MDR HIV and Total Therapeutic Failure

Douglas G. Fish, MD
Albany Medical College
Albany, New York
Cali, Colombia
March 30, 2007
Objectives

- Case study
- Definitions
- Fitness
- Pathogenesis of resistant virus
- Concepts of therapy in setting of resistant virus
- Recommendations
Multi-Drug Resistance

- Resistance to more than one drug in a class
- Resistance to more than one class
- Triple or quadruple-class drug resistance
Resistance Evolution in Setting of Stable HAART

- Observational cohort study of 98 patients on stable antiretroviral therapy with measurable VL and at least 2 genotype assessments
  - 98% on NRTI
  - 69% on PI
  - 28% on NNRTI
  - 14% on NNRTI and PI
  - 88% had at least 1 BL mutation

Resistance Evolution in Setting of Stable HAART

- 27% acquired 1 new mutation, 33% acquired 2 or more
- Rate of accumulation of mutations approx 1.5 mutations/yr
- Acquisition of new mutations was:
  - Associated with absence of mutations on first genotype
  - Inversely associated with baseline VL
  - Most strongly associated with increasing VL slope on therapy

Selective Pressure of Therapy

- Treatment begins
- Viral load
  - Drug-susceptible quasispecies
  - Drug-resistant quasispecies

Time
Selective Pressure of Therapy

- Inadequate potency
- Inadequate drug levels
- Inadequate adherence
- Pre-existing resistance
Successive Therapies

Regimen 1

Drug-susceptible quasispecies

Drug-resistant quasispecies

Regimen 2
What Is the “Resistance Penalty” of Continued Nonsuppressive Therapy?

- Studies of resistance accumulation in states of "incomplete viral suppression"
  - 68% with new mutations after median of 22 mos\(^1\)
  - 33% with new TAMs, 2% K65R during 96 wks of FU\(^2\)
  - 60% with new mutations after median of 9.3 mos, but no shift on virtual phenotype\(^3\)
- Studies lack results of subsequent switches
- No fully powered randomized studies of early vs deferred switching

---

Dichotomous Pathways to Resistance

TAMs emerge sequentially with ZDV- and d4T-containing regimens after M184V


Higher-level ZDV resistance
More NRTI cross-resistance
Less effect of M184V

Lower-level ZDV resistance
Less NRTI cross-resistance
Greater effect of M184V
Low-Level Viremia Associated With Low Short-term Risk of Progression

- CHORUS database; N = 3009
- Entry: stable VL for ≥ 6 mos
- Stratified into 3 groups
  - VL < 400 c/mL
  - VL 400-20K c/mL
  - VL > 20K c/mL
- Endpoints: death or AIDS event
- Mean follow-up: 3 yrs
- Results independent of pretreatment CD4+
- Conclusion: Low to moderate viremia on treatment is not associated with clinical progression

Treatment Interruption Strategies
SMART Study: CD4-Guided Intermittent Therapy

- Planned 8-year open-label study in treatment-experienced patients (n=5472)
  - Baseline median CD4: 598 cells/mm$^3$; 30% with uncontrolled viremia
    - 95% were treatment experienced and on HAART for 6 years
    - 25% had prior AIDS
  - CD4-guided intermittent therapy
    - Stop: CD4 >350 cells/mm$^3$
    - Resume: CD4 <250 cells/mm$^3$
  - Continuous therapy

SMART Study: CD4-Guided Intermittent Therapy

- **January 10, 2006**
- DSMB recommended stopping further enrollment to the study
  - Significantly increased risk of disease progression (AIDS or death) in the CD-guided intermittent therapy (relative risk 2.5) versus the continuous-therapy arm
- Mean follow-up: 15 months
  - 25% had been followed for >2 years

SMART Study: CD4-Guided Intermittent Therapy

- CD4-guided intermittent therapy had an increased risk of:
  - HIV disease progression or death, death, serious HIV disease progression, and severe complications
  - Outcomes did not differ by nadir CD4 cell count

- Conclusions
  - Caution against using this structured treatment-interruption strategy
  - Other strategies might still be effective

