Transmitted and Acquired HIV Drug Resistance in Africa

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ART scale-up and emergence of HIVDR

- Increasing ARV drug selective pressure at population-level leads to increased selection of drug-resistant HIV variants
- Most patients worldwide receive ART under a public health approach with restricted drug options, limited adherence support and lab monitoring, decentralized service delivery
- Pool of resistant viruses will predominantly emerge in these settings
Should we fear a dramatic increase in HIVDR?

"Widespread, unregulated access to ARV drugs in sub-Saharan Africa could lead to the rapid emergence of resistant viral strains, spelling doom for the individual, curtailing future treatment options, and leading to transmission of resistant virus."


"If compliance and careful follow-up of patients is not achieved, we will see a dramatic increase in multidrug-resistant HIV mutants..."

Lancet 2001
Risk factors

+ 

Primary or transmitted resistance (TDR)

Drug Resistance Mutations (DRMs) selected under ARV drug pressure

Acquired or secondary resistance (ADR)

The patient is infected with a virus that carries DRMs (natural variation or resistance transmission)

Reservoir of resistant HIV

Onward transmission

Poor response to ART
Transmitted and Pretreatment HIV Drug Resistance
PASER network: Monitoring cohort

- 13 routine ART sites in 6 countries
- >3000 adults initiating or switching ART
- Annual HIV-RNA and (if >1000c/ml) \textit{pol} genotyping
Pretherapy DR in ARV-naïve patients
PASER-M cohort at ART initiation 2007-2009

2590 participants
2436 pol sequences

Any DRM: 5.6%
NRTI: 2.5%
NNRTI: 3.3%
NRTI + NNRTI: 1.2%

Most common DRMs:
K103N, Y181C/I, G190A/S, TAMs, M184V

Estimated increase/yr since ART rollout
Any DRM: 38% (13-68) (p=0.001)
NNRTI: 35% (1-81) (p=0.041)

WHO 2009 Surveillance Drug Resistance Mutation list
Hamers et al. for PASER. Lancet Inf Dis 2011
Global trends in antiretroviral resistance in treatment-naive individuals with HIV after rollout of antiretroviral treatment in resource-limited settings: a global collaborative study and meta-regression analysis

Ravindra K Gupta, Michael R Jordan, Binta J Sultan, Andrew Hill, Daniel H J Davis, John Gregson, Anthony W Sawyer, Raph L Hamers, Nicaise Ndembi, Deenan Pillay, Silvia Bertagnolio

Lancet 2012; 380: 1250–58
Published Online
July 23, 2012
http://dx.doi.org/10.1016/S0140-6736(12)61038-1

26,102 patients from 191 datasets from 42 countries in Africa, Asia, Latin America
Prevalence of HIVDR in ARV-naïve individuals, by time since ARV rollout

Every circle is a study and the size of the circle is proportional to the precision of the estimate from the individual study.

Gupta et al. Lancet 2012
WHO TDR surveys
2004-2010

72 surveys
WHO TDR surveys: Mutation Prevalence
n=3588, pooled analysis from 82 surveys

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

WHO 2009 Surveillance Drug Resistance Mutation list

WHO 2009 Surveillance Drug Resistance Mutation list

WHO HIV Drug Resistance Report 2012
Pretherapy DR doubles risk of virological failure and acquired HIVDR in 1st year of ART

*PASER-M cohort*

- **No PDR** (n=2404)
- **PDR and fully-active ART** (n=52)
- **PDR and partially-active ART** (n=123)

Multivariate analysis adjusted for sex, age, calendar year, WHO clinical stage, BMI, pretherapy HIV RNA and CD4, prior ARV use, type of NRTI and NNRTI.

Hamers et al. Lancet Inf Dis 2012
Pretherapy DR reduces CD4 recovery

PASER-M cohort

Linear mixed model adjusted for age, sex, pretreatment CD4 and HIV RNA, subtype, calendar year, NRTI and NNRTI, prior ARV, adherence

Hamers et al. Lancet Inf Dis 2012
### Pretreatment DR associated with 5-fold increase in regimen switching in first 2 yrs of ART

**PASER-M cohort**

<table>
<thead>
<tr>
<th></th>
<th>Number of events</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR</td>
<td>95%CI</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>88</td>
<td>HR</td>
<td>95%CI</td>
</tr>
<tr>
<td><strong>Pre-treatment drug resistance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fully active regimen</td>
<td>70</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Partially active regimen</td>
<td>18</td>
<td>4.73</td>
<td>2.82, 7.94</td>
</tr>
</tbody>
</table>

*Adjusted for gender, age & site

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**Switch to second-line regimen**

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Fully active regimen</td>
<td>[0, 1]</td>
<td>[0, 1]</td>
</tr>
<tr>
<td>Partially active regimen</td>
<td>[4, 6]</td>
<td>[4, 6]</td>
</tr>
</tbody>
</table>

