HIV DRUG RESISTANCE IN AFRICA

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Joint Clinical Research Centre, Kampala

Interest Meeting
Mombasa
May 10th 2012
Scope

1. HIV-DR testing in Africa
2. The Epidemiology of HIV-DR in Africa
3. HIVDR Surveillance
4. Ways to minimise preventable HIV-DR
5. Wrap up.
Background

• ART programmes in Africa have been nurtured with donor funding largely from PEPFAR and other agencies e.g. The Global fund, The Clinton Foundation.

• As these ART in-country programmes mature, they will increasingly face new challenges that require careful planning with a smart balance between short and long term goals and consequences.
The Primary Challenge:

• The enormous need for HIV care and treatment in the setting of under-resourced health care systems that urgently need:
  – Sustainability of funding for ART continuity
  – Maintaining efficient ARV logistics systems
  – Emerging resistance to ARVs
  – Structural barriers to Universal ART access
Genotypic resistance testing at JCRC, Kampala

FICRS 2009: Juliet Akao, Samar Mehta; unpublished.
WHO-HIVDR prevention and assessment approach

1. Monitoring of HIVDR early warning indicators
2. Acquired HIV-DR Surveys
3. Transmitted HIVDR surveys
4. Supporting a network of accredited HIVDR genotyping laboratories for HIV-DR surveillance.
EARLY WARNING INDICATORS FOR HIVDR
HIV-DR Early Warning Indicators (EWIs)

- ART site factors that are associated with the emergence of preventable HIV-DR
  
  - Can be acted upon at the ART site or programme level to prolong the long-term efficacy of the current ART options.

WHO 2010
WHY EWIs

1. EWIs evaluate factors associated with HIVDR prevention without requiring laboratory testing for drug resistance.

2. EWIs are monitored either at all ART sites in the country or at representative sites.

3. ART site profiles, completed annually, inform the interpretation of EWI results, and guide corrective public health interventions.

4. EWI monitoring provides the evidence base for public health action to prevent and address HIVDR.
Recommended EWIs (WHO)....2010

1. ART prescribing practices (100%)
2. Patients lost to follow-up 12 months after ART initiation (<20%)
3. Patients on appropriate first-line ART at 12 months (>70%)
4. On-time ARV drug pick-up (>80%)
5. ART clinic appointment keeping (80%)
6. ARV drug supply continuity (100%)
7. Optional:
   I. Patient adherence to ART (80%)
   II. Viral load suppression 12 months after ART initiation (70%)
Proportions of facilities that met the HIVDR EWI Targets: 2007 Vs 2008

Wilford Kirungi et al, 2011
Proportion(%) of facilities that met HIVDR EWI Targets across 13 Sites* (2007-2009), PASER study

* ART Clinics in Uganda, Kenya, Nigeria, South Africa, Zambia & Zimbabwe

Sigaloff et al, Clinical Infectious Diseases 2012;54(S4):S294–9
EWI from 2107 ART clinics in Africa, Asia, Latin America & Caribbean (2004-2009)

Bennett et al, Clinical Infectious Diseases 2012;54(S4):S280–9
Time to virologic failure (>50) and ART adherence by on time drug refill

TRANSMITTED HIV-DRUG RESISTANCE (TDR)
Factors likely to promote TDR

• Resistance among those on ART
  – Poor adherence to effective regimens
  – Adherence to failing regimens
  – Drug stock out
  – Use of Non-suppressive (ineffective) regimens
    • E.g. NRTI mono or dual therapy, NNRTI monotherapy as used in some PMTCT regimens
  – Substandard ARVs
    • Poor manufacturing practices
Trend in TDR in South Africa

Prevalence of transmitted drug resistance

Year

2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010

Manasa J, AIDS RESEARCH AND HUMAN RETROVIRUSES Volume 27, Number 4, 2011
## HIV Drug Resistance Threshold Surveys (HIVDR-TS) in Uganda

<table>
<thead>
<tr>
<th>Site</th>
<th>Population</th>
<th>n</th>
<th>%</th>
<th>Year</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Kampala CSW</td>
<td>41</td>
<td>2.3</td>
<td>2008-2010</td>
<td>Ssemwanga et al, Clinical Infectious Diseases 2012;54(S4):S339–42</td>
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<tr>
<td>Mbale ART Clinic</td>
<td>209</td>
<td>12</td>
<td>2007-2009</td>
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<td>Fortportal ART Clinic</td>
<td>182</td>
<td>10</td>
<td>2009-2009</td>
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</tbody>
</table>

- Genotypic analysis of samples from newly diagnosed patients in CDC National HIV Surveillance System (N = 12,668)

The viral load and HIV transmission

No transmission occurred <1,500 copies/ml

Quinn T. Et al NEJM 2000;342:921-9
Persistence of Transmitted Resistance in Primary HIV Infection

- **Primary resistance**
  - **US; F/U median 9 months**
    - **n=11** Persistent resistance
    - **n=2** Reversion to wild type
  - **UK; F/U up to 3 years**
    - **n=16** Persistent resistance
    - **n=14** Persistent resistance
    - **n=2** Reversion to wild type

*Variable persistence according to mutations: TAMs persist, K103N persists, PI persist, MDR persist*

Little et al. 11th CROI 2004, San Francisco, CA. Abs 36LB.
VIROLOGIC FAILURE
Virologic failure on treatment

• Virologic failure to first line ART by 48 weeks can develop in 10–20% of individuals as a result of:
  1. suboptimal medication adherence,
  2. pre-existing drug resistance
  3. emergence of drug resistance