### CD4-Guided Intermittent Therapy (average follow-up: 14 months)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV progression or death</td>
<td>2.5 (1.8-3.6)</td>
</tr>
<tr>
<td>Death</td>
<td>1.9 (1.2-3.0)</td>
</tr>
<tr>
<td>Disease progression</td>
<td></td>
</tr>
<tr>
<td>Serious</td>
<td>6.1 (1.8-20.6)</td>
</tr>
<tr>
<td>Non-serious</td>
<td>3.3 (1.9-5.7)</td>
</tr>
<tr>
<td>Serious progression of disease or death</td>
<td>2.2 (1.4-3.3)</td>
</tr>
<tr>
<td>Severe complications</td>
<td></td>
</tr>
<tr>
<td>Death due to CV, liver, or renal disease</td>
<td>1.5 (1.0-2.2)</td>
</tr>
<tr>
<td>Nonfatal</td>
<td></td>
</tr>
<tr>
<td>CV events</td>
<td>1.5 (1.0-2.5)</td>
</tr>
<tr>
<td>Hepatic events</td>
<td>1.4 (0.5-3.9)</td>
</tr>
<tr>
<td>Renal events</td>
<td>2.5 (0.5-13.0)</td>
</tr>
</tbody>
</table>

More Rapid CD4+ Slope at Same VL on Treatment vs off Treatment

- PLATO collaboration of 13 HIV cohorts
- Patients with 3-class virologic failure; n = 2448
- At any given viral load level, patients on treatment had more favorable CD4+ cell count slopes (ie, slower rates of decline per yr) than those off treatment

Fitness and Replication Capacity
Viral Fitness

- Replication capacity = ability of a patient’s HIV to replicate *in vitro* in the absence of drug
- Is the patient’s virus “fit” or “unfit”?  
- Resistant virus tends to be “unfit” virus

Deeks S. 45th ICAAC, Washington DC 2005, #674
Viral Fitness

- Viral fitness affects the rate of HIV disease progression
- Potential clinical utilities of viral fitness assay
  - Predictor of disease progression
  - Facilitates treatment decisions after therapy failure

Deeks S. 45th ICAAC, Washington DC 2005, #674
3TC Alone vs Treatment Interruption in Patients Failing 3TC-Based Rx

- In contrast to treatment interruption arm, 3TC alone resulted in
  - Smaller recovery in replication capacity
  - No further selection of resistance mutations

NRTIs Retain Activity Even With Drug Resistance

- Discontinue PIs, continue NRTIs (n = 15)
- Discontinue NRTIs, continue PIs (n = 5)

Studies of Enfuvirtide Resistance and Effects of Discontinuation

- Low genetic barrier to ENF resistance\(^1\)
  - Resistance to ENF present at earliest time of virologic failure
  - Failure often associated with rapid viral rebound to baseline

- Conflicting data on benefit of continued ENF therapy
  - ENF stopped in 22 patients with detectable viremia on ENF\(^2\)
    - Minimal viral rebound despite \(\uparrow\) fitness, return of ENF susceptibility
  - ENF added to failing regimen (n = 54)\(^3\)
    - V38A/E mutation detected most frequently, in approximately 28%

  - Associated with CD4+ count increase despite virologic failure

Some ARVs can influence HIV RNA and CD4+ T-cells despite resistance.

Understanding residual ARV activity and fitness effects may be useful for managing ARV-experienced subjects.

