HIV Drug resistance-implications for therapy

Deenan Pillay
Africa Centre for Health and Population Studies, UKZN

University College London
Potential implications of HAART without virological monitoring: Therapy failure?

- Treatment onset
- Virological failure (>1000c/mL)
- Clinical failure (AIDS events)

CD4 count

VL

VL 1000

increasing resistance
All viruses are archived and can re-emerge

Resistance testing only detects the majority virus population in plasma
IMPACT OF VIRAL VARIATION/QUASISPECIES

**Viral load**

- First phase viral decline as an "in vivo" phenotype
HOW TO DEFINE RESISTANCE?

• Genotype- mutations, collections of mutations
• In vitro phenotype – fold resistance, gene of choice
• Clinical response- complexity of multiple drugs
Phenotyping

Inhibition of viral replication (%)

100

50

Drug concentration

Susceptible strain

IC_{50}

Wild type

Resistant strain

IC_{50}

Resistance

IC_{50}
ZDV/3TC/ABC: Example of Slow Stepwise Appearance of Mutations in Subjects With Virologic Failure

- **M184V**
- **D67N/D, K70R/K, M184V**
- **M184V, T215T/Y**
- **M41L/M, M184V, T215Y**
- **M41L, M184V, T215Y**
- **M41L, M184V, L210L/W, T215Y**

**Legend:**
- WT = Wild Type
- Study week
- Plasma HIV-1 RNA Log
- ABC = 6.2, ZDV = 12.2 fold
- ABC = 5.9, ZDV = 4.1 fold
- 28 weeks of M184V only
The intensity of virological monitoring is associated with resistance to 1st line HAART

Gupta et al CID 2009
INCIDENCE OF RESISTANCE IN VIROLOGICAL FAILURES ON 1ST LINE NNRTI- OR bPI-CONTAINING REGIMENS: A META ANALYSIS

Gupta et al, LID 2009
Antiviral dynamics determines HIV evolution and predicts therapy outcome

Rosenbloom et al, Nat Med 2012
Assessment of Second-Line Antiretroviral Regimens for HIV Therapy in Africa

Virological response
Emerging resistance
High rates of re-suppression after virological failure on first line therapy in the absence of routine monitoring: 96 week data from the DART NORA substudy

<table>
<thead>
<tr>
<th>Week 48 VL (copies/ml)</th>
<th>ABC</th>
<th>NVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 96 VL (copies/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1000</td>
<td>148</td>
<td>149</td>
</tr>
<tr>
<td>1000 - 9,999</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>10,000 - 99,999</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>≥100,000</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>180</td>
<td>156</td>
</tr>
<tr>
<td>&lt;1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000 - 9,999</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10,000 - 99,999</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥100,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adjusted total % (95% CI):
- ABC: 71.1% (65.4-76.1)
- NVP: 88.7% (84.6-91.9)

Gupta et al Clin Inf Dis 2014
Evidence on HIV drug resistance testing

Dunn et al., 2007
Population impact of drug resistance - will spread of HIV drug resistance require change of 1st line therapy?
TDR and time since roll out

East Africa:
Estimated proportion with NNRTI TDR 8 years after start of roll out = 7.4%

Gupta et al, Lancet, 2012
Also: Frenz et al; AIDS rev 2012
Models predict a dramatic population effect of HIV Universal test and Treat

Granich et al 2008 Lancet
POPART intervention; modelling outcome

E

Zambia: Arm A

- Contamination (From Outside Area)
- From Treated
- From Other Untreated
- From Acute

F

Zambia: Arm B

- Contamination (From Outside Area)
- From Treated
- From Other Untreated
- From Acute

Christophe Fraser
Will ART expansion in SA lead to a relative increase in HIV drug resistance?