• Transmitted Drug Resistance:
  1. limits the choice of first-line ART
  2. decreases efficacy of subsequent ARVs
  3. Increases the risk of treatment failure
The Effect of TDR on ART Response (European Cohort)

Wittkop et al, Lancet Infect Dis 2011;11: 363–71
Baseline Minority NNRTI Resistance and the Risk of Virologic failure

(b)

Percent with virologic failure

- 90% for NNRTI MV detected
- 46% for No NNRTI MV detected
- 67% for NNRTI MV detected
- 50% for No NNRTI MV detected
- 42% for NNRTI MV detected
- 27% for No NNRTI MV detected
- 26% for NNRTI MV detected
- 9% for No NNRTI MV detected

NNRTI adherence

- <60% adherence: 10
- 60%-79% adherence: 11
- 80%-94% adherence: 6
- ≥95% adherence: 26

Jonathan Z. Li, AIDS 2012, 26:185–192
Baseline Minority NNRTI Resistance and the Risk of Virologic failure

<table>
<thead>
<tr>
<th>HR</th>
<th>1.8</th>
<th>1.4</th>
<th>2.3</th>
<th>3.5</th>
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<tbody>
<tr>
<td></td>
<td>(1.1-2.5)</td>
<td>(0.5-3.7)</td>
<td>(0.9-5.8)</td>
<td>(2.3-5.4)</td>
</tr>
</tbody>
</table>

Jonathan Z. Li, AIDS 2012, 26:185–192
Exposure to Single dose NVP and ART Failure in the OCTANE study

ART Outcomes of Women that received Perinatal SDNevirapine for PMTCT

ZDV vs Maternal HAART for PMTCT

TAMs start to emerge at 12 weeks and at 24 weeks they were detectable in 63% of patients.

Scott-Dryden Peterson, CROI 2010

Christine Katlama, JAMA, 1996;276:118-125
## NNRTI Resistance after SDN in PMTCT

<table>
<thead>
<tr>
<th>Viral Subtype</th>
<th>Standard sequencing %</th>
<th>Ultra deep Sequencing %</th>
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<tbody>
<tr>
<td>C</td>
<td>69</td>
<td>70-87</td>
</tr>
<tr>
<td>A</td>
<td>19</td>
<td>42</td>
</tr>
<tr>
<td>D</td>
<td>36</td>
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<tr>
<td>CRF02</td>
<td>21</td>
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</tbody>
</table>

Subtype C and HIVDR

• Earlier (12Wks vs >40Wks) and more frequent emergence of K65R in vitro tissue culture vs Subtype B

• An excess of K65R and V106M in Subtype C Samples from Malawi, Zimbabwe, Botswana & Ethiopia
Probable explanation for the preferential Selection of K65R in Subtype C

The Subtype C Reverse nucleotide template has difficulty in reading codon 65 and Subtype B may stay longer at codon 67.

Wainberg et al, Viruses 2010, 2, 2493-2508
The ART monitoring strategy and HIVDR
Implications of HAART Without Viral Load Monitoring

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

Deenan Pillay
ART monitoring Strategy and time to Switch to Second-line

Shorter time to ART switch (16.3 Vs 21.8 months, P<0.001).

Keiser et al, AIDS 2009, 23:1867–1874,
**Evolution of resistance in the DART Study**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mutations at 24 weeks</th>
<th>Additional Mutations at 48 Wks</th>
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<tbody>
<tr>
<td>A</td>
<td>184V</td>
<td>67N, 70R, 215F</td>
</tr>
<tr>
<td>B</td>
<td>41L, 67N, 70R, 184V, 215Y</td>
<td>210W</td>
</tr>
<tr>
<td>C</td>
<td>184V</td>
<td>41L, 67N, 210W, 215Y</td>
</tr>
<tr>
<td>D</td>
<td>67N, 70R, 184V</td>
<td>41L, 215Y, 219Q</td>
</tr>
<tr>
<td>E</td>
<td>67N, 70R, 215F</td>
<td>184V, 219E</td>
</tr>
<tr>
<td>F</td>
<td>67N, 70R, 184V, 215N</td>
<td>41L, 215Y</td>
</tr>
<tr>
<td>G*</td>
<td>41L, 67N, 181I, 184V, 215Y</td>
<td>70R</td>
</tr>
</tbody>
</table>

*Lost Y181I at Wk48

*Deenan Pillay, DART Study.*
ART monitoring Strategy and the emergence of resistance

**Any thymidine analogue mutations**
- NNRTI clinical trials
- Cohort (frequent monitoring)
- Cohort (infrequent or no monitoring)

**M184V/I mutation**
- NNRTI clinical trials
- Cohort (frequent monitoring)
- Cohort (infrequent or no monitoring)

**Major NNRTI**
- NNRTI clinical trials
- Cohort (frequent monitoring)
- Cohort (infrequent or no monitoring)

**K65R mutation**
- NNRTI clinical trials
- Cohort (frequent monitoring)
- Cohort (infrequent or no monitoring)

Percentage of all patients starting HAART with resistance at 48 weeks (95% CI)

Key take home messages.....1

1. There is a variable increase in HIVDR across Africa but TDR is less than 15%

2. Uninterrupted ART supply and ART adherence are key aspects of the ART programmes that urgently need to be addressed to minimize preventable HIVDR

3. The PMTCT practices of the last decade (non-use of Maternal HAART) have contributed to early virologic failure. The use of Maternal HAART should be rapidly scaled up in PMTCT programmes.
Key Take home messages.....2

1. Late detection of Virologic failure increases the complexity of HIVDR. Low cost Viral Load technologies are needed to reduce its impact.

2. Preferential development of K65R mutation may compromise the role of Tenofovir as a second-line option in HIV subtype C infections.