HIV Genotypic Resistance in a Resource Limited Setting

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ART Need and Coverage

- 33 million people HIV infected (2/3 in SSA, 5.6 M in SA)
- 14.3 million people need ART*
- 5.3 million people receiving ART

*2010 Guidelines
UNAIDS 2010
WHO 2010
Public Health Dilemma

- Increasing number of HIV-infected patients requiring therapy
  - Increasing number of infections
  - Opt-out testing (HCT)
  - Earlier treatment (per WHO)
  - Increasing coverage for treatment (>40%)
  - Decreasing mortality among treated

- Limited capacity and resources to manage existing patients on therapy
Therapeutic Goals

- Virological suppression
  - SA: 2 VL > 1000 separated by 3 months
  - US: VL <200 by 24 wks and < 50 by 48 wks (1 log drop by 4 wks) and remain undetectable

- CD4 reconstitution
  - Persistently low CD4 count or unexplained CD4 count decline
  - Return to CD4 baseline or lower or 30-50% CD4 decline
  - Failure to increase CD4 count by 25-50 cells over 1st year
  - Failure to reach absolute CD4 count above 100 cells in 1st year

- Halt disease progression
  - New malignancy, wasting or OI
  - Recurrence of prior OI
  - Time frame: at least 2-3 months on treatment to exclude immune reconstitution inflammatory syndrome or unmasking
  - Onset or recurrence of symptomatic disease (WHO stage III)
Determinants of ART Response

The Threat

Access to Potent cART (Properly prescribed Combinations)

Acceptance, Adherence and Uptake

Behavioral, Socioeconomic and Cultural Factors

Pharmacokinetics, Absorption, Metabolism, Drug Interactions

Systemic and Intracellular Concentration

Inhibition of Viral Replication

Viral Replication Capacity, Virulence and Resistance

Increased Immune Activation, Immunologic Decline, Disease Progression, Increased Transmission, Poor QOL and High Mortality

Ongoing Viral Replication

Host Immune and Intrinsic Factors

Decreased Immune Activation, Immune Reconstitution, Arrested Disease Progression, Decreased Transmission, Improved QOL and Survival

Nachega/Marconi IDDT 2011
How Mutations Arise: K→N = K103N

• Innate HIV strain & subtype differences
  • Genetically distinct variants
  • Group M (subtypes A-D, F-H, J, K), Group O

• HIV replication is error prone*:
  - DNA Replication 1 / 1,000,000,000
  - HIV-1 Replication 4 / 10,000
  - RNA Synthesis 1 / 10,000
  - Airline Baggage Loss 1 / 200
  - Good Typist 1 / 100

• 10 billion viral particles produced per day; all possible mutations emerge daily; quasispecies

• Persistence of mutation depends upon fitness

*Modified from http://hivinsite.ucsf.edu
Viral Fitness
Virologic Suppression

Adequate Drug Pressure
Able to Fully Suppress

Time after starting ART

Drug-susceptible virus

Adapted from CCO O'Brien
Acquired Multi-Drug Resistance

Inadequate Drug Pressure
Allowing Replication to Occur

Drug-susceptible virus
Single-drug resistant virus
Multi-drug resistant virus

Viral load

Time after starting ART

Treatment begins

Selection of resistant virus

De Novo Mutation
Recombination Event or Second De Novo Mutation

Adapted from CCO O'Brien
Transmitted Multi-Drug Resistance

Adequate Drug Pressure Unable to Fully Suppress

Selection of resistant virus

Drug-susceptible virus
Multi-drug resistant virus

Treatment begins

Viral load

Time after starting ART

Adapted from CCO O’Brien
Independent Predictors of Resistance

- High baseline RNA
- Low baseline CD4
- Moderate levels of adherence
- Prior suboptimal ART
- Duration of therapy
- Sequential single ARV additions
Effect of Drug Concentration

• Incomplete suppression of viral replication selects for treatment resistant strains
Drug Concentrations after Treatment Interruption

S. Taylor et al. 11th CROI, 2004  Abs 131
Adherence, Resistance and Drug Class

Maggiolo et al *HIV Clin Trials* 2007, Hatano et al *JAIDS* 2010
NNRTI Resistance Mechanism