Meta-analysis demonstrates importance of M184V minority assays

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Standard</th>
<th>AS-PCR</th>
<th>N</th>
<th>Contingency correction</th>
<th>Ratio of new detections (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K103N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metzner 2005</td>
<td>4</td>
<td>5</td>
<td>49</td>
<td></td>
<td></td>
<td>1.25 (1.00, 1.94)</td>
</tr>
<tr>
<td>Metzner 2007</td>
<td>0</td>
<td>4</td>
<td>74</td>
<td>Yes</td>
<td></td>
<td>9.00 (1.00, 122.79)</td>
</tr>
<tr>
<td>Metzner 2007</td>
<td>0</td>
<td>3</td>
<td>15</td>
<td>Yes</td>
<td></td>
<td>7.00 (1.00, 91.11)</td>
</tr>
<tr>
<td>Johnson 2008</td>
<td>0</td>
<td>8</td>
<td>205</td>
<td>Yes</td>
<td></td>
<td>17.00 (1.16, 250.20)</td>
</tr>
<tr>
<td>PBay 2008</td>
<td>0</td>
<td>1</td>
<td>48</td>
<td>Yes</td>
<td></td>
<td>3.00 (1.00, 28.84)</td>
</tr>
<tr>
<td>Buckton 2009</td>
<td>10</td>
<td>12</td>
<td>165</td>
<td></td>
<td></td>
<td>1.20 (1.00, 1.55)</td>
</tr>
<tr>
<td>Coovadia 2009</td>
<td>3</td>
<td>9</td>
<td>60</td>
<td></td>
<td></td>
<td>3.00 (1.19, 7.56)</td>
</tr>
<tr>
<td>Hauser 2009</td>
<td>0</td>
<td>2</td>
<td>20</td>
<td>Yes</td>
<td></td>
<td>5.00 (1.00, 59.66)</td>
</tr>
<tr>
<td>Metzner 2009</td>
<td>0</td>
<td>6</td>
<td>93</td>
<td>Yes</td>
<td></td>
<td>13.00 (1.00, 186.42)</td>
</tr>
<tr>
<td>Metzner 2009</td>
<td>0</td>
<td>1</td>
<td>26</td>
<td>Yes</td>
<td></td>
<td>3.00 (1.00, 28.84)</td>
</tr>
<tr>
<td>Paredes 2009</td>
<td>8</td>
<td>19</td>
<td>183</td>
<td></td>
<td></td>
<td>2.38 (1.40, 4.02)</td>
</tr>
<tr>
<td>Toni 2009</td>
<td>0</td>
<td>3</td>
<td>30</td>
<td>Yes</td>
<td></td>
<td>7.00 (1.00, 91.11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.21 (1.49, 3.29)</td>
</tr>
<tr>
<td>D+L Subtotal</td>
<td>(I-squared = 54.4%, p= 0.012)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.44 (1.22, 1.70)</td>
</tr>
<tr>
<td>I-V Subtotal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M184V</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metzner 2005</td>
<td>1</td>
<td>6</td>
<td>49</td>
<td></td>
<td></td>
<td>6.00 (1.00, 35.91)</td>
</tr>
<tr>
<td>Metzner 2007</td>
<td>0</td>
<td>11</td>
<td>74</td>
<td>Yes</td>
<td></td>
<td>23.00 (1.53, 345.98)</td>
</tr>
<tr>
<td>Metzner 2007</td>
<td>0</td>
<td>4</td>
<td>15</td>
<td>Yes</td>
<td></td>
<td>9.00 (1.00, 122.79)</td>
</tr>
<tr>
<td>Johnson 2008</td>
<td>0</td>
<td>1</td>
<td>205</td>
<td>Yes</td>
<td></td>
<td>3.00 (1.00, 28.84)</td>
</tr>
<tr>
<td>Buckton 2009</td>
<td>1</td>
<td>13</td>
<td>165</td>
<td></td>
<td></td>
<td>13.00 (1.98, 85.46)</td>
</tr>
<tr>
<td>Metzner 2009</td>
<td>0</td>
<td>11</td>
<td>91</td>
<td>Yes</td>
<td></td>
<td>23.00 (1.53, 345.98)</td>
</tr>
<tr>
<td>Metzner 2009</td>
<td>0</td>
<td>6</td>
<td>26</td>
<td>Yes</td>
<td></td>
<td>13.00 (1.00, 186.42)</td>
</tr>
<tr>
<td>Toni 2009</td>
<td>0</td>
<td>4</td>
<td>30</td>
<td>Yes</td>
<td></td>
<td>9.00 (1.00, 122.79)</td>
</tr>
<tr>
<td>Vignokes 2009</td>
<td>0</td>
<td>15</td>
<td>35</td>
<td>Yes</td>
<td></td>
<td>31.00 (2.03, 473.77)</td>
</tr>
<tr>
<td>D+L Subtotal</td>
<td>(I-squared = 0.0%, p= 0.878)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.32 (4.46, 19.44)</td>
</tr>
<tr>
<td>I-V Subtotal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.32 (4.46, 19.44)</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis
Objective

• To assess the impact of transmitted drug resistance mutations on virological and immunological response up to 16 months after starting a combination antiretroviral therapy (cART)

• Specific analyses:
  • Transmitted drug resistance and fully active treatment
  • 2NRTI + 1NNRTI or 2NRTI + 1boosted PI regimen

Study population

• HIV infected patients regardless of age
• Start of cART after 1.1.1998
• ≥1 sample taken before antiretroviral treatment for genotypic testing
**Methods**

- **Virologic endpoint:**
  - time to first of two consecutive viral load > 500 copies/mL after six months of therapy

- **Definition TDR (two steps):**

  ![](image)

---

1 Bennett PlosOne 2009, 2 Liu CID 2006
Characteristics at the time of starting cART

- 10,056 patients from 25 cohorts
  - 76% male
  - Median age 38 years
  - 56% of European origin
  - 69% harboured a subtype B virus
  - Pre-treatment viral load and CD4 counts were 5 log10 cp/mL and 218 cells/μL
  - Transmission risk groups: 50% homosexual, 32% heterosexual, 8% IDUs and 2.1% perinatal

- 9.5% (n=954) patients harboured a virus with ≥1 mutation
  - 49.8% (n=475) received a fully active treatment
  - 50.2% (n=479) harboured a virus predicted to have at least low level resistance for ≥1 prescribed drug
Virological failure according to TDR

In adjusted analysis*:

- Patients with resistance to ≥1 drug:
  - significant higher risk of VF compared to patients without mutations
  - HR: 3.3 (2.5; 4.4) \(P<10^{-4}\)

- Patients receiving a fully active cART and patients with mutation:
  - risk of VF was not significantly different
  - HR: 1.4 (0.9; 2.3) \(P=0.17\)

*All models stratified by cohort; multivariable models adjusted for: Gender, age, pre-treatment viral load and CD4 count, year of treatment start, previous AIDS diagnosis, subtype, HIV transmission risk group, origin
Impact of TDR according to treatment strata

*All models stratified by cohort; multivariable models adjusted for: Gender, age, pre-treatment viral load and CD4 count, year of treatment start, previous AIDS diagnosis, subtype, HIV transmission risk group, origin.
Outcomes at week 96, according to the FDA snapshot definition.

ART = antiretroviral therapy; ATV/r = atazanavir plus ritonavir; DRV/r = darunavir plus ritonavir; FDA = U.S. Food and Drug Administration; RAL = raltegravir.
Conclusion

• Differential resistance on 1\textsuperscript{st} line therapy
• Impact of resistance is a function of therapeutic availability
• Increase transmission of resistance likely with extended roll out