Management of HIV Treatment Failure: A Case-based Discussion

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ART Need and Impact

- 33 million people HIV infected
- 9.7 million people need ART*
- 3 million people receiving ART
- Tremendous impact, especially if treated early
- Challenge for retention in care and optimal adherence

*Old guidelines
UNAIDS 2007
WHO 2008
Determinants of ART Response

The Threat

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

Ongoing Viral Replication

Host Immune and Intrinsic Factors

Viral Replication Capacity, Virulence and Resistance

Inhibition of Viral Replication

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

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

Determinants of ART Response

Toxicity, Adverse Effects, Tolerability, Treatment Fatigue
Case Presentation

- 40 year old male presented with mild oral thrush.

- Past Medical History: TB Meningitis 1yr and 2 months before current presentation.

- CD4 = 13 (4 months before current presentation)
Regimen 1a
(first therapeutic combination)

- For 10 months after presentation
- stavudine+lamivudine+efavirenz (D4T+3TC+EFV)
- VL = 580, CD4 = 109 (5 months after presentation)
- Month 10 – hospitalized for lactic acidosis (lactate = 7.7)
What would you do?
A. Continue the regimen
B. Stop the d4T
C. Stop the 3TC
D. Stop the EFV
E. Stop the entire regimen
F. Other
<table>
<thead>
<tr>
<th>1&lt;sup&gt;st&lt;/sup&gt; line</th>
<th>ARV Comb</th>
<th>Regimen Class</th>
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<tbody>
<tr>
<td>All pts eligible for treatment</td>
<td>NEW</td>
<td>1a</td>
</tr>
<tr>
<td></td>
<td>TDF + 3TC/ FTC + NVP/EFV</td>
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</tr>
<tr>
<td>Current 1&lt;sup&gt;st&lt;/sup&gt; line.</td>
<td>OLD</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td>D4T + 3TC + NVP/EFV</td>
<td></td>
</tr>
<tr>
<td>Contraindication to TDF/Kidney disease</td>
<td>AZT + 3TC + EFV/NVP ABC + 3TC + EFV/NVP</td>
<td>New 1c</td>
</tr>
</tbody>
</table>
Therapeutic Goals

• VL <400 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)
**Adverse Effects**

**Life Threatening**
- Hypersensitivity reaction (ABC, NVP)
- Pancreatitis (ddl, ddC, d4T)
- Lactic acidosis (NRTIs)
- Hepatitis (NNRTIs, PIs, d4T/ddI)
- SJS (NVP)

**Acute/Early**
- Gastrointestinal (ZDV, ddl, PIs)
- Jaundice (ATV, IDV)
- Renal stones (IDV)
- Anemia, neutropenia (ZDV)

**Chronic/Long term**
- Asthenia (ZDV)
- Central Nervous System (EFV)
- Rash (NNRTIs)
- Peripheral Neuropathy (ddC, d4T, ddl)
- Metabolic – glucose intolerance, lactate, lipids, fatty liver, osteoporosis (PIs, d4T, TDF)
- Morphologic – fat loss, fat gain (d4T, PIs?)
- Renal (TDF)
- Cardiovascular (ABC)
Regimen 1b
(2\textsuperscript{nd} therapeutic combination)

- Discontinued regimen 1a as inpatient (All drugs stopped at once)
- 2 months after adverse event started (1 yr after presentation):
  - **Zidovudine** + Lamivudine + Efavirenz
    - (AZT + 3TC + EFV)
- 1yr 3 months after initial presentation: admission to McCord for pancreatitis, discontinued Regimen 1b – all drugs stopped at once for one month; then resumed for 3 months.
- VL = 1300 - 3800, CD4 = 126 - 241 (1yr - 1yr 7 mos)
LS: ARV Timeline

10 Mos.

D4T + 3TC + EFV

1yr 3mos

AZT + 3TC + EFV

1yr 5mos

AZT + 3TC + EFV

1yr 7mos

What would you do?
A. Continue the current regimen
B. AZT + DDI + EFV
C. AZT + 3TC + LPV/r
D. TDF + 3TC + LPV/r
E. EFV + LPV/r
F. EFV + LPV/r + 3TC
G. Other
Therapeutic Monitoring