NNRTI Resistance Mutations

- Most common: K103N, Y181C
- Others: L100I, V106A/M*, V108I, Y188L, G190A/S, P225H
- Other substitutions in loci close to the above may induce NNRTI resistance
- Low genetic barrier; no decrease in RC

*V106M more common in Subtype C
NRTI Resistance Mechanisms

Dichotomous TAM Pathways to NRTI Resistance

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


ZDV or d4T

Unknown factors

Unknown factors

41L 210W 215Y

I

II

67N 70R 219Q

Higher-level ZDV resistance
More NRTI cross-resistance
Less effect of M184V
More common with hx ZDV dual NRTI

Lower-level ZDV resistance
Less NRTI cross-resistance
Greater effect of M184V
More common with hx ZDV mono
## NRTI Resistance Mutations

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Selected by</th>
<th>Effects on other NRTIs</th>
</tr>
</thead>
</table>
| 184V     | 3TC, FTC    | - Loss of susceptibility to 3TC, FTC, ↓ viral fitness  
- ↓ susceptibility to ABC, ddl (clinically insignificant)  
- Delayed TAMS and ↑ susceptibility to AZT, d4T, TDF |
| TAMs     | AZT, d4T    | - ↓ susceptibility to all NRTIs based on number of TAMs  
- More resistance with 41/210/215 than 67/70/219 pathway  
- Prevent K65R |
| 151M, 69ins | AZT/ddI, ddl/ddI/d4T | - Resistance to all NRTIs (Q151M not TDF), ↑ susc NNRTI  
- T69ins: TDF resistance |
| 65R*     | TDF, ABC, ddl | - Variable ↓ susceptibility to TDF, ABC, ddl (and 3TC, FTC)  
- ↑ susceptibility to AZT |
| 74V      | ABC, ddl    | - ↓ susceptibility to ABC, ddl  
- ↑ susceptibility to AZT, TDF |
| 44D, 118I | AZT, d4T    | - increases NRTI resistance (with 41/210/215 pathway) |

*more rapidly selected in Subtype C

JE Gallant MD MPH: 10th RW Program Clinical Update, accessed at http://iasusa.org
### Mutations Selected by PIs

<table>
<thead>
<tr>
<th>PIs</th>
<th>Mutations</th>
<th>Codon 10</th>
<th>Codon 16</th>
<th>Codon 20</th>
<th>Codon 24</th>
<th>Codon 32</th>
<th>Codon 33</th>
<th>Codon 34</th>
<th>Codon 36</th>
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<tbody>
<tr>
<td>Atazanavir +/- ritonavir</td>
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<td>16</td>
<td>20</td>
<td>24</td>
<td>32</td>
<td>33</td>
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<td>85</td>
<td>88</td>
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<td>93</td>
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<tr>
<td>Darunavir/ritonavir</td>
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<td>11</td>
<td>32</td>
<td>33</td>
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<td>76</td>
<td>84</td>
<td>89</td>
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<tr>
<td>Fosamprenavir/ritonavir</td>
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<td>10</td>
<td>32</td>
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<tr>
<td>Indinavir/ritonavir</td>
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<td>90</td>
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</table>
Aspects Unique to Subtype C

• NRTI
  – TAMs
  – K65R

• NNRTI
  – V106M
  – A98G more frequent
  – G190A/S more/PM
  – 35, 48, 121 and 166 (less mutations)
  – Rapid accumulation (Barth AIDS 2008)

• PI
  – M (not L) 89I/V + L90M (Abecasis AIDS 2005)
  – More D30N after NFV in Botswana than in Ethiopia/Israel
  – 13 and 64 more frequently mutated
  – 20, 53, 63, 74 and 82 less frequently mutated
  – 36, 89 and 93 more frequent PMs

