HIV The Basics
Resistance 101: Interpreting and Using the Data

Sources: IAS - http://www.iasusa.org
DHHS - http://www.aidsinfo.nih.gov/guidelines/

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Acknowledgements:

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Objectives

• At the conclusion of this presentation, listeners should be better able to:

• Identify the most clinically significant antiretroviral resistance mutations associated with various classes of HIV drugs

• Select appropriate types of antiretroviral resistance tests and implement these tests into their clinical practice to maximize successful patient outcomes
Off-Label Disclosure:

There will be no off-label/investigational uses discussed in this presentation.
What is Resistance & How Does It Occur?

- The ability of HIV to multiply in the presence of suppressive level of antiretroviral drugs; Does not make HIV more pathogenic
  - Perhaps less pathogenic? Mutations may impair viral fitness.
- Can occur as primary transmission of resistant virus (TDR)
- Can occur with sub-suppressive levels of anti-viral drugs & then natural selection of mutant strains
  - Partial adherence to regimen
  - Sub-optimal dosing of drugs
  - Drug interactions
  - Incomplete absorption in intestinal tract

Viral Resistance is the Outcome of Viral Replication, Mutations & Selection Pressure

US Transmitted Drug Resistance: Newly Diagnosed

• 2007 CDC surveillance for TDR detected 16% of pts with new HIV diagnosis & mutations
  – Most common: NNRTI
  – 83% had single mutation

Primary Resistance in Young Pts: 55 recently infected pts (16-24 yo) from 15 US cities; approx. 50% AA; 25% Hisp.

<table>
<thead>
<tr>
<th>Resistance</th>
<th>By Genotype</th>
<th>By Phenotype</th>
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<tbody>
<tr>
<td>Overall</td>
<td>18%</td>
<td>22%</td>
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<tr>
<td>NNRTI</td>
<td>15%</td>
<td>18%</td>
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<tr>
<td>PI</td>
<td>3.6%</td>
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<tr>
<td>NRTI</td>
<td>4%</td>
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Resistance Testing: DHHS Guidelines

• Recommended in acute HIV infection
• Should be done for all pregnant women prior to therapy, or for those entering pregnancy with a detectable HIV VL on therapy
• In chronic infection, recommended for all patients on entry into care, regardless of treatment plan
• Perform when managing suboptimal VL decrease
• In the setting of viral failure, testing should be done while the patient is on therapy, or within 4 wks of stop
• Recommended to assist in selecting active drugs for pts with viral failure & \( \text{VL} > 1000; \text{Consider in VL} > 500 \)

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-adults and adolescents. DHHS. December 1, 2009; 1-161.
Methods & Limitations of Resistance Testing

• Genotype:
  – Direct sequencing of viral genes reverse transcriptase and protease, less commonly integrase and envelope
  – Resistance to specific drugs is predicted based on known mutations
  – Mutations are detected only if mutant virus is at least 10-20% of virus population; minor variants can be missed

• Phenotype
  – Grow virus in culture with various amounts of drugs added
  – Direct measure of viral resistance
  – Does not explore the underlying mutations, just their affect on the ability of the drug to stop the virus

• Resistance tests are most accurate in assessing the current regimen; if resistance has ever been detected, then archived mutations exist
  – If no drug pressure exists, “wild type” virus will often overgrow the mutant strains

Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-adults and adolescents. DHHS. Dec 1, 2009; 1-161.
Genotypes

• Involve sequencing of various HIV genes and comparing results to reference wild type (wt) strain

• **Primary mutations** decrease drug susceptibility
  – Example: **M 184 V** in Reverse Transcriptase (RT)
  – 184 refers to amino acid (AA) position 184 in RT
  – M (methionine) is the wt AA; V (valine) is the mutant
  – “Mixtures” are when both wt and mutant AA’s are detected: M 184 M/V

• **Secondary mutations** are selected after 1° mutations and may have a limited or cumulative effect

• **Multi-Drug Resistance (MDR) mutations** can decrease susc. to many or all drugs in a single class

Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-adults and adolescents. DHHS. Dec 1, 2009; 1-161.
HIV Phenotype

