Selection of resistance in clinical practice

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Points to be covered:

- Transmitted drug resistance
- Resistance patterns in first-line failures in adults
- Second-line outcome data and resistance observed in second-lines.
- Possible third-line options?
Transmitted Drug Resistance
# Transmitted Drug Resistance in SA

Table 1: Prevalence classification of transmitted drug resistance (TDR) in selected provinces of South Africa as per the WHO recommended method of using annual antenatal survey (ANLUR) specimens, 2005 – 2011.

<table>
<thead>
<tr>
<th>Province</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Green: Low (&lt;5%) prevalence classification of HIV TDR; Orange: moderate (5-15%) prevalence classification of TDR. NC: not classifiable. GP = Gauteng, KZN = KwaZulu-Natal, OFS = Orange Free State, EC = Eastern Cape, WC = Western Cape. NRTI = nucleoside reverse transcriptase inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor.</td>
</tr>
</tbody>
</table>
Surveillance of HIV Drug Resistance

Stanford Resistance Database HIV-1 Drug Resistance in ARV-naive Populations
Compendium of published virus sequences from 46,765 persons, 264 studies
Transmitted HIVDR (WHO surveys) Mutation Prevalence

Overall prevalence: 3.1%
K103N or S: 0.8%
D67N/G, K101E/P, Y181C and M184V: between 0.3 – 0.4%

Note: drug resistance mutations as defined by WHO 2009 Surveillance Drug Resistance Mutation (SDRM) list

(n=3588, pooled analysis from 82 surveys)  WHO IAS 2012
MTN009 resistance patterns in worked screened for a PrEP study in 2010-2011

- Parikh et al., PLOSone 2013
### Transmitted Resistance in Recently Infected Individuals

<table>
<thead>
<tr>
<th>Class</th>
<th>Mutation</th>
<th>Number</th>
<th>Class</th>
<th>Mutation</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>M41L</td>
<td>1</td>
<td>NNRTI</td>
<td>L100I</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>D67N</td>
<td>1</td>
<td></td>
<td>K103N</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>K70R</td>
<td>1</td>
<td></td>
<td>Y181C</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>M184V</td>
<td>1</td>
<td>PI</td>
<td>I85V</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>L210W</td>
<td>1</td>
<td></td>
<td>M46L</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Timing of ARV rollout in country/region</th>
<th>2005 N</th>
<th>DRM %</th>
<th>2006 N</th>
<th>DRM %</th>
<th>2007 N</th>
<th>DRM %</th>
<th>2008 N</th>
<th>DRM %</th>
<th>2009 N</th>
<th>DRM %</th>
<th>p-value</th>
<th>b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>45</td>
<td>0</td>
<td>118</td>
<td>5</td>
<td>115</td>
<td>5</td>
<td>81</td>
<td>5</td>
<td>49</td>
<td>4</td>
<td>8.2</td>
<td>0.056</td>
</tr>
<tr>
<td>Rwanda Early 2004</td>
<td>17</td>
<td>0</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>20</td>
<td>2</td>
<td>10.0</td>
<td>3</td>
<td>15.0</td>
<td>0.081</td>
</tr>
<tr>
<td>Kenya Late 2003</td>
<td>1</td>
<td>0</td>
<td>18</td>
<td>1</td>
<td>5.6</td>
<td>0</td>
<td>16</td>
<td>0</td>
<td>19</td>
<td>0</td>
<td>10.0</td>
<td>0.796</td>
</tr>
<tr>
<td>Masaka, Uganda Mid-2004</td>
<td>6</td>
<td>0</td>
<td>13</td>
<td>1</td>
<td>7.7</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>13</td>
<td>0</td>
<td>14.0</td>
<td>0.327</td>
</tr>
<tr>
<td>Entebbe, Uganda Mid-2004</td>
<td>0</td>
<td>—</td>
<td>6</td>
<td>3</td>
<td>50.0</td>
<td>6</td>
<td>1</td>
<td>16.7</td>
<td>2</td>
<td>18.2</td>
<td>0</td>
<td>0.088</td>
</tr>
<tr>
<td>Zambia Late 2002</td>
<td>21</td>
<td>0</td>
<td>61</td>
<td>0</td>
<td>50.0</td>
<td>1</td>
<td>2.0</td>
<td>18</td>
<td>0</td>
<td>19</td>
<td>3</td>
<td>15.8</td>
</tr>
<tr>
<td>Cape Town Early 2004</td>
<td>0</td>
<td>—</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>33.3</td>
<td>0</td>
<td>—</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Price, Wallis et al., ARHR 2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Meta-analysis from the Stanford Database