### Antiviral activity and fitness in drug-resistant HIV

<table>
<thead>
<tr>
<th>ARV class</th>
<th>Antiviral activity</th>
<th>Fitness effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PIs</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>ENF</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

Deeks S. 45th ICAAC, Washington DC 2005, #674
Considerations in setting of ARV resistance

- NRTIs should be continued
- Data on role of PIs show variable results
- ENF has modest fitness effect in setting of resistance, without obvious benefits
- NNRTIs have no apparent role in setting of resistance
Patient Management Strategies
Drug Resistance Testing in Clinical Practice

- Indications for use of resistance testing have greatly expanded
- Genotype preferred
  - Treatment naive: acute or chronic infection
  - Early virologic failure
  - Patient no longer on therapy
- Phenotype, virtual phenotype, or combined phenotype/genotype preferred
  - High-level resistance to NRTIs or PIs on genotype
  - Multiple regimen failure with limited treatment options
- Optimal selection of next regimen requires integration of resistance data, treatment history, and results from clinical studies
TORO Studies: Predictors of HIV RNA < 400 copies/mL

<table>
<thead>
<tr>
<th>BL Factor</th>
<th>OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+ &gt; 100 cells/mm³</td>
<td>2.4</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>RNA &lt; 100,000 c/mL</td>
<td>1.8</td>
<td>&lt; .0032</td>
</tr>
<tr>
<td>≤ 10 prior ARVs</td>
<td>2.4</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>≥ 2 active ARVs in background</td>
<td>2.3</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>


% Patients With VL < 400 c/mL by Number of Positive Prognostic Factors by Simplified Model

- ENF + OB
- OB

*P < .05

n = 135 56 182 89 174 94 121 67 49 28
Dual Protease Inhibitor Regimen versus a Nucleoside-Containing Regimen

- Open-label study conducted at sites in U.S. and Canada
- Subjects were antiretroviral-naïve with plasma VL>1000 copies/mL
- No CD4 restriction for enrollment
- 30 Subjects randomized 1:1 to the two treatment categories below

**Screening (N=30)**

- LPV/r 400/100mg BID + SQV 800mg BID
  - n=16

- LPV/r 400/100mg BID + ZDV/3TC (300/150 mg) BID
  - n=14

Cameron D. et al. ICAAC. Abstract H-523. 2005
Dual Protease Inhibitor Regimen versus a Nucleoside-Containing Regimen

<table>
<thead>
<tr>
<th>48 week efficacy results</th>
<th>LPV/r + SQV</th>
<th>LPV/r + ZDV/3TC</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL &lt;50 (ITT)</td>
<td>63% (N=16)</td>
<td>50% (N=14)</td>
<td>NS</td>
</tr>
<tr>
<td>VL &lt;50 (observed data)</td>
<td>77% (N=13)</td>
<td>78% (N=9)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean change in CD4 from baseline</td>
<td>+141</td>
<td>+187</td>
<td>NS</td>
</tr>
</tbody>
</table>

- Similar frequency and types of moderate or severe adverse events were noted between the 2 treatment groups

Cameron D. et al. ICAAC. Abstract H-523. 2005
Guidelines for Choosing a Nonsuppressive “Holding Regimen”

- *Never* use an NNRTI
  - NNRTI mutations have no beneficial impact on fitness
  - Accumulation of additional mutations may result in cross-resistance to second-generation NNRTIs
- Choose PIs and/or NRTIs based on resistance and tolerability/toxicity considerations

Acknowledgement: Gallant JE.
Deeks S. 45th ICAAC, Washington DC 2005, #674
Guidelines for Choosing a Nonsuppressive “Holding Regimen”

- Always use 3TC or FTC
  - Simple and well-tolerated drugs
  - M184V decreases fitness
  - Increased activity of ZDV, d4T, TDF
- Continue therapy until availability of at least 2 new active drugs

Acknowledgement: Gallant JE.
Patient 2004

- 52 I’m male with HIV diagnosed in 1989
- Currently off ARV therapy one month secondary to hepatitis: AST 174 (was 25) IU/L; ALT 195 (was 24) IU/L
- No underlying viral hepatitis
- Meds include isoniazid for latent TB, pravastatin and gemfibrozil
- Prior to HAART disruption:
  - CD4 502 cells/cmm & VL 360 c/ml
Previous HAART One Month Earlier