- **DART Lancet 2010** – Uganda/Zimbabwe: no difference in clinical outcomes unless CD4 monitor after 2 yrs (VL not included)
- **Rawizza CROI 2010** – Nigeria: 45% of VF missed with CD4 only, 44% IF not accurate and delayed
- **Rewari JAIDS 2010** – VL monitor CD4/clinical failures, 25% suppressed
Timing of Switch

- **Ive CROI 2009** – SA: Time to switch (>5 vs ≤ 5 mos from 1st VL) for VF asssd w/ being alive & in care; many not switched ever (22.2%) with 55.8% alive-in care
- **Gupta Lancet ID 2009** – Resistance 48 wks higher in less frequently monitored pts (>12 wks)
- **Keiser TMIH 2010** – Cumulative annual mortality difference 4 vs 12% in failures switch vs not
- **SA**: If VL > 1K c/mL (SAHIVSOC) or > 5K c/mL (WHO/DOH) on 2 VL separated by 1-3 mos of adherence counseling
## Second-line SA Guidelines

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<th>2nd Line</th>
<th>ARV Comb</th>
<th>Regimen Class</th>
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<td>Failing D4T or AZT</td>
<td>TDF + 3TC + LPV/r</td>
<td>2a</td>
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<tr>
<td>Failing TDF</td>
<td>AZT + 3TC + LPV/r AZT + ddI or TDF + LPV/r</td>
<td>2b</td>
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<tr>
<td>Salvage</td>
<td>DRV, ETR, RTG, MVC</td>
<td>3?</td>
</tr>
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How Resistance Mutations Arise

- 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
Virologic Suppression

Adequate Drug Pressure
Able to Fully Suppress

Drug-susceptible virus

Adapted from CCO O'Brien
Acquired Multi-Drug Resistance

Inadequate Drug Pressure
Allowing Replication to Occur

Selection of resistant virus

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

Viral load

Time after starting ART

De Novo Mutation
Recombination Event or Second De Novo Mutation

Adapted from CCO O’Brien
Transmitted Multi-Drug Resistance

<5% in SA and KZN in particular
Recent report from Zambia 6% (Hamers JAIDS 2010)
Change in Resistance with STI

Deeks et al. NEJM 2001
Effect of Drug Concentration

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

NNRTI Longer Half-Life

Drug Concentrations after Treatment Interruption

Last Dose
Day 1
Day 2+

Zone of potential replication

MONOTHERAPY

S. Taylor et al. 11th CROI, 2004 Abs 131
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.
Regimen 2a  
(3rd therapeutic combination)

- At 1yr 7mos started:
  - efavirenz + lopinavir/ritonavir (EFV + LPV/r)

- CD4: 480 (1yr 11mos) - 124 (2yr 10mos)

- VL: 7900 (1yr 11mos) – 252873 (2yr 10mos)
## LS: ARV Timeline

<table>
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<tr>
<th>Duration</th>
<th>Medication Combination</th>
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<tr>
<td>10mos</td>
<td><strong>D4T + 3TC + EFV</strong></td>
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<tr>
<td>1yr 3mos</td>
<td><strong>AZT + 3TC + EFV</strong></td>
</tr>
<tr>
<td>1yr 5mos</td>
<td><strong>AZT + 3TC + EFV</strong></td>
</tr>
<tr>
<td>2yr11mos</td>
<td><strong>EFV + LPV/RTV</strong></td>
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</tbody>
</table>