Sub-Saharan Africa

Overall

NRTI

NNRTI

PI

% Resistance

Years Since ART Scale-Up

Rhee et al., PLOS Medicine 2015
Transmitted HIVDR (WHO surveys)

Prevalence of NNRTI resistance mutations: % of genotypes

Antiretroviral therapy coverage: % of people living with HIV receiving ART

Notes: p-value adjusted for region: 0.039. Odds-ratio = 1.49 (95% CI 1.07-2.08)

WHO IAS 2012
Impact of Resistance—at start of treatment

- Transmitted and Primary Resistance:
  - NNRTI mutations most frequent—esp children exposed to ARV via PMTCT (Jordan et al., 2017 CID).
  - Kenya found that age in females associated with PDR; Silverman et al., JID 2017).

- Effect on first-line regimens?
  - Adult Females: OCTANE study.
  - Children (sdNVP exposed): suppressed VL on PI changed to NNRTI 20% VF with NNRTI mutations (Coovaid et al., 2010).
Drug Resistance: First-line Treatment
Overview of First-line failure Mutations

- **M184V** → **3TC/FTC**
- **NNRTI Mutations**
  - K103N
  - Y181C
  - H221Y
  - V106M/A/I
  - G190A
  - K101E
  - E138A
  - A98G
- **K65R** → **TDF/d4T**
- **TAMs (≥3)** → **AZT/d4T**

**Pattern differs**

**Antagonistic effect of K65R and TAMs**

**Time on a Failing Regimen**
Y181C is selected by NVP more than EFV
V106M is selected more by EFV (34%) than NVP (2%)
Wider range mutations selected for by EFV rather than NVP
Small % NNRTI (5%) alone

Wallis et al., JAIDs 2010
Overview of First-line failure Mutations

- **NNRTI Mutations**
  - K103N
  - Y181C
  - H221Y
  - V106M/A/I
  - G190A
  - K101E
  - E138A
  - A98G

- **K65R**

- **TAMs (≥3)**

- **3TC/FTC**

- **EFV/NVP**

- **TDF/d4T**

- **AZT/d4T**

- **Pattern differs**

- **Antagonistic effect of K65R and TAMs**

**Time on a Failing Regimen**
TAMs Patterns after d₄T or AZT

TAMs associated with first line regimen containing d₄T (blue) or AZT (red). The AZT containing regimen had a higher frequency of TAMs compared to the d₄T regimen

Wallis et al., JAIDs 2010
Subtype C development of V106 M instead of V106A (Brenner, et al., 2003; Morris et al., 2003)

K103N at greater frequency and higher levels in women with subtypes C and D rather than A (Flys; JAIDS, 2006)

Culture studies have revealed K65 R occurs faster in HIV-1 subtype C (Brenner, AIDS 2006).

11% of patients infected with CRF02_AG majority failing a TNF based regimen in Nigeria developed K65R (Hawkins, JAIDS 2009).
Overview of First-line failure Mutations

M184V → 3TC/FTC

NNRTI Mutations

K103N
Y181C
H221Y
V106M/A/I
G190A
K101E
E138A
A98G

K65R → TDF/d4T

TAMs (≥3) → AZT/d4T

Pattern differs

Antagonistic effect of K65R and TAMs

Time on a Failing Regimen
Comparison of rate of acquisition of TAMS, NNRTI and 3TC mutations from time of first virological breakthrough.