- Lopinavir/r (kaletra) recently changed to atazanavir/r (reyataz/norvir) for lipids
- Nucleoside backbone of stavudine (zerit), abacavir (ziagen), & tenofovir (viread)
- Intolerant to zidovudine (retrovir) and didanosine (videx)
- One month after HAART disruption:
  - CD4 250 cells/cmm
  - VL 700,000 c/ml; phenotype ordered
**Drug**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Patient (IC50 G/M)</th>
<th>Fold Change</th>
<th>Increasing</th>
<th>Drug Susceptibility</th>
<th>Decreasing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Zidovudine</td>
<td>1.06</td>
<td>0.60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td>Viread</td>
<td>6.15</td>
<td>0.85</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Epivir</td>
<td>2.89</td>
<td>0.71</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stavudine</td>
<td>Zerit</td>
<td>6.44</td>
<td>0.84</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Viread</td>
<td>0.015</td>
<td>0.92</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Retrovir</td>
<td>0.026</td>
<td>0.92</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Drug**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Patient (IC50 G/M)</th>
<th>Fold Change</th>
<th>Increasing</th>
<th>Drug Susceptibility</th>
<th>Decreasing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delavirdine</td>
<td>Rescriptor</td>
<td>0.9026</td>
<td>2.22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Sustiva</td>
<td>2.0012</td>
<td>0.74</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Viramune</td>
<td>0.123</td>
<td>1.34</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Drug**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Patient (IC50 G/M)</th>
<th>Fold Change</th>
<th>Increasing</th>
<th>Drug Susceptibility</th>
<th>Decreasing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amprenavir</td>
<td>Agenerase</td>
<td>0.0143</td>
<td>1.31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenavir</td>
<td>Reyataz</td>
<td>0.00140</td>
<td>1.26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td>Crixivan</td>
<td>0.0003</td>
<td>1.80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopinavir</td>
<td>Kaletra</td>
<td>0.4527</td>
<td>1.41</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Viread</td>
<td>0.0105</td>
<td>1.89</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Norvir</td>
<td>0.0183</td>
<td>1.62</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Fortovase</td>
<td>0.092</td>
<td>1.36</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Replication Capacity (RC)**

```
| RC | |
|----|
| 213% |
```

Replication capacity (RC) indicates the ability of the virus to replicate in the absence of drug. Range represents 95% confidence interval around RC measurement. 100%medium RC of wild-type strains.
## Drug Resistance Profile

### NRTI (Nucleoside Reverse Transcriptase Inhibitors)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC</td>
<td>Y</td>
<td></td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>NRTI Mutations</td>
<td>K70R, L74V, M184V, K219IQ</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### NNRTI (Non-nucleoside Reverse Transcriptase Inhibitors)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>DMY</td>
<td>Y</td>
<td></td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>NNRTI Mutations</td>
<td>L100I, K103N</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### PI (Protease Inhibitors)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AMP</td>
<td>Y</td>
<td></td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### General Notes

- Phenotype/Genotype Comments (clinical significance may vary):
  - 2 - Phenotypic measurement reflects possible enhanced susceptibility due to mutations at positions 53, 74, 100, and/or 181.
  - 3 - Phenotypic measurement reflects possible enhanced susceptibility due to M184I or V.
  - Predictions of susceptibility based on genotype does not match measured phenotype.
  - 4 - Mutations in addition to M184I or V may be required for phenotypic resistance.
  - 11 - L74V or K103N considered major resistance mutations for ddI.
  - 16 - Genotypic correlates of susceptibility not accounted for by current rules.

- This test was developed and its performance characteristics determined by ViroLogic, Inc. It has not been cleared or approved by the U.S. Food and Drug Administration.
HIV-1 GENOTYPE: RT/Pr GENES

RT GENE MUTATIONS

M184V

ASSOCIATED NRTI RESISTANCE: SEE BELOW

3TC (lamivudine or Epivir)
ddC (zalcitabine or Hivid)
ddi (didanosine or Videx)
ABC (abacavir or Ziden)

ASSOC. NNRTI RESISTANCE: NONE

Pr GENE MUTATIONS

L10I, K20M, M46I, L65C, I64V, A71 V, I84V, L90M

ASSOCIATED PI RESISTANCE: SEE BELOW

NFV (nelfinavir or Viracept)
SQV (saquinavir or Invirase)
IDV (indinavir or Crixivan)
RTV (ritonavir or Norvir)

INTERPRETIVE GUIDELINES:

Using the associated resistance chart as a guide (see below), review RT gene mutations and associated RTI resistance first. List RTI options. Then review Pr gene mutations and associated PI resistance. List PI options. Combine RTI, PI options. HIV-1 inhibitors screened by this assay are listed at the end of the report.