- **Initial**: D4T + 3TC + EFV
- **1yr**: AZT + 3TC + EFV
- **1yr 5mos**: AZT + 3TC + EFV
- **2yr11mos**: EFV + LPV/RTV
<table>
<thead>
<tr>
<th>Mutation</th>
<th>Nucleoside reverse transcriptase inhibitor (NRTI)</th>
<th>Non-nucleoside reverse transcriptase inhibitor (NNRTI)</th>
<th>Protease Inhibitor (PI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>lamivudine (3TC), emtricitabine (FTC)</td>
<td>delavirdine (DLV), efavirenz (EFV), nevirapine (NVP)</td>
<td>indinavir/r (IDV/r) nelfinavir (NFV)</td>
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<tr>
<td>Intermediate</td>
<td></td>
<td></td>
<td>atazanavir/r (ATV/r) fosamprenavir/r (FPV/r) lopinavir/r (LPV/r), saquinavir/r (SQV/r)</td>
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<tr>
<td>Resistance</td>
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<td></td>
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<tr>
<td>Low/Potential</td>
<td>abacavir (ABC) didanosine (DDI)</td>
<td>etravirine (ETR)</td>
<td>darunavir/r (DRV/r) tipranavir/r (TPV/r)</td>
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<tr>
<td>Low Resistance</td>
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<tr>
<td>Susceptible</td>
<td>zidovudine (AZT) stavudine (D4T) tenofovir (TDF)</td>
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</tr>
<tr>
<td>Mutation</td>
<td>Nucleoside reverse transcriptase inhibitor (NRTI)</td>
<td>Non-nucleoside Reverse Transcriptase inhibitor (NNRTI)</td>
<td>Protease Inhibitor (PI)</td>
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</table>
| High Resistance | D67N                                             | K103N, V106M                                         | Major mutations: M46I, I54V, V82A, L76V  
Minor mutations: L10F, A71V |
| Intermediate Resistance | delavirdine (DLV), efavirenz (EFV), nevirapine (NVP) | indinavir/r (IDV/r), nelfinavir (NFV), lopinavir/r(LPV/r), fosamprenavir/r (FPV/r) |
| Low/Potential Low Resistance | zidovudine (AZT), stavudine (D4T) | etravirine (ETR)                                         | atazanivir/r (ATV/r), saquinavir/r (SQV/r) |
| Susceptible  | lamivudine (3TC), abacavir (ABC), didanosine (DDI), emtricitabine (FTC), tenofovir (TDF) | | darunavir/r (DRV/r), tipranavir/r (TPV/r) |
HIV-1 Resistance Testing

• Phenotype
  • Trait or behavior resulting from genotype
  • Antiviral susceptibility
  • Best for multiple PI mutations

• Genotype
  • Sequence of nucleotide bases
  • Specific base pair changes or mutations causing resistance found for viruses present at least 20%
  • Genetics of resistance must be known
  • Best done on treatment and VL > 500-1K and < 100K
  • Requires expert opinion to be most useful
Evidence: Resistance Testing for Care

- Supporting Use
  - GART
  - VIRADAPT
  - Havana
  - VIRA 3001
  - CERT
  - RealVirfen

- Not Supporting Use
  - ARGENTA
  - NARVAL
  - CCTG 575
  - CERT
### Clinical Indications

<table>
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<tr>
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<th>DHHS[29]</th>
<th>IAS-USA[27]</th>
<th>EuroGuidelines[28]</th>
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<td>&lt;1 year HIV-1 Infection</td>
<td>Consider*</td>
<td>Recommend</td>
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<td>1-2 years HIV-1 Infection</td>
<td>Consider*</td>
<td>Recommend</td>
<td>Recommend*</td>
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<td>HIV-1 Infection &gt;2 years</td>
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<td>Consider*</td>
<td>Consider*</td>
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<td>PEP (Source Patient)</td>
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<td>Treatment Failure*</td>
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<tr>
<td>Pregnancy</td>
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<tr>
<td>Pediatric</td>
<td>—</td>
<td>—</td>
<td>Recommend**</td>
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</tbody>
</table>

*Initial failure or Suboptimal reduction at 4 weeks (B-II)
Subsequent/Salvage Failure (A-II)

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* when source of infection has known drug-resistant HIV-1 or local seroprevalence is >5 or 10%
* when detectable plasma HIV-1 RNA and treatment initiated or changed
** when mother was viremic and on treatment at time of delivery
— not discussed

DHHS = Department of Health and Human Services
IAS = International AIDS Society
PEP = post-exposure prophylaxis with ART

Source: Lab Med © 2006 American Society for Clinical Pathology
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

