with Transmitted Drug Resistance

- Wittkop et al. Lancet ID 2011

"Quad" therapy with NNRTI Resistance

<table>
<thead>
<tr>
<th>NNRTI Resistance Mutation</th>
<th>Number of Subjects at Time</th>
<th>Week 48: Success</th>
<th>Failure</th>
<th>Resistance Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Primary NNRTI Mutation</td>
<td>96 (13.3%)</td>
<td>33 (40.0%)</td>
<td>27 (32.1%)</td>
<td>33 (40.0%)</td>
</tr>
<tr>
<td>K103N</td>
<td>17 (3.3%)</td>
<td>5 (30.0%)</td>
<td>12 (72.5%)</td>
<td>5 (30.0%)</td>
</tr>
<tr>
<td>Y181I</td>
<td>6 (1.9%)</td>
<td>2 (33.3%)</td>
<td>4 (66.7%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>A34G</td>
<td>11 (1.9%)</td>
<td>11 (100%)</td>
<td>0 (0%)</td>
<td>11 (100%)</td>
</tr>
<tr>
<td>Y181V</td>
<td>7 (1.9%)</td>
<td>7 (100%)</td>
<td>0 (0%)</td>
<td>7 (100%)</td>
</tr>
<tr>
<td>E138A/F</td>
<td>10 (1.7%)</td>
<td>10 (100%)</td>
<td>0 (0%)</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>V106I/C</td>
<td>4 (1.7%)</td>
<td>4 (100%)</td>
<td>0 (0%)</td>
<td>4 (100%)</td>
</tr>
<tr>
<td>L10W</td>
<td>7 (2.0%)</td>
<td>7 (100%)</td>
<td>0 (0%)</td>
<td>7 (100%)</td>
</tr>
<tr>
<td>M41L</td>
<td>2 (0.3%)</td>
<td>2 (100%)</td>
<td>0 (0%)</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>F227L</td>
<td>1 (0.2%)</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
<td>1 (100%)</td>
</tr>
</tbody>
</table>

White et al. CRW Sitges 2012 #4

J. J. Eron, Jr, MD

IAS–USA

June 18, 2013
Case #5

- 62 yo white man with very long treatment history that included EFV, most NRTI, and several PIs who moves to Washington DC and arrives in your clinic. He is on TDF/FTC plus LPV/r and RAL. His CD4 is 500 and his VL is 6,700. His cr. is 0.7 and his ALT is 29. HCV Ab neg and HBV immune.
- He states VL had been ‘undetected’ but with the move he missed several refills. He is now back to his usual good adherence (misses 2-3 doses per month)

Case #5

What resistance test(s) do you want?

1. Standard RT/pro genotype
2. Genotype and phenotype (RT/pro)
3. Tropism testing
4. Integrase resistance genotype
5. Integrase resistance phenotype
6. 2 and 3 and 4
7. 2 and 3 and 5
8. Something else

Case #5

- RT and PR genotype shows
  - 103N and 188L (Stanford ETR fold est FC = 5.3)
  - 184V, 41L, 210W 215Y (TDF est fold change 2.1)
  - L10I, 54V, 82A and 90M (DRV est fold change 2.0)
- Integrase genotype
  - 155H
- Tropism
  - Dual mixed
Case #5

RT and PR genotype shows 303N and 388L (Stanford ETR fold est FC = 5.3) 184V, 41I, 210W, 215Y (TDF est fold change 2.1) L10I, 54V, 82A and 90M (DRV est fold change 2.0) Integrase genotype 155H, Tropism Dual mixed

What would you do now?
1. Change to DRV/r, etravirine, TDF/FTC
2. Change to DRV/r, etravirine, TDF/FTC and ZDV (consider adding MVC)
3. Stop all therapy
4. Stop RAL and continue partially active therapy awaiting dolutegravir
5. Stop RAL and LPV/r and continue TDF/FTC awaiting dolutegravir
6. Continue all current therapy
7. Something else

InSTI resistance mutations and DTG FC

Subjects, n
- Cohort I 3 2 4 4 12 2
- Cohort II 2 1 8 6 6 1

Change from Baseline in Plasma HIV-1 RNA at Day 11 (log_{10} c/mL) Against Baseline DTG FC

Baseline DTG FC in IC50 Relative to Wild Type Virus

Dolutegravir (DTG, S/GSK1349572, 572)