ASSOCIATED-RESISTANCE REFERENCE CHART

Nucleoside analogs (NRTI):

Principal Accessory NRTI Resistance
75 65, 69, 74 d4T
184 62, 75, 77, 116 3TC, ddI, ddC
151 62, 75, 77, 116 ZDV, ddI, ddC, d4T, 3TC
215 and/or 41 67, 70, 210, 219 ZDV
215 AND: 65 or 69 or 74 ZDV, ddI, ddC
215 and 184 ZDV, ddI, ddC, 3TC (Comments continued on next page)
Clinical Follow-up

- 1 week of fevers, highest 103 F
- Mild anorexia
- No cough
- Myalgias; eye movements caused aching
- Exam revealed new, diffuse lymph node enlargement of 1-1.5 cm in neck, axillae, and groin
Clinical Course

- No new sex partners
- AST back to 23, & ALT to 28 IU/L off HAART
- Work-up for acute hepatitis B & C negative
- Hepatitis A – vaccinated previously; immune
- CD4 nadir 140 cells/cmm
- Highest-ever VL 820,000 c/ml
Clinical Course

- HAART resumed
  - Stavudine, abacavir, tenofovir, ritonavir, atazanavir

- HIV RNA resuppressed

- After one month of HAART, isoniazid resumed
Key Points

- There can be rapid reversion to wildtype virus from latent reservoirs.

- Antiretroviral history is the most important guide to a new regimen.

- Acute retroviral syndrome may occur, apart from the initial HIV infection.
Case 2

- 63 yo male
- HIV since
- CD4+ 76 cells/cmm
- VL 130,000 c/ml
- HAART: emtricitabine/tenofovir/ritonavir/saquinavir, and enfuvirtide
**PhenoSense GT**

**Combination HIV Drug Resistance Assay**

**ViroLogic Inc.**
Clinical Reference Laboratory
Patrick Joseph, MD, Medical Director
345 Daly Point Boulevard
Albany, NY 12208
USA

**Client:** 00654
**Project:** 00073
**Phone:** (518)262-2155
**Fax:** (518)262-4756

**Patient Name:**
**DOB:** 12/15/2004
**Patient ID:** H046
**Gender:** M
**Date Received:** 12/15/2004 10:15:00
**Date Processed:** 12/17/2004 10:45:00
**Date of Test:** 12/31/2004 08:32:26
**Referring Physician:** DOUGLAS FISH, 66 HACKETT BLVD, Albany NY 12208 USA
**Comments:**

**HIV-1 Subtype:** B

### Drug Sensitivity

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Brand Name</th>
<th>Gene Change</th>
<th>Drug Sensitivity</th>
<th>Net Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Ziden</td>
<td>+0.47</td>
<td>Increasing</td>
<td>Reduced Sens.</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>Vidaq</td>
<td>-1.96</td>
<td>Decreasing</td>
<td>Reduced Sens.</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Emtriva</td>
<td>MAX</td>
<td>Increasing</td>
<td>Reduced Sens.</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Epivir</td>
<td>MAX</td>
<td>Increasing</td>
<td>Reduced Sens.</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Zerit</td>
<td>-2.20</td>
<td>Decreasing</td>
<td>Reduced Sens.</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Rettov</td>
<td>+4.35</td>
<td>Increasing</td>
<td>Reduced Sens.</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Viread</td>
<td>+1.12</td>
<td>Increasing</td>
<td>Reduced Sens.</td>
</tr>
</tbody>
</table>