Orrell et al. 2009 Antiviral Therapy
<table>
<thead>
<tr>
<th>Site</th>
<th>Malawi Lilongwe (Hosseinipour et al., 2009)</th>
<th>South Africa Cape Town (Orrell et al., 2009)</th>
<th>South Africa Johannesburg (Wallis et al., 2010)</th>
<th>South Africa Durban (Marconi et al., 2008)</th>
<th>South Africa CIPRA-SA (Wallis et al., 2012)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size</td>
<td>96</td>
<td>110</td>
<td>226</td>
<td>115</td>
<td>67</td>
</tr>
<tr>
<td>Clinical Sites</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Switch Criteria</td>
<td>Clinical or Immunological</td>
<td>HIV RNA &gt;5000 copies/ml</td>
<td>HIV RNA &gt;5000 or 1000 copies/ml</td>
<td>HIV RNA &gt;1000 copies/ml</td>
<td>HIV RNA &gt;1000 copies/ml</td>
</tr>
<tr>
<td>Frequency of Monitoring</td>
<td>Not Applicable</td>
<td>6 monthly HIV RNA &amp; CD4+ T-cell</td>
<td>6 monthly HIV RNA &amp; CD4+ T-cell</td>
<td>6 monthly HIV RNA &amp; CD4+ T-cell</td>
<td>3 monthly HIV RNA &amp; CD4+ T-cell</td>
</tr>
<tr>
<td>% with failure &amp; resistance</td>
<td>95%</td>
<td>85%</td>
<td>83%</td>
<td>83.5%</td>
<td>82%</td>
</tr>
<tr>
<td>M184V/I</td>
<td>81%</td>
<td>78%</td>
<td>72%</td>
<td>64.3%</td>
<td>67.2%</td>
</tr>
<tr>
<td>NNRTI</td>
<td>93%</td>
<td>86%</td>
<td>78%</td>
<td>Unknown</td>
<td>75%</td>
</tr>
<tr>
<td>K103N</td>
<td>28%</td>
<td>55%</td>
<td>38%</td>
<td>51%</td>
<td>50%</td>
</tr>
<tr>
<td>V106M</td>
<td>7%</td>
<td>31%</td>
<td>17%</td>
<td>19%</td>
<td>14%</td>
</tr>
<tr>
<td>&gt; 3 TAMS</td>
<td>44%</td>
<td>23%</td>
<td>11%</td>
<td>32.2%</td>
<td>1.5%</td>
</tr>
<tr>
<td>K65R</td>
<td>19%</td>
<td>9%</td>
<td>4.5%</td>
<td>2.6%</td>
<td>3%</td>
</tr>
<tr>
<td>Q151M</td>
<td>19%</td>
<td>Not Reported</td>
<td>2.5%</td>
<td>0.9%</td>
<td>0%</td>
</tr>
<tr>
<td>NRTI+NNRTI</td>
<td>91%</td>
<td>83%</td>
<td>73%</td>
<td>64.3%</td>
<td>63%</td>
</tr>
</tbody>
</table>
Predicted level of intermediate/high level resistance

Percentage intermediate/high level resistance

- 3TC/FTC: 94%
- ABC: 66%
- D4T: 60%
- DDI: 62%
- TDF: 43%
- ZDV: 42%
- EFV: 97%
- NVP: 97%
- ETR: 58%
- RPV: 65%
- ATV: 0%
- LPV: 0%
- DRV: 0%
Over 4 timepoints (T0=2008; T1=2011; T2=2013; T3=2015)
Level of NRTI and NNRTI and dual resistance increased overtime.

Mulu et al., PlosOne 2017
Impact of First-line Drug Resistance on Second-line Outcome
Long-Term Clinical Impact of d4T

- d4T resistance can go do two distinct pathways impact the future use of TNF or AZT

- Increased susceptibility to AZT if have K65R (alone) or K70E; found in 5.3%;

- Increase susceptibility to TNF if have >2 TAMs or Q151M; found in 22%.

Tang et al., JID 2013
- Used NVP over EFV increase risk of M184V, TAMS, Q151M, K65R.
- Longer treatment increase risk of M184V, TAMS, Q151M but not K65R.
- Subtype C and CRF01_AE associated increased risk of K65R.

Tang et al., JID 2013
TNF more likely to remain active after first-line d4T treatment.
What are the second-line options:

- LPV/r and two NRTIs;
- With the high level of NRTI resistance would LPV/r monotherapy be an option;
- Should we use two new class or drug LPV/r and RAL.
- RAL versus DTG and 2 NRTIs
Thailand, A5230 and EARNEST Studies

- Compared LPV/r-monotherapy with LPV/r plus 2 NRTI
- Showed that monotherapy was inferior in suppressing HIV-1 RNA levels to <50 copies/mL
- Even in the presence of NRTI mutations the NRTI in combination with a boosted PI still provide some effectiveness.