- Phenotype refers to the growth characteristics virus in vitro; most useful for etravirine or PI’s; also non-subtype B HIV
- Standard phenotypic testing
  - Results usually expressed as fold-change in susceptibility compared to a laboratory control isolate
  - Interpretation of drug activity dependent on methodology used to define cutoffs (clinical, biological, technical)
- Virtual phenotype testing
  - Matches genotypic data against database of virus samples with paired GT and PT data
  - Confidence level based on number of matching genotypes within the database

√ Clinical cutoffs: based on pt virological response in clinical trials
Biologic cutoffs: based on natural variability of wt viruses from naïve pts
Technical cutoffs: based on assay variability w/ repeated testing of pt samples

Phenotypic Susceptibility: Relationship Between Drug Concentration and Viral Inhibition

Inhibition of Virus Replication (%) vs. Drug Concentration

- Wild-type IC₅₀
- Resistant IC₅₀

Fold change

Phenotypic Susceptibility: Relationship Between Drug Concentration and Viral Inhibition

Inhibition of Virus Replication (%)

Fold change

Wild-type IC₅₀

Resistant IC₅₀

Drug Concentration

Interpreting Phenotypes
Clinical Cutoffs differ for each drug

Probability of response

Lower clinical cutoff
Response is significantly reduced

“Zone of Intermediate Response”

Fold Change

Upper clinical cutoff
Response is unlikely

TFV cutoff analysis obtained from clinical trial data

Average change in viral load over 24 weeks

DAVG$_{24}$ > 0.5 log (%)

Tenofovir fold change

J Acquir Immune Defic Syndr 2008;48:26–34
Miller, et al 5th Resistance Workshop 2001, Scottsdale
Correlative and Clinical Outcomes Databases* Virtual Phenotype

- Routine clinical testing
- Clinical trials
- Research collaborations

Genotypic data >373,000
Phenotypic data >93,000
Correlative database >58,000 G/Ps

Nucleotide sequence (...AAGTC TCCGCAT GCATA...)

Virtual Phenotype™-LM engine

Clinical Outcomes Database
>21,000 patients or
>8,800 Treatment Change Episodes

Calculated Fold-Change values in IC_{50}
Clinical Cut-Offs

*Status Dec 08

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<th>DRUGS</th>
<th>0.00</th>
<th>1.00</th>
<th>2.00</th>
<th>3.00</th>
<th>4.00</th>
<th>(95% confidence limits)</th>
<th>CCO 1</th>
<th>CCO 2</th>
<th>BCO</th>
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<td>Tipranavir/r</td>
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<td>1.5</td>
<td>7.0</td>
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<td>Darunavir/r</td>
<td>DRV/r</td>
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<td>2.4 (2.2-2.7)</td>
<td>10.0</td>
<td>106.9</td>
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</table>
Which Resistance Test When? (DHHS)

- Genotype preferred due to faster result, lower cost and enhances sensitivity for detecting “mixtures”
  - In anti-retroviral naïve patients
  - In patients with sub-optimal viral response on therapy
  - Virologic failure on a first or second regimen

- Phenotype
  - “Addition of phenotypic testing to genotypic testing is generally preferred for persons with known or suspected complex drug resistance mutation patterns, particularly to protease inhibitors”

- Virtual Phenotype (not specifically stated in DHHS)
  - As a substitute when actual phenotype not available
HIV-1 Reverse Transcriptase

www.cs.stedwards.edu/chem/Chemistry/CHEM43/CHEM43/ViralP/function.html
Major nRTI Mutations

- **M184V** – diminishes viral fitness by approx. 50%*
  - Resistance to lamivudine and emtricitabine
  - Some resistance to didanosine and abacavir
  - **Restores** some activity to zidovudine/d4t, tenofovir

- **K65R**
  - Broad resistance to all nRTI; but ↑ susc. to AZT

- **L74V**
  - Resistant to abacavir & DDI; ↑ susc. to AZT, TDF

- **TAMs – 215, 41, 210, 67, 70, 219:** ↓ susc. to all nRTI
  - Selected by a prior tx history of AZT, D4T
  - More resistance w/ 41/210/215 than 67/70/219 path
  - **44D, 118I:** ↑ nRTI resistance with 41/210/215 path