**NNRTI Mutations:**


**NNRTI: NVP**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Brand Name</th>
<th>Gene Change</th>
<th>Drug Sensitivity</th>
<th>Net Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delavirdine</td>
<td>Rescriptor</td>
<td>14</td>
<td>Increasing</td>
<td>Reduced Sens.</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Sustiva</td>
<td>69</td>
<td>Increasing</td>
<td>Reduced Sens.</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Viramune</td>
<td>MAX</td>
<td>Decreasing</td>
<td>Reduced Sens.</td>
</tr>
</tbody>
</table>

**PI Mutations:**

- K103N, V108I, Y181C, G190A

**PI: ATV**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Brand Name</th>
<th>Gene Change</th>
<th>Drug Sensitivity</th>
<th>Net Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>Reyataz</td>
<td>30</td>
<td>Increasing</td>
<td>Reduced Sens.</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Lexiva</td>
<td>44</td>
<td>Increasing</td>
<td>Reduced Sens.</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Cordov</td>
<td>24</td>
<td>Increasing</td>
<td>Reduced Sens.</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>Kostra</td>
<td>102</td>
<td>Increasing</td>
<td>Reduced Sens.</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Viracept</td>
<td>35</td>
<td>Increasing</td>
<td>Reduced Sens.</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Norvir</td>
<td>260</td>
<td>Increasing</td>
<td>Reduced Sens.</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Fortovase</td>
<td>28</td>
<td>Increasing</td>
<td>Reduced Sens.</td>
</tr>
</tbody>
</table>

**PI Mutations:**


**Replication Capacity (RC):**

- **% of wild-type viruses:** 1.3%
- **RC (Range 0.79%-2.5%)**

Replication capacity (RC) indicates the ability of the virus to replicate in the absence of drug. Ranges represent 95% confidence interval around RC measurement. 100% = median RC of wild-type viruses.
Replication Capacity - 2004

Virus Replication Capacity = 1.3%
(Range 0.79%-2%)

Replication capacity (RC) indicates the ability of the virus to replicate in the absence of drug. Range represents 95% confidence interval around RC measurement. 100% = median RC of wild-type viruses.
**December, 2006**

---

### PHENOSENSE HIV Drug Resistance Assay

**66 AMC**  
**66 Hackett Blvd**  
**Albany, NY 12208**  
**USA**

**Patient Name:**  
**DOB:** 05/04/1946  
**Date Received:** 12/28/2006 11:20  
**Comments:**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Cutoffs (Lower - Upper)</th>
<th>Fold Change</th>
<th>Increasing Drug Susceptibility</th>
<th>Decreasing Drug Susceptibility</th>
<th>Assessed</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Zigagen</td>
<td>(4.9 - 6.9)</td>
<td>12</td>
<td></td>
<td></td>
<td>Drug</td>
<td>Resistant</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Videx</td>
<td>(1.3 - 2.2)</td>
<td>3.88</td>
<td></td>
<td></td>
<td>Drug</td>
<td>Resistant</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Emtriva</td>
<td>(3.5)</td>
<td>&gt;MAX</td>
<td></td>
<td></td>
<td>Drug</td>
<td>Resistant</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Epivir</td>
<td>(3.5)</td>
<td>&gt;MAX</td>
<td></td>
<td></td>
<td>Drug</td>
<td>Resistant</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Zerit</td>
<td>(1.7)</td>
<td>1.86</td>
<td></td>
<td></td>
<td>Drug</td>
<td>Partially Sensitive</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Viread</td>
<td>(1.4 - 4)</td>
<td>28</td>
<td></td>
<td></td>
<td>Drug</td>
<td>Resistant</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Retrovir</td>
<td>(1.9)</td>
<td>96</td>
<td></td>
<td></td>
<td>Drug</td>
<td>Resistant</td>
</tr>
</tbody>
</table>