EARNEST:

- trial showed similar results on the use of NRTI with boosted PI in the presence of complex NRTI resistance
97% of subjects had ≥1 NRTI or NNRTI mutation at start of the study.

More AE in the PI arm compared to the RAL arm.

Non-inferiority of the RAL and LPV/r arm compared to control arm (LPV/r and 2/3 NRTIs)
Outcome of PI-based treatment, by NRTI susceptibility

Paton et al., Lancet HIV 2017
Comparison of the second-line studies

- LPV/r monotherapy-inferior
- RAL and LPV/r non-inferior to LPV/r and 2NRTIs
- SPRING-2 DTG versus RAL non-inferior (88% vs 85%)
- FLAMINGO: DTG versus DRV/r superior (90% vs 83%).

Unanswered questions:
- Would there be a long term difference?
- Would we see superiority if we looked closer at different drug resistance profiles.
Drug Resistance: Second-Line Treatment
665 participants:
- Confirmed viral failure on a PR-based second-line regimen
- 20 sites in 10 countries
- Real-time HIV drug resistance testing was performed
- Resistance mutations and scores were determined using the Stanford algorithm (v6.2).
- Associations of drug class resistance with HIV-1 subtype, screening HIV RNA, and nadir CD4 were evaluated.

Wallis et al., CROI 2016
High-Level or Intermediate Resistance, by drug class

<table>
<thead>
<tr>
<th>Number of classes with resistance</th>
<th>Total (n=665)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible/Low resistance to 3 drug classes</td>
<td>146 (22%)</td>
</tr>
<tr>
<td>Resistance to 1 drug class</td>
<td>137 (21%)</td>
</tr>
<tr>
<td>Resistance to 2 drug classes</td>
<td>207 (31%)</td>
</tr>
<tr>
<td>Resistance to 3 drug classes</td>
<td>175 (26%)</td>
</tr>
</tbody>
</table>

- 665 of the 683 plasma samples were available for analysis.
- Median HIV RNA $4.5 \log_{10}$ copies/ml.
- Median CD4 65 cells/mm$^3$.
- HIV subtype C (48%), B (20%) and A1 (18%).

NRTIs: 3TC/FTC (100%); TDF (84%), AZT (76%).

NVP (63%) and EFV (56%).

At time of screening, mainly TDF (67%) and 3TC (90%) were prescribed with either LPV/r (55%) or ATV/r (43%).
**RAL: Impact of using it in Second-line studies?**

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Raltegravir group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants analysed for genotyping</td>
<td>55</td>
<td>49</td>
</tr>
<tr>
<td>Participants with data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protease and reverse transcriptase*</td>
<td>43</td>
<td>42</td>
</tr>
<tr>
<td>Integrase†</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td>No new resistance mutations in protease, reverse transcriptase, or integrase</td>
<td>37/43 (86.0%)</td>
<td>39/47 (83.0%)</td>
</tr>
<tr>
<td>NRTI-associated mutations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Met184Val</td>
<td>2/43 (4.7%)</td>
<td>0/42 (0.0%)</td>
</tr>
<tr>
<td>Thymidine analogue mutation</td>
<td>2/43 (4.7%)†</td>
<td>0/42 (0.0%)</td>
</tr>
<tr>
<td>Lys65Arg or Lys70Glu</td>
<td>0/43 (0.0%)</td>
<td>0/42 (0.0%)</td>
</tr>
<tr>
<td>59 insertion complex</td>
<td>2/43 (4.7%)</td>
<td>0/42 (0.0%)</td>
</tr>
<tr>
<td>151 insertion complex</td>
<td>1/43 (2.3%)</td>
<td>0/42 (0.0%)</td>
</tr>
<tr>
<td>Protease inhibitor-associated mutations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Integrase strand transfer inhibitor-associated mutations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thr66Ala</td>
<td>0/46 (0.0%)</td>
<td>1/47 (2.1%)</td>
</tr>
<tr>
<td>Tyr143Arg or Tyr143Cys or Tyr143His</td>
<td>0/46 (0.0%)</td>
<td>1/47 (2.1%)</td>
</tr>
<tr>
<td>Asn155His</td>
<td>0/46 (0.0%)</td>
<td>5/47 (10.6%)</td>
</tr>
</tbody>
</table>