*Castagna et al. XV WAC; July 11-16, 2004; Bangkok, Abstract WeOrB 1286*
Multinucleoside & Nucleotide Resistance

- Multinucleoside resistance is typically associated with high level resistance to most nucleosides:
  - Q151M complex; selected for by AZT/DDI use; TDF susceptibility preserved
  - serine insertions - 69S(S,S); selected for by DDI/D4T; assoc. with TDF resistance
  - multiple NAMS, especially with M184V
  - K65R – only ZDV reliably active; some d4T/TDF/ABC activity possible, but reduced

- Tenofovir resistance: K65R, 41/210/215Y, but may retain phenotypic (and clinical) activity
Tenofovir Susceptibility Ranges

Green dots = patient viruses from Monogram database

Grouped by shared mutational pattern

Current genotype algorithms would assess all viruses as Resistant

Fold Change

Response expected

Reduced or no response expected

ARS Question #1

When a treatment-experienced pt’s genotype shows K65R, the most likely interpretation is:

1. The pt is and will always be always highly resistant to tenofovir, so it should be stopped
2. The patient has developed the primary tenofovir resistance mutation, but tenofovir may still retain some activity in this pt
3. The pt has transmitted drug resistance from another individual
4. AZT is *not* likely to be effective in this pt
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Major NNRTI mutations

- **K103N**
  - Most common NNRTI mutation
  - High level resistance to efavirenz & nevirapine *but not* etravirine

- **Y181C**
  - High level resistance to nevirapine & intermediate to efavirenz
  - Some etravirine resistance, but provides a mutational foundation for development of higher levels of resistance
  - 98/101/106/108/188/G190A also important; *in non-clade B, 106*

- There is broad cross resistance between nevirapine and efavirenz due to low genetic barriers
  - A single mutation can eliminate activity of EFV or NVP
  - *No impact of NNRTI mutations on viral fitness*, so continued use of NNRTI in the face of resistance adds nothing

Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-adults and adolescents. DHHS. Dec 1, 2009; 1-161.
First and Second-Generation NNRTI’s

NVP (Nevirapine)  EFV (Efavirenz)  ETR (Etravirine)

Etravirine: Second generation NNRTI

- May retain activity against HIV with NNRTI resistance from NVP or EFV
  
  \textit{K103N alone does not affect etravirine}

- Has a higher genetic barrier than other NNRTI, therefore a mutation score has been developed
  
  \textbf{Y181C} yields a “resistance weight factor” of 2.5 (intermediate)

  \textbf{G190A} yields a “resistance weight factor” of 1 (low)

- In a study of 14,940 samples submitted for resistance testing: 5,482 (36.7%) had resistance to EFV or NVP, but 67.2% remained sensitive to ETR by genotype and 76.4% by phenotype

Etravirine Resistance Score

Weighted mutation score corresponded to response rates as follows:

- **0-2:** 74% (highest response)
- **2.5-3.5:** 52% (intermediate response)
- **≥ 4:** 38% (reduced response)

**Weighted Mutation Score**

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<th>Weighted Mutation Score</th>
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<th>1.5</th>
<th>2.5</th>
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</table>

ARS Question #2

Pick the most correct statement regarding the potential for “sequencing” NNRTI’s:

1. After a pt develops a K103N mutation on efavirenz, nevirapine is often effective
2. A Y181C mutation completely eradicates the clinical effect of etravirine
3. A provider need not worry about a genotype with “transmitted” K103N in a newly diagnosed pt, since TDF/FTC/EFV is a potent triple ARV
4. Etravirine, combined with additional ARV’s, may be effective for individuals who have failed TDF/FTC/EFV starting regimens
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Figure 2. CRF01_AE protease in complex with p1-p6 (green). Amino acid changes in monomer A (cyan) are indicated in red, and changes in monomer B (magenta) are indicated in blue. (Bandaranayake et al. JV. 2008)
Major protease mutations

• “Signature” mutations for non-boosted PI
  – **D30N**: nelfinavir; no cross-resistance
  – **I50L**: unboosted ATV (RTV boosting alters mutations)
  – **I50V**: fosamprenavir; some cross-resistance to lopinavir
  – **G48V**: saquinavir; no cross-resistance
  – **L90M**: often follows unboosted PI’s; causes cross-res.