**NNRTI**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Cutoffs (Lower - Upper)</th>
<th>Fold Change</th>
<th>Increasing Drug Susceptibility</th>
<th>Decreasing Drug Susceptibility</th>
<th>Assessed</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delavirdine</td>
<td>Rescriptor</td>
<td>6.0</td>
<td>46</td>
<td></td>
<td></td>
<td>Drug</td>
<td>Resistant</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Sustiva</td>
<td>3.0</td>
<td>254</td>
<td></td>
<td></td>
<td>Drug</td>
<td>Resistant</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Viramune</td>
<td>4.0</td>
<td>85</td>
<td></td>
<td></td>
<td>Drug</td>
<td>Resistant</td>
</tr>
</tbody>
</table>

**PI**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Cutoffs (Lower - Upper)</th>
<th>Fold Change</th>
<th>Increasing Drug Susceptibility</th>
<th>Decreasing Drug Susceptibility</th>
<th>Assessed</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>Reyataz</td>
<td>2.2</td>
<td>108</td>
<td></td>
<td></td>
<td>Drug</td>
<td>Resistant</td>
</tr>
<tr>
<td>Darunavir</td>
<td>Prezista</td>
<td>4.2</td>
<td>108</td>
<td></td>
<td></td>
<td>Drug</td>
<td>Resistant</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Lexiva</td>
<td>2.0</td>
<td>108</td>
<td></td>
<td></td>
<td>Drug</td>
<td>Resistant</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Crinonene</td>
<td>2.1</td>
<td>59</td>
<td></td>
<td></td>
<td>Drug</td>
<td>Resistant</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>Kaletra</td>
<td>0.9</td>
<td>59</td>
<td></td>
<td></td>
<td>Drug</td>
<td>Resistant</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Viracept</td>
<td>3.6</td>
<td>116</td>
<td></td>
<td></td>
<td>Drug</td>
<td>Resistant</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Nonvir</td>
<td>2.3</td>
<td>59</td>
<td></td>
<td></td>
<td>Drug</td>
<td>Resistant</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Invirase</td>
<td>1.7</td>
<td>42</td>
<td></td>
<td></td>
<td>Drug</td>
<td>Resistant</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>Aptivir</td>
<td>2.0</td>
<td>24</td>
<td></td>
<td></td>
<td>Drug</td>
<td>Resistant</td>
</tr>
</tbody>
</table>

**Replication Capacity (RC)**

- **Virus Replication Capacity = 31%**
- **Range: 19%-49%**

Replication capacity (RC) indicates the ability of the virus to replicate in the absence of drug. Range represents 95% confidence interval around RC measurement. 100% = median RC of wild type viruses.
Replication Capacity - 2006

Virus Replication Capacity = 31%
(Range 19%-49%)

Replication capacity (RC) indicates the ability of the virus to replicate in the absence of drug. Range represents 95% confidence interval around RC measurement. 100%=median RC of wild-type viruses.

31%
### Enfuvirtide Fold Change – 230; December 2006

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Patient IC50 (µg/mL)</th>
<th>Fold Change</th>
<th>Drug Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enfuvirtide</td>
<td>Fuzeon</td>
<td>8.8494</td>
<td>230</td>
<td></td>
</tr>
</tbody>
</table>

**Fold Change in IC50 of Patient Virus in relation to distribution of enfuvirtide-naive viral isolates**: 

![Graph showing distribution of patient samples](image)

- **Susceptibility Cutoff**
- **Patient Sample**
Key Points

- High-grade resistance to all available antiretroviral therapies
- Enfuvirtide discontinued due to side effects, high-grade resistance, and probable loss of fitness effect
- Awaiting 2 new drugs - ? integrase inhibitor and CCR5 antagonist
Summary Recommendations

- Intermittent antiretroviral therapy inferior to continuous therapy
- Discontinue NNRTI, after failing it
- Need 2 or more active drugs for best chance of virological suppression
- Avoid adding a single drug to a failing regimen, unless patient likely to die otherwise
Web Addresses/ Phone Numbers

- Clinical Care Options for many slides
  www.clinicaloptions.com/hiv
- www.aidsetc.org
- www.HIVguidelines.org
- www.aidsinfo.nih.gov
- www.cdc.gov
- www.hivandhepatitis.com

Email:
  Fishd@mail.amc.edu