**HR 5.39**

**p < 0.001**

*Adjusted for gender, age & site

*Courtesy of Bernice Hoenderboom*
Acquired HIV Drug Resistance
Rapid accumulation of mutations when first-line ART is continued despite virological failure

Longitudinal genotyping analysis at first detection of Virological Failure (t1) and 6-12 months after (t2)

Steep increase in TAMs (+250%) and K65R (+100%) between t1-t2

NNRTI susceptibility is already lost at first detection of VF
Absence of VL monitoring leads to loss of drug susceptibility

Cohort 1 (n=100)  
Virological failure by routine pVL test, 12 mo ART

Cohort 2 (n=161)  
Clinico-immunological failure, 26 mo ART

Stanford hivdb algorithm

Hamers CID12; Sigaloff JID12
Clinical impact on 2nd line ART?

WHO guidelines: 2NRTIs+NNRTI $\rightarrow$ 2 new/recycled NRTIs + bPI

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Second-line treatment in the Malawi antiretroviral programme: high early mortality, but good outcomes in survivors, despite extensive drug resistance at baseline*

MC Hosseinipour,1,2 JJ Kumwenda,3,4 R Weigel,5 LB Brown,2 D Mzinganjira,1 B Mhango,3 JJ Eron,2,6 S Phiri5 and JJ van Oosterhout1,7

1University of North Carolina Project, Lilongwe, Malawi, 2University of North Carolina, Chapel Hill, NC, USA, 3Department of Medicine, University of Malawi College of Medicine, Blantyre, Malawi, 4Johns Hopkins Project, Blantyre, Malawi, 5Lighthouse Trust, Lilongwe, Malawi, 6UNC Center for AIDS Research, Chapel Hill, NC, USA and 7Malawi-Liverpool Wellcome Trust, University of Malawi College of Medicine, Blantyre, Malawi

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Second-Line Antiretroviral Treatment Successfully Resuppresses Drug-Resistant HIV-1 After First-Line Failure: Prospective Cohort in Sub-Saharan Africa

Kim C. E. Sigaloff,1,2 Raph L. Hamers,1,2 Carole L. Wallis,3 Cissy Kityo,4 Margaret Siwale,5 Prudence Ivey,3 Mariette E. Botes,6 Kishor Mandalaya,7 Maureen Wellington,8 Akin Osibogun,9 Wendy S. Stevens,2 Michèle van Vugt,10 and Tobias F. Rinke de Wit,1,2 the PharmAccess African Studies to Evaluate Resistance (PASER)

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NRTI backbone: residual activity vs toxicity?
Europe-Africa Research Network for Evaluation of Second-line Therapy (EARNEST) Trial

**Trial design (1)**

- HIV positive adolescents / adults (n=1200)
  - 1st line NNRTI-based regimen >12m; > 90% adherence last 1m
  - Failure by WHO (2010) clinical, CD4 (VL-confirmed) or VL criteria

**RANDOMIZE**

- PI + 2-3 NRTIs (NRTIs according to local standard of care)
- PI + RAL (12 wk induction)
- PI (Monotherapy)

**FOLLOW-UP FOR 144 WEEKS**

**Primary outcome at week 96:**
- **Good HIV disease control** — defined as all of:
  - Alive and no new WHO4 events from 0-96 weeks AND
  - CD4 cell count > 250 cells/mm³ at 96 weeks AND
  - VL < 10,000 c/ml OR > 10,000 c/ml without PI res. mutations at 96 weeks

14 Sites:
- Uganda
- Zimbabwe
- Malawi
- Kenya
- Zambia

April 2010 - April 2011:
- 1277 patients randomised

**Monitoring:**
- Clinical and CD4
- Every 12-16 wks

Paton, IAS 2013
VL suppression at 96 weeks

- **PI/RAL vs PI/NRTI:** P = 0.36
- **PImono+ vs PI/NRTI:** P = 0.002

<table>
<thead>
<tr>
<th>Condition</th>
<th>&lt;10000 c/ml</th>
<th>&lt;1000 c/ml</th>
<th>&lt;400 c/ml</th>
<th>&lt;50 c/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI/NRTI</td>
<td>91%</td>
<td>88%</td>
<td>86%</td>
<td>74%</td>
</tr>
<tr>
<td>PI/RAL</td>
<td>93%</td>
<td>87%</td>
<td>86%</td>
<td>73%</td>
</tr>
<tr>
<td>PImono+</td>
<td>83%</td>
<td>67%</td>
<td>61%</td>
<td>44%</td>
</tr>
</tbody>
</table>

P values:
- P = 0.36
- P < 0.0001
- P = 0.97
- P = 0.88

Paton, IAS 2013
Resistance at 96 weeks
(predicted in whole population)

- TDF/ZDV/ABC/ddI
- RAL
- LPV

% of randomised patients with intermediate/high level resistance

- PI/NRTIs: 4 (X), 2
- PI/RAL: 0* (X), 2, 1
- PI mono+: 0 (X), 18

Note: assuming susceptible if VL<1000 c/ml at week 96; and using inverse probability weighting for VL>1000 c/ml with missing genotype at week 96 based on those with observed genotypes.