### 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  
- ↓ susceptibility to ABC, ddI (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 |
| 151M, 69ins | AZT/ddI, ddI/ddI/d4T           | - Resistance to all NRTIs (Q151M not TDF), ↑ susc NNRTI  
- T69ins: TDF resistance |
| 65R*      | TDF, ABC, ddl                   | - Variable ↓ susceptibility to TDF, ABC, ddI (and 3TC, FTC)  
- ↑ susceptibility to AZT |
| 74V       | ABC, ddI                        | - ↓ susceptibility to ABC, ddI  
- ↑ 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
Dichotomous TAM Pathways to NRTI Resistance

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

6 identified:

ZDV or d4T

Unknown factors

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

Higher-level ZDV resistance
More NRTI cross-resistance
Less effect of M184V
More common with hx ZDV mono
## Protease Inhibitor (PI) Resistance Mutations

<table>
<thead>
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<th>Cons</th>
<th>23</th>
<th>24</th>
<th>30</th>
<th>32</th>
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<th>46</th>
<th>47</th>
<th>48</th>
<th>50&lt;sup&gt;+&lt;/sup&gt;</th>
<th>53</th>
<th>54</th>
<th>73</th>
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<td>F</td>
<td>IL</td>
<td>V</td>
<td>VM</td>
<td>L</td>
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<td>VTALM</td>
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<td>ATFS</td>
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<td>FPV/r</td>
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Aspects Unique to Subtype C

• **NRTI**
  - TAMs
  - K65R

• **NNRTI**
  - V106M directly (not A)
  - 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
Regimen 2b (4th therapeutic combination)

- 2yr 11mos – present

- Lamivudine + efavirenz + lopinavir/ritonavir
  (3TC + EVF + LPV/r)

- CD4: 134 (3yr 1mo)

- VL: 1268 (3yr 1mo) - 420000 (3yr 7mos)
LS: ARV Timeline

10mos
- **D4T + 3TC + EFV**
  - Initial

1yr 3mos
- **AZT + 3TC + EFV**
  - 1yr

1yr 5mos
- **AZT + 3TC + EFV**
  - 1yr 7mos

2yr 11mos
- **EFV + LPV/r**
  - present
- **3TC + EFV + LPV/r**
Viral Load

Aug 07 | Jun 08 | Aug 08 | Nov 08 | Feb 09 | Jun 09 | Aug 09 | Sep 09 | Jan 10 | April 10 | Oct 10
---|---|---|---|---|---|---|---|---|---|---
580 | 1300 | 190000 | 3800 | 7900 | 610000 | 700000 | 430000 | 252873 | 1268 | 420000
Discussion

• Development of resistance to NNRTIs and PIs in the face of previous NRTI toxicity (lactic acidosis, pancreatitis) significantly limits ARV options.
• What would you do now?
  A. Discontinue therapy
  B. Continue 3TC/EFV/LPV/r
  C. TDF + RAL + DRV/r
  D. RAL + ETR + DRV/r
  E. TDF + ETR + DRV/r
  F. TDF + RAL + ETR + DRV/r
  G. Other
HIV Drug Resistance after VF: No Small Problem

- Worldwide estimates of 3-30% virologic failure within one year of first ART (300K – 3M)*
- 40-95% individuals VF have ≥ 1 major resistance mutation
- 1.2-25.5% of individuals on ART will have resistance within one year (110K – 2.5M)*
- Over time triple class failure will accumulate

* Calculated for 9.7 M requiring ART
Prevalence of Resistance

Average rate of VF at 12 mos: 4-8%*

*Recent reports from rural KZN as high as 40% (Dahab BMC PH 2010)
Pillay et al, ARHR 2008

- 39 children + 26 adults from 2000-2003 in Johannesburg; most adults received 3TC/ZDV/EFV; 21% had prior suboptimal tx
- 91% ≥ 1 major mutation; 14% K65R (D4T/DDI)
- No difference in Y181C, more K103N in adults despite sdNVP
- Frequent PI mutations due to higher use of PI (especially RTV)
• 8 clinics in Cape Town from 2002-2007, 75% resuppressed after detectable
• Few mutations in 120 ART naïve (K65R, Y181C, G190A)
• 110 VF patients with 93.6% resistance; 78% M184V, 9% K65R (D4T regimen)
• 23% TAMs, more often if >180 d (NS); 4-6 mos window between VL samples
• 88% had > 1 NNRTI mutation, 28% with one, 42% with two, 15% with three
Clinical Outcomes at 6 mo