  – Boosted PI’s (LPV/r, FPV/r, SQV/r, ATV/r, DRV/r) usually do not select for resistance if used as 1st PI

• However, if 1st-line boosted PI failure is not addressed promptly, secondary resistance mutations can accumulate; ideally obtain phenotype to evaluate

Resistance to Atazanavir:

V32I, M46I, I50L, I54L, A71V, V82A, I84V, N88S, L90M

- When given as an initial unboosted PI; selects for I50L & A71V
- If used as a subsequent PI; selects for I54L, I84V
- Cross-resistance to ATV induced by common PI mutations: V82A & L90M
- In vitro, ATV selects for V32I, M46I, I84V, N88S

Lopinavir Mutation Score

- 8, 30, 32, 46, 47, 48, 50, 54, 82, 84, 90
- Clinical response rates decrease when:
  - LPV mutation score > 5 ("GT-R")
  - LPV IC$_{50}$ fold-change > 10 ("PT-R")
- Report suggesting that as few as 4 mutations can be associated with high-level resistance (Prado, AIDS, 2002)
- I50V confers 48X odds ratio of a FC >10 to LPV/r, even if there are fewer than 6 mutations (Parkin, Antivir Ther 7:S23, 2002)
- Add. mutations not described above associated with LPV phenotypic resistance from clinical trial samples:
  - 10, 20, 24, 53, 63, 71

Lopinavir Susceptibility Ranges

Fold Change

M46I +
I54V +
V82A +
L90M

I54V +
V82A +
L90M

M46I +
I84V +
L90M

No response expected
Partial response expected
Response expected

Parkin, Neil T; Chappey, Colombe; Petropoulos, Christos J. AIDS: 2 May 2003 - Volume 17 - Issue 7 - pp 955-961
Darunavir Mutation Score:
V11I, V32I, I33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V

- Approved in 1st-line & treatment-experienced pts
- May be used QD in treatment-experienced pts if there are zero DRV resistance mutations
- POWER studies showed patients treated with darunavir and optimized background meds had VL < 50 c/mL greater than for comparator PIs
- Response to darunavir was found to be dependent on 11 PI mutations at baseline

The presence of the V82A mutation in patients with three DRV RAMs was associated with a virological response comparable to that observed in patients with 2 DRV RAMs.

Tipranavir: Resistance

• The most common mutations that developed on tipranavir therapy: **L33V/I/F, V82T, and I84V**

• Reduced virologic responses assoc. with PI mutations:

• Note: in very treatment-experienced patients requiring sequencing of protease inhibitors:
  – **70% of pts with reduced susceptibility to tipranavir were susceptible to darunavir**
  – **53% of pts with reduced susceptibility to darunavir were susceptible to tipranavir**

Darunavir and Tipranavir Have Unique Resistance Profiles:

**DRV and TPV Mutations vs IAS-USA Protease Gene Resistance Mutations**

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<th>11</th>
<th>32</th>
<th>33</th>
<th>47</th>
<th>50</th>
<th>54</th>
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</table>

International AIDS Society – USA; [www.iasusa.org](http://www.iasusa.org); Johnson et al. Topics in HIV Med 2009
Raltegravir: Mutation Pathways Leading to Resistance Identified

Raltegravir: First HIV Integrase Inhibitor

- Raltegravir failure is assoc. with integrase mutations in at least 3 genetic paths defined by at least 2 mutations:
  - Major mutations: 148, 155, or 143 +/- minor changes
- Most common/most resistant = Q148H plus G140S
- Q148H/K/R or Y143R/H/C associated with high-level phenotypic resistance (> 100-fold change in IC\(_{50}\))
- N155H associated with low-level phenotypic resistance (< 50-fold change in IC\(_{50}\))
- Continued raltegravir in the presence of viral failure & resistance is not recommended
- Cross-resistance from RAL-assoc. mutations may confer reduced susceptibility to investigational integrase inhibitors

Raltegravir Resistance Evolution

Integrase Assay Determines RAL Susceptibility

- Phenotypic integrase resistance assay now available
  - Amplification threshold: VL > 500
  - Biological cutoff for RAL is FC > 1.5
  - Report does not detail genotypic mutations