*One patient in RAL/PI with intermediate/high level resistance to TDF had moved to 3TC TDF ALV at week 4 due to rash.
Novel ART Strategies for HIV Treatment and Prevention: At the Cost of HIVDR?
ART eligibility is increasing

Estimated millions of people eligible for ART in LMIC in 2011

1. CD4 ≤ 200
   Recommended since 2003

2. CD4 ≤ 350
   Recommended since 2010

3. CD4 ≤ 350 + TasP
   Incremental approach 2012

4. CD4 ≤ 500
   Ongoing systematic review of evidence (GRADE review)

5. All HIV+
   “Test and treat”

ART regardless of CD4 count for:
- Serodiscordant couples *
- Pregnant women
- Key populations (SW, IDU, MSM)

* HTPN 052 trial

Gottfried Hirnschall WHO, IAS Conference July 26, 2012
Early ART initiation: does the preventive effect outweigh the increase of TDR?

Mathematical model based on combined ADR and TDR data from PASER-M cohort in Kampala and Mombasa

TDR prevalence will increase:
- <200 cells/μL: 9.4%-12.3%
- <350 cells/μL: 11.6%-13.4%
- <500 cells/μL: 17.8%-18.7%

Effect of initiating ART at different CD4 thresholds

TDR prevalence
Infections averted
Over 10-year period

Nichols et al. aids 2014
But the number of new HIV infections averted far exceeds incident cases of TDR.
Increase in TDR prevalence due to early ART initiation will be eliminated if access to 2nd-line ART is increased to 80-100%.
Pre-Exposure Prophylaxis for HIV (PrEP)

• TDF-FTC effective in iPRESX, Partners PrEP, TDF2; not effective in FEM-PREP and VOICE (TDF) because of non-adherence

• Concerns, in regard to HIVDR:
  1. Already HIV-infected when starting PrEP
  2. Non-adherent and infected while on PrEP
  3. TDF-FTC also in first-line treatment: loss of future drug options?

• 5 cases of HIVDR have been detected in iPReX, Partners PrEP, TDF2 (total of 118 infections averted)
  → All had unrecognized (acute) infections (acquired DR)
  → No documented cases of transmitted HIVDR
PrEP will have a limited impact on HIVDR prevalence in sub-Saharan Africa

Comparison of 3 independent mathematical models

![Graph comparing ART alone vs ART+PrEP](attachment:graph.png)
What is the role of HV drug resistance testing in patient management in Africa?

• Restricted access due to high cost, technical complexity, lack of lab infrastructure and trained staff, complex sample transport, turnaround time, quality control, clinical interpretation

• **1st line failure:**
  • empirical 2\textsuperscript{nd} line seems effective
  • GT may identify patients with wild-type virus (20-30%), thereby averting/delaying more expensive 2\textsuperscript{nd} line ART

• **2nd line failure:**
  • may guide drug choice in 3\textsuperscript{rd} line from available options
What is the role of resistance testing in patient management in Africa?

• Increased uptake is anticipated → Updated South Africa guidelines recommend GT in all 2\textsuperscript{nd} line failures

• Cost-effectiveness will depend on prevalence of wild-type virus, timely response (switch) to genotype results, test cost, available drug options [Levison CID2013]

• Online clinical support tool based on prediction models for treatment response \textit{without need for genotyping}
  
  https://www.hivrdi.org/treps
Summary & Conclusions - 1

- Transmitted/pretreatment HIVDR (particularly to NNRTI) is increasing over time in areas surveyed in Africa
  - Still within the expected levels and rates
  - Compromises response to first-line ART

- Fear of resistance is not an argument against ART expansion, but improved program functioning needed.

- Excellent clinical and virological outcomes of 2nd line bPI +2NRTI, but not bPI monotherapy
  - Residual activity of NRTI backbone (despite NRTI resistance)
  - No long-term data
• Predictions say that early ART initiation will drive TDR, but this will be outweighed by new infections averted (no empirical data).

• Predictions say that HIVDR from treatment scale-up will far exceed that from PrEP (no empirical data).

• Standardized, population-based surveillance of HIVDR is imperative → integrated into routine M&E programs

• Operational research on novel ART strategies needed to assess adherence, retention and HIVDR development
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- David van de Vijver, Brooke Nichols – Erasmus MC
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