N = 186 120 20 46
Died, clinic default = 5 3 2 0

HC Hosp/OI ND

*/† Significant
Murphy AIDS 2010
Active ARVs Based on Genotype

TDF > ABC > ETV greatest activity against majority of isolates

<table>
<thead>
<tr>
<th>Time Period</th>
<th>N</th>
<th>Alive and in care</th>
<th>Undetectable viral load</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>382</td>
<td>89% (95% CI: 86-92%)</td>
<td>78% (95% CI: 73-83%)</td>
</tr>
<tr>
<td>April 2004 – December 2007*</td>
<td>328</td>
<td>78% (95% CI: 73-82%)</td>
<td>77% (95% CI: 72-82%)</td>
</tr>
</tbody>
</table>

- Fox et al (Joburg) JAIDS 2009 – 77% VL suppressed on second-line tx
- Manosuthi (Thailand) AIDS Res Ther 2009– LPV/r + recycled 3TC
- Wallis et al (Joburg) JAIDS 2010
- SKT – 28 remaining 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
Adherence

- 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% adherence
- Parienti CID 2010 Average adherence to boosted protease inhibitor therapy, rather than the pattern of missed doses, predicts failure
Pharmacy refill increases after initiation of 2nd line therapy, then declines; associated with virologic response
Recycling/Resuppression

Hoffmann et al CID 2009
Factors Associated with VF and Drug Resistance in a RLS

- Most patients start ART late or very late
- Virologic monitoring is infrequent or absent
- Fewer regimens available and switches less frequent
- More frequent side effects and toxicities due to malnutrition and drug interactions
- Large LTFU rate
- Frequent OIs which complicate therapy
- Social stigma
- Continued use of mono/dual NRTI; SDNVP
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)
Barriers to Clinical Care

- Poverty/Economic
  - Transportation
  - Food Insecurity
  - Disability Grants
  - Poor social support

- Institutional
  - Long wait times
  - Negative staff experiences
  - Poor health literacy
  - Limited substance abuse treatment and mental health facilities

- Sociocultural
  - Perceived stigmatization
  - Influence of charismatic churches
  - Traditional healers
  - Gender Inequalities

- Political
  - Migration
  - Controversy over provision of HIV Tx
  - Traditional beliefs about HIV/AIDS

Kagee J Health Pscyhol, Global Public Health 2010
Western Cape
Barriers to Adherence

- Barriers to Care
- Symptoms/QOL
- Psychosocial

- Tired of taking ARVs
- Fear of taking ARVs in front of others
- Difficulty swallowing
- Remembering to take pills
- Side effects
- Cost of meds

Peltzer *BMC Public Health* 2010
Bhat *Euro J Clin Microb ID* 2010
Maqutu *AIDS Beh* 2010
Sarna *Pub Health Rep* 2010
Approach to Switching

• Review ART history (resistance testing only effective for current regimen), assess adherence and counsel (encourage disclosure, memory devices, etc), tolerability, and PK issues; repeat VL in 1-3 months if clinically stable
• Distinguish 1st/2nd from multiple failures
• Perform resistance testing while on drugs if available and identify susceptible drug/drug classes (if WT consider non-adherence or absorption)
• Consider novel strategies (boosting, multidrug regimens)
• Design a regimen with 3 or more active drugs if possible (SA use TDF/3TC/LPV/r)
• Consider new agents through trials and EAP (ETR, RTG, DRV, MVC)
• If no options available, always better to continue on regimen if tolerating
Key Questions

1. Can we predict who will get virologic failure in advance of its occurrence?
2. Amongst those who develop virologic failure, can we predict who will and who will not have drug resistance in the absence of genotypic testing?
3. Can we target those who are most vulnerable with broad programmatic or public health-based interventions to prevent virologic failure from occurring?
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
• Virologic monitoring crucial, can even resuppress with adherence counseling and close monitoring in select populations
• 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
• Significant concern for patients without resistance (reinforces importance of adherence/access to care)
• Adherence (pharmacy refill) = good predictor response

Virologic failure is bad w/ or w/o resistance