- Integrase genotype assays may be available; useful for determining susceptibility to 2nd generation agents

- Transmitted RAL resistance (N155H +2 minors*) now reported; consider baseline RAL resistance testing prn

ARS Question #3

Select the most correct statement about what is currently known about raltegravir resistance

1. Virologic rebound to raltegravir leads to a single major resistance pathway
2. Transmitted RAL resistance has now been reported, so baseline RAL resistance testing may be considered in high-use areas
3. Once raltegravir resistance has been identified, the drug should still be continued
4. Today, a RAL resistance genotype is the most easily available predictive test to measure resistance
ARS Question #3

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Defining Co-Receptor Tropism

- CCR5 and CXCR4 are the primary chemokine co-receptors used by HIV to enter CD4+ T cells

Typical HIV Tropism Patterns

- **CCR5-tropic (R5)**
- **CXCR4-tropic (X4)**
- **Dual/mixed-tropic (D/M)**

There are 2 HIV coreceptors: **CCR5 & CXCR**; both are also chemokine receptors.

- Most viruses can use only CCR5: **R5 viruses**
- R5 viruses binding CCR5 is associated with **virus transmission**
- Some viruses can use both coreceptors: **called Dual-Tropic or Mixed-Tropic HIV (D/M)**; a few use only CXCR4: **X4 viruses**
Maraviroc

• First HIV CCR5 inhibitor / CCR5 chemokine antagonist

• Effective against strains that use the CCR5 co-receptor for cell entry
  – Little effect on viruses which use CXCR4 co-receptor, or which use both

• Activity of maraviroc is tested by co-receptor “tropism” test, which is not a resistance test

• CCR5 tropism (R5 virus) in ~85% of naïve patients, ~50% of experienced patients

Mechanisms of Maraviroc Resistance

- **Major:** Outgrowth of Dual/Mixed or X4 virus from pre-existing minority population present at levels too low to be detected by current tropism assays
  - Minor: Virus remains R5, with true resistance
    - Mutations in HIV gp120 that allow HIV to bind to CCR5 even though maraviroc is also bound
    - Most mutations are variable changes in the V3 loop
    - No consistent signature mutations for MRV resistance
- **Because a unique viral drug binding site is not mutated**
  - Genotyping cannot be used to predict CCR5 inhibitor efficacy; phenotype test must be used

Maraviroc-Resistant Virus Can Use Compound-Bound Receptors to Enter Cells

- Different resistance characteristics vs. other ARVs due to host cell target
  - Maraviroc-resistant HIV-1:
    - Associated with mutations in the pattern of amino acids in the V3 loop of gp120
    - Substitutions outside the V3 loop of gp120 may also contribute to reduced susceptibility to maraviroc
  - MRV-resistant HIV can enter cells via CCR5 even when MRV is bound

Virologic Failure With Maraviroc Was Most Frequently Associated With Lamivudine Resistance Mutations

Includes all virologic failures with evaluable post-baseline genotypic and phenotypic data

- Most maraviroc recipients with virologic failure (n=85) had lamivudine resistance
- Most efavirenz recipients with virologic failure (n=56) had efavirenz resistance
- Resistance to lamivudine, zidovudine and efavirenz was determined genotypically; resistance to maraviroc was defined as concentration response curves that did not reach 95% inhibition
- 14% (12/85) of recipients who failed on maraviroc had CXCR4-using virus at the time of treatment failure
Mechanisms of Virologic Failure in Naive Patients Treated with Maraviroc in the Merit Trial

Virologic Failure With Maraviroc-containing Regimens

86%

R5-tropic HIV Detected at Failure

Maraviroc-Resistant

9% (7 pts)

Maraviroc-Susceptible

91%

14%

Dual/Mixed HIV Detected at Failure

Conclusions

• Resistance can occur in patients new to ARV
• Resistance testing can be used to optimize an antiretroviral regimen
  – Must use in context of treatment history and results of all prior resistance tests
  – Goal for all HIV infected patients is HIV RNA < 50
• Factors other than resistance may cause regimen failure
• Resistance testing is reliable and cost-effective but must be interpreted in context and may require expert advice
• Cannot detect “minority” populations (<10-20%?)
• Cannot detect archived resistant virus in reservoirs