Martinez-Cajas JIAS 2009
Importance of ARV Resistance

• ONE key factor in treatment failure
• Limits activity of single agents and through cross resistance mutations can limit many agents
• Understanding development of resistance allows choice and sequencing of therapy (vs toxicities)
• Subsequent therapy is typically more toxic, requires more monitoring, more pills and is more costly
• Independently linked to mortality and AIDS, OR 1.75-3.0 (Hogg 2006, EUROSIDA 2009)
• Resistant virus can be transmitted resulting in a major public health concern
• Complicates programmatic algorithms for clinical care, PMTCT, TB treatment, etc.
HIV Drug Resistance after VF: No Small Problem

- Worldwide estimates of 3-30% virologic failure within one year of first ART (430K – 4.3M)*
- 40-95% individuals VF have ≥ 1 major resistance mutation
- 1.2-25.5% of individuals on ART will have resistance within one year (172K – 3.6M)*
- Over time triple class failure will accumulate

* Calculated for 14.3 M requiring ART
<table>
<thead>
<tr>
<th>ARV Treatment</th>
<th>Survival in 40 years</th>
<th>Viral Load &lt; assay</th>
<th>Clinical Events</th>
<th>Epidemiologic Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ARVs</td>
<td>1-5%</td>
<td>&lt;1-5%</td>
<td>Multiple OI’s</td>
<td>Death, Transmission</td>
</tr>
<tr>
<td>Complete Adherence</td>
<td>50%</td>
<td>&gt;90%</td>
<td>Few</td>
<td>Excellent</td>
</tr>
<tr>
<td>Incomplete Adherence</td>
<td>25%</td>
<td>&lt;25%</td>
<td>Chronic disease state, multiple OI’s</td>
<td>Transmission, Resistance, Salvage Tx, Cost</td>
</tr>
</tbody>
</table>
Projected ARV Resistance in Africa

TDR <5% in SA overall, but 5-15% in 17% of countries worldwide (Zambia 6% Hamers JAIDS 2010 and Uganda, Vietnam, Mexico, Brazil CROI 2011, KZN 5-15% NNRTI 2009 not published)
Baseline Resistance

[Graph showing prevalence of HIV-1 drug resistance across different cities and countries, including Harare, Pretoria, White River, Johannesburg, Nairobi, Mombasa, Lusaka, Lagos, Fort Portal, Mbale, and Kampala. The graph indicates varying levels of resistance across these locations.]
Resistance after First-Line ART

Percentage of Subjects

- ≥ 1 signif mutation
- Dual Class
- Triple Class
- NRTI
- NNRTI
- PI

Marconi CID 2008
Risk Factors for Drug Resistance (Multivariable Analysis)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>Confidence Interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt;35)</td>
<td>3.27</td>
<td>0.92-11.63</td>
<td>0.07</td>
</tr>
<tr>
<td>Recent OI (within 6 months of study enrollment)</td>
<td>2.20</td>
<td>0.70-6.88</td>
<td>0.18</td>
</tr>
<tr>
<td>CD4 count at study enrollment</td>
<td>0.87</td>
<td>0.23-3.33</td>
<td>0.84</td>
</tr>
<tr>
<td>HIV-1 RNA Viral Load at study enrollment &lt;100,000 c/mL</td>
<td>7.97</td>
<td>0.82-77.21</td>
<td>0.10</td>
</tr>
</tbody>
</table>

CID 2008
### Summary of Resistance evaluations in Resource Limited settings

<table>
<thead>
<tr>
<th></th>
<th>South Africa</th>
<th>South Africa</th>
<th>Thailand</th>
<th>South Africa</th>
<th>Malawi</th>
<th>India</th>
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<tbody>
<tr>
<td><strong>N sequenced</strong></td>
<td>115</td>
<td>226</td>
<td>98</td>
<td>94</td>
<td>94</td>
<td>138</td>
</tr>
<tr>
<td><strong>Clade</strong></td>
<td>C</td>
<td>C</td>
<td>AE</td>
<td>C</td>
<td>C</td>
<td>C</td>
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<tr>
<td><strong>Monitoring Strategy</strong></td>
<td>Virologic</td>
<td>Virologic</td>
<td>Virologic</td>
<td>Virologic</td>
<td>Clinical</td>
<td>Clinical</td>
</tr>
<tr>
<td><strong>Median CD4 at failure</strong></td>
<td>161</td>
<td>165</td>
<td>159</td>
<td>214</td>
<td>68</td>
<td>144</td>
</tr>
</tbody>
</table>