Data are n (%). Participants must have a confirmed plasma viral load of less than 200 copies per mL followed by a viral load 200 copies per mL or more to be deemed as having virological failure. We excluded participants who either did not have a viral load of more than 500 copies per mL or who withdrew consent. 104 participants were assessed for mutations at virological failure, of whom 95 had a successfully amplified and sequenced sample.* 19 participants missing data for failure to amplify. †11 participants missing data for failure to amplify. □Both participants previously had none, now have one.

**Table 2: Emergent mutations in participants who had virological failure**
Highly divergent resistance profiles were observed among study candidates being evaluated for 3rd-line ART in RLS.

The majority remained susceptible to 2nd-line regimens (69%) but others had high level resistance to 2 (31%) and 3 drug classes (26%).

Routine clinical parameters were not discriminatory for the extent of resistance.

These results indicate that objective measures of ART adherence and access to both resistance testing and newer ARVs are needed to guide 3rd-line ART in RLS.

Wallis et al., CROI 2016
Impact of First and Second-line Drug Resistance on Possible Third-line Options
Predicted Level of Intermediate and high level resistance.

Wallis et al., CROI 2016
### A5230: ETR and RPV resistance, by site

<table>
<thead>
<tr>
<th>No of mutations: RPV</th>
<th>Total (N=148)</th>
<th>Wits (N=23)</th>
<th>Chiang Mai (N=27)</th>
<th>YRG CARE (N=16)</th>
<th>Kamuzu (N=50)</th>
<th>KCMC (N=32)</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min, Max</td>
<td>0.5</td>
<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
<td>0.5</td>
<td>0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median (Q1,Q3)</td>
<td>1(0,2)</td>
<td>0(0,1)</td>
<td>2(1,2)</td>
<td>1(0,2)</td>
<td>2(1,2)</td>
<td>1.5(1.0,2)</td>
<td></td>
</tr>
<tr>
<td>10%,90%</td>
<td>0.3</td>
<td>0.2</td>
<td>1.3</td>
<td>1.4</td>
<td>0.4</td>
<td>0.3</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stanford Resist Score: RPV</th>
<th>Total (N=148)</th>
<th>Wits (N=23)</th>
<th>Chiang Mai (N=27)</th>
<th>YRG CARE (N=16)</th>
<th>Kamuzu (N=50)</th>
<th>KCMC (N=32)</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min, Max</td>
<td>0.75</td>
<td>0.30</td>
<td>0.65</td>
<td>0.70</td>
<td>0.75</td>
<td>0.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median (Q1,Q3)</td>
<td>25(0.35)</td>
<td>0.30</td>
<td>35(10.45)</td>
<td>12.5(0.0,35.0)</td>
<td>30(10.40)</td>
<td>0.575</td>
<td></td>
</tr>
<tr>
<td>10%,90%</td>
<td>0.60</td>
<td>0.20</td>
<td>9.60</td>
<td>0.65</td>
<td>0.05</td>
<td>0.65</td>
<td></td>
</tr>
</tbody>
</table>

| Susceptible                 | 48(32%)       | 16(70%)     | 3(11%)            | 7(44%)          | 12(24%)       | 10(31%)     |          |
| Potential Low level         | 10(7%)        | 1(4%)       | 4(15%)            | 1(6%)           | 3(6%)         | 1(3%)       |          |
| Low-level Resistance        | 20(14%)       | 5(22%)      | 1(4%)             | 3(19%)          | 7(14%)        | 4(13%)      |          |
| Intermediate Resistance     | 51(34%)       | 1(4%)       | 13(48%)           | 2(13%)          | 23(46%)       | 12(38%)     |          |
| High level Resistance       | 19(13%)       | 0(0%)       | 6(22%)            | 3(19%)          | 5(10%)        | 5(16%)      |          |

### No of mutations: ETR

<table>
<thead>
<tr>
<th>Total (N=148)</th>
<th>Wits (N=23)</th>
<th>Chiang Mai (N=27)</th>
<th>YRG CARE (N=16)</th>
<th>Kamuzu (N=50)</th>
<th>KCMC (N=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min, Max</td>
<td>0.5</td>
<td>0.3</td>
<td>0.4</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Median (Q1,Q3)</td>
<td>2(1.2)</td>
<td>0(0,2)</td>
<td>2(1,3)</td>
<td>1.5(0,0,2.0)</td>
<td>2(1.3)</td>
</tr>
<tr>
<td>10%,90%</td>
<td>0.3</td>
<td>0.2</td>
<td>1.3</td>
<td>0.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

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</thead>
<tbody>
<tr>
<td>Min, Max</td>
<td>0.75</td>
<td>0.30</td>
<td>0.65</td>
<td>0.70</td>
<td>0.75</td>
<td>0.65</td>
</tr>
<tr>
<td>Median (Q1,Q3)</td>
<td>25(0.35)</td>
<td>0.30</td>
<td>35(10.45)</td>
<td>12.5(0.0,35.0)</td>
<td>30(10.40)</td>
<td>0.575</td>
</tr>
<tr>
<td>10%,90%</td>
<td>0.60</td>
<td>0.20</td>
<td>9.60</td>
<td>0.65</td>
<td>0.05</td>
<td>0.65</td>
</tr>
</tbody>
</table>

| Susceptible               | 47(32%)       | 16(70%)     | 3(11%)            | 7(44%)          | 12(24%)       | 9(28%)      |
| Potential Low level       | 11(7%)        | 1(4%)       | 4(15%)            | 1(6%)           | 3(6%)         | 2(6%)       |
| Low-level Resistance      | 20(14%)       | 5(22%)      | 1(4%)             | 3(19%)          | 7(14%)        | 4(13%)      |
| Intermediate Resistance   | 51(34%)       | 1(4%)       | 13(48%)           | 2(13%)          | 23(46%)       | 12(38%)     |
| High level Resistance     | 19(13%)       | 0(0%)       | 6(22%)            | 3(19%)          | 5(10%)        | 5(16%)      |
Phenotyping to determine the place of second generation NNRTIs in third-line studies.

- Phenotypic analysis different from genotypic prediction in subtype C samples (either full RT or partial RT).
- The predicted genotype an phenotype were concordant for NVP, EFV and 3TC, the drugs administered as first-line treatment.
- TDF, RPV and ETR misclassified 17, 30 and 30% respectively of isolates which demonstrated phenotypic susceptibility despite estimated genotypic resistance.
- This may result from the presence of compensatory and/or epistatic mutations in RT which increase susceptibility to ETR, RPV and TDF.
**Overview of the A5288 Protocol**

**Cohort A**
No resistance to NRTIs, PIs, or NNRTIs
Continue 2nd line regimen; NRTIs can be modified

**Cohort B**
Susceptible to DRV/RTV and ETR ± resistance to NRTIs
Randomized 1:1 to cohort B1 or B2 (if HepB +, assigned to RAL, DRV/RTV, + TDF, FTC, or 3TC [at least two])

**Cohort C**
Resistance to ETR ± resistance to NRTIs
Best available NRTIs, RAL and DRV/RTV

**Cohort D**
Multiple NRTI resistance and/or DRV/RTV resistance
Best available regimen, includes study-provided and any locally-available drugs

- **Cohort B1**
  Best available NRTIs, RAL and DRV/RTV

- **Cohort B2**
  ETR, RAL and DRV/RTV

- **Cohort B3**
  HBV positive
  Best available NRTIs, RAL and DRV/RTV

**Screening Process up to 120 days-genotyping**

**Allocation to Cohort Based on ARV History and Genotype; Initiation of Study Regimen**

**All Cohorts:** At participating sites, randomize 1:1 to CPI+SOC or SOC
Conclusions

- Both transmitted resistance and first-line resistance is increasing. Two are directly related and high levels in certain areas review current first-line treatment.

- First-line resistance profiles are more consistent; whereas second-line are highly divergent impact use of when to perform resistance testing.

- Longer leave an individual on a failing regimen more complex the resistance patterns impact third/salvage regimens.
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• ACTG A5230
• ACTG A5288

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