May be related to method of treatment monitoring, prior use of mono/dual therapy, duration of therapy and regimen

<table>
<thead>
<tr>
<th></th>
<th>Bots-wana</th>
<th>Bots-wana</th>
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</thead>
<tbody>
<tr>
<td>N sequenced</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Median CD4 at failure</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Monitoring Strategy</td>
<td>Virologic</td>
<td>Virologic</td>
</tr>
<tr>
<td>Median CD4 at failure</td>
<td>20</td>
<td>NR</td>
</tr>
</tbody>
</table>

RFVF Study – McCord Hospital

- Between 3 Aug 2010 and 17 Mar 2011 – 585 patients initiated TDF/3TC/NNRTI
- 33 (5.6%) patients VF after 6 months
- 18 (54.5%)* VF patients had K65R/N
- Additional mutations with K65R/N
  - Y115F (5), L74V (1), Y115F/S (1), M184V (3), T69D/N (2), K70T (1)
  - V179D (4), Y181C (6), V106M (13), Y188C (3), G190A/E (6), V108I (1), A98G (1), K103N (6)
  - No M184V/I
- Median baseline CD4 94 cells/uL (49-160)
- Median VL at VF 47,000 copies/mL (30,212-267,537)

*Compared to 2-5% in subtype B
Virologic Suppression at 6 mo

<table>
<thead>
<tr>
<th>Group</th>
<th>Percentage of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>72.6%</td>
</tr>
<tr>
<td>Resistance</td>
<td>75%</td>
</tr>
<tr>
<td>No Resistance</td>
<td>75%</td>
</tr>
<tr>
<td>No Genotype</td>
<td>78.3%</td>
</tr>
</tbody>
</table>

N =

186 120 20 46

*/† Significant

Murphy AIDS 2010
SARCS Adherence

Pharmacy refill increases after initiation of 2\textsuperscript{nd} line therapy, then declines; associated with virologic response

Murphy CROI 2011
Clinical Outcomes at 6 mo

N = 186
Died, clinic default = 5

*† Significant

Murphy AIDS 2010
## Risk Factors for Death at 6 mos after Switch

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N</th>
<th>24-Week Mortality no. (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>141</td>
<td>8 (6)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>71</td>
<td>4 (6)</td>
<td>0.98</td>
</tr>
<tr>
<td>Male</td>
<td>70</td>
<td>4 (6)</td>
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</tr>
<tr>
<td>HIV-1 drug resistance at initial ART failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 resistance mutation</td>
<td>122</td>
<td>5 (4)</td>
<td></td>
</tr>
<tr>
<td>No resistance</td>
<td>19</td>
<td>3 (16)</td>
<td>0.04</td>
</tr>
<tr>
<td>Subsequent regimen type</td>
<td></td>
<td></td>
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<tr>
<td>LPV/r-based ART</td>
<td>114</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>NNRTI-based ART</td>
<td>20</td>
<td>3 (15)</td>
<td>0.004</td>
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<tr>
<td>CD4 cell count at initial ART failure (cells/ul)</td>
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</tr>
<tr>
<td>≥200</td>
<td>58</td>
<td>0 (0)</td>
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</tr>
<tr>
<td>100-199</td>
<td>52</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>50-99</td>
<td>17</td>
<td>2 (12)</td>
<td></td>
</tr>
<tr>
<td>0-49</td>
<td>12</td>
<td>3 (25)</td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA viral load at initial ART failure (copies/mL)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>400,4,999</td>
<td>33</td>
<td>0 (0)</td>
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<tr>
<td>5,000-29,999</td>
<td>50</td>
<td>6 (12)</td>
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<tr>
<td>30,000-99,999</td>
<td>30</td>
<td>0 (0)</td>
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<tr>
<td>≥100,000</td>
<td>27</td>
<td>2 (7)</td>
<td>0.05</td>
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<tr>
<td>WHO clinical stage at initial ART failure</td>
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<tr>
<td>Stage I</td>
<td>22</td>
<td>0 (0)</td>
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<tr>
<td>Stage II</td>
<td>25</td>
<td>2 (8)</td>
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</tr>
<tr>
<td>Stage III</td>
<td>42</td>
<td>4 (10)</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>22</td>
<td>2 (9)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Causes of death were determined in 7 of 8 patients (tuberculosis, N=3; gastroenteritis, N=2; lactic acidosis, N=1; suspected central nervous system mass, N=1, unknown cause, N=1).  
1 Seven patients did not initiate a regimen after virologic failure and three patients from this group died.  
2 One patient who died did not have a CD4 count at first ART failure  
3 One patient who survived did not have a viral load within 8 weeks of first ART failure  
4 Thirty patients who survived did not have a recorded WHO staged at first ART failure  

Murphy AIDS 2010

NS in MV for VF or Death
Second-Line Outcomes

TDF > ABC > ETR greatest activity against majority of isolates

- Fox et al (Joburg) *JAIDS* 2010 – 77% VS on 2nd line for 1 year
- Wallis *AIDS Res Treat* 2011 – 2nd line VF mostly nonadherence (7% PI mutations) and 1st line mutations
- Van Zyl (Cape Town) *JAIDS* 2011 – Hair Sampling Study, 93 LPV/r, 40% VF, 2 with PI mutations
- Johnston (Joburg) *CROI* 2011 – Workplace > Community program 2nd line VF (RF time VF)
- LPV/r monotherapy *CROI* 2011 – ACTG 5230 87% VS vs STAR (inferior); both TDF/FTC intens high VS
- Sunpath/Moosa (Durban) – 28 LPV/r failures, only 3 with triple-class resistance
Salvage Therapy

Switch early

• Cost
  – LPV/r = R14.5-16.5/d
  – EFV = R4.8-5.4/d
• Additional lost classes and challenge of getting salvage regimens
• Complex regimens
  – Drug-Drug Interactions
  – Side Effects
  – Monitoring

Switch later

• Additional resistance mutations
  – Limiting future intra-class options
  – Transmitted resistance
• Immunologic and clinical decline
• Serious non-AIDS events
Recycling/Resuppression

Geng *CROI* 2009 – 360 pts Uganda VS; 37 (15%) VF 2 yrs; 50%, 21% resupp NNRTI, PI, 29% not (2 on PI); of NNRTI resupp, 36% TI>48h, 29% sporadic, 36% >95% adh

Rosen *JIAS* 2011 – GRT cost neutral, identify reasons for VF, conserve options, generate info about emerging resistance
Third-Line Agents

• PI: Darunavir
• INT: Raltegravir/Elvitegravir
• NNRTI: Etravirine/Rilpivirine
• CCR5: Maraviroc
HIVDR Early Warning Indicators (EWI)

- Programmatic Level*
  - Prescribing practices
  - LTFU 12 mos ART
  - Retention on 1st Line ART at 12 mos/VL UD
  - Timely ARV pickup
  - ARV appointments
  - ARV shortages
  - Adherence
  - Baseline HIVDR

- Individual Level
  - Pharmacy Refill Data/Clinic Visits
  - Pill Counts/Self-Reported Adherence
  - Clinical Risk Factors
  - Baseline Minority Drug Resistance
  - Psychosocial Risk Factors

*WHO recommends (http://www.who.int/hiv/topics/drugresistance/indicators/en/index.html)
Summary

• Consider all aspects of the treatment paradigm
• Overall prevalence of resistance among patients in urban SA with first virologic failure 60-94%
  – >50% dual-class resistance, rare triple-class
• Age, Lower VL, OIs associated with resistance
• Second-line therapy with boosted-PI is effective after single and dual class resistance, but costly
• Other than new classes, TDF has greatest activity against majority of isolates; potential for rapid selection K65R
• Significant clinical concern for patients without resistance (reinforces importance of adherence/access to care)
• Virologic monitoring crucial to prevent resistance; can even resuppress with adherence counseling and close monitoring in select populations; Resistance testing is cost-neutral
• Adherence (pharmacy refill) = good predictor response

VIROLOGIC FAILURE IS BAD W/ OR W/O RESISTANCE
## Acknowledgments

**McCords Hospital**
- Henry Sunpath
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