The new epidemic of drug resistant HIV-1

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Centre for HIV and STI
National Institute for Communicable Diseases

ICREID – March 2018
Status of the global HIV epidemic (2016)

36.7 million people now estimated to be living with HIV
[30.8–42.9 million]

During 2016...

1.8 million people newly infected
[1.6–2.1 million]

1.0 million HIV-related deaths
[830 000–1.2 million]
People living with HIV by WHO region (2016)

36.7 million people living with HIV globally

- Africa: 25.6 million
- Americas: 3.3 million
- South-East Asia: 3.5 million
- Europe: 2.4 million
- Eastern Mediterranean: 360,000
- Western Pacific: 1.5 million
Anti-retroviral targets in the HIV life cycle

Siliciano JD and Siliciano RF, Curr Opinions in Virology 2013
Antiretroviral options

WHO recommended ART for adults and adolescents: NNRTI-based (1\textsuperscript{st}-line) regimens

- Test & Treat
- No resistance testing performed at ART start irrespective of prior exposure.
- Viral Load monitoring at least annually
- If VL>1000cpm, intensified adherence counselling and repeat VL
- If VL >1000cpm, then switch to 2\textsuperscript{nd} line.
- No resistance testing performed at 1L failure

1 pill QD

<table>
<thead>
<tr>
<th>NNRTI</th>
<th>NRTI</th>
<th>NRTI</th>
</tr>
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<tbody>
<tr>
<td>Efavirenz (600 mg)</td>
<td>Emtricitabine (200 mg)</td>
<td>Tenofovir DF (300 mg)</td>
</tr>
</tbody>
</table>
PI-based (2\textsuperscript{nd} line) regimens for adults and adolescents

- **PI**
  - Ritonavir-boosted lopinavir (LPV/r)
  - OR
  - Atazanavir (ATZ) + Rotinavir

- **NNRTI**
  - Efavirenz (600 mg)

- **NRTI**
  - Emtricitabine (200 mg)
  - Tenofovir DF (300 mg)

- **NRTI**
  - Zidovudine (AZT)
  - OR
  - Zidovudine (AZT) + Tenofovir DF

- >3 pills BID

- Viral Load monitoring annually
- If VL >1000cpm after 12mo Rx, then access 3\textsuperscript{rd} line where available
- Resistance testing is recommended at PI regimen failure
Global rates of ART coverage

UNAIDS/WHO estimates 2017
«90-90-90» - ambitious target aimed at ending AIDS

- **90%** diagnosed
- **90%** on treatment
- **90%** virally suppressed

**In 2020**
- 90% of all people living with HIV will know their HIV status
- 90% of all people diagnosed with HIV will receive sustained antiretroviral therapy
- 90% of all people receiving antiretroviral therapy will be virally suppressed

Zero new HIV infections.
Zero discrimination.
Zero AIDS-related deaths.

UNAIDS
HIV testing and care continuum (2016)

- People living with HIV: 36.7 m
- Aware of HIV status: 25.5 m (7.5 m, 90%)
- On treatment: 19.5 m (10.2 m, 90%)
- Viral load suppressed: 16.0 m (10.7 m, 90%)

UNAIDS/WHO estimates
The Fast-Track

NO SCALE-UP—maintain 2013 coverage levels

New HIV infections in low- and middle-income countries (millions)

AIDS-related deaths in low- and middle-income countries (millions)

New HIV infections in different population groups, low- and middle-income countries, 2030

RAPID SCALE-UP—achieve ambitious targets

New HIV infections in low- and middle-income countries (millions)

AIDS-related deaths in low- and middle-income countries (millions)

MAJOR BENEFITS:

21 MILLION AIDS-related deaths averted by 2030

28 MILLION HIV infections averted by 2030

5.9 MILLION HIV infections among children averted by 2030

15- FOLD return on HIV investments

Without scale-up, the AIDS epidemic will continue to outrun the response, increasing the long-term need for HIV treatment and increasing future costs.

Rapid scale-up of essential HIV prevention and treatment approaches will enable the response to outpace the epidemic.

2030
How HIV drug resistance arises

- Mutation rate of HIV: $\sim 3 \times 10^{-5}$ nucleotides/replication cycle
- $10^{11}$ virions generated during $10^7$ – $10^8$ rounds of replication/day

Richmann DD et al, Sci Am 1998; B Larder AIDS 2001
Identification of HIV drug resistance mutations

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (nRTIs)$^a$

Multi-nRTI Resistance: 69 Insertion Complex$^b$ (affects all nRTIs currently approved by the US FDA)

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<td>M</td>
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<td>K</td>
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<td>T</td>
<td>K</td>
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<td>41</td>
<td>62</td>
<td>69</td>
<td>70</td>
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<td>L</td>
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Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)$^{a,m}$

Efavirenz

<table>
<thead>
<tr>
<th>L</th>
<th>K</th>
<th>K</th>
<th>V</th>
<th>V</th>
<th>Y</th>
<th>Y</th>
<th>G</th>
<th>P</th>
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<tbody>
<tr>
<td>100</td>
<td>101</td>
<td>103</td>
<td>106</td>
<td>108</td>
<td>181</td>
<td>188</td>
<td>190</td>
<td>225</td>
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<td>I</td>
<td>P</td>
<td>N</td>
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MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS$^{p,q,r}$

Atazanavir +/- ritonavir$^s$

| L | G | K | L | V | L | E | M | M | G | I | F | I | D | I | I | A | G | V | I | I | N | L | L |
| 10| 16| 20| 24| 32| 33| 34| 36| 46| 48| 50| 53| 54| 60| 62| 64| 71| 73| 82| 84| 85| 88| 90| 93|   |   |   |   |
| I | E | R | I | I | Q | I | I | V | L | L | L | E | L | V | C | A | V | V | S | M | L |   |   |   |   |
| F | M |   | F | V | V |   |   |   |   |   |   |   |   |   |   | M | V | T | T | F | V | L | A | I |
| C | T | V |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

Wensing et al Topics in Antiviral Med. 2017
HIV drug resistance

- Drug resistant variants are selected during treatment failure
- Drug resistance variants similarly cause treatment failure
- May compromise virion fitness
- Cross resistance within drug classes
- Different genetic barriers to drug resistance between drug classes
- Drug resistance mutations can fade in the absence of drug pressure
Epidemiology of HIV drug resistance

• Infection with drug resistant HIV occurs by one of three major mechanisms:
  
  – **Acquired resistance** following non-suppressive treatment (secondary resistance)
  
  – **Transmitted resistance** (primary resistance)
  
  – **Pre-treatment resistance** - levels of HIVDR in ARV drug-naive people initiating ART or people with prior ARV drug exposure(s) initiating or reinitiating first-line ART.
Global epidemiology of acquired HIVDR
Patterns of HIVDR at NNRTI regimen failure

M184V → NNRTI → K65R / TAMS

Time on treatment

Pillay, ARHR 2008: n=26 2000-03 GP
Marconi, CID 2008: n=115 2005-06 KZN
Hoffmann, CID 2009: n=68 2002-06 GP
Orrell, AT 2009: n=120 2002-07 WC
Wallis, JAIDS 2010: n=226 2005-09 GP
Murphy, AIDS 2010: n=141 2005-09 KZN
El Khatib, AIDS 2010: n=129 2008 GP
Singh, JAIDS 2011: n=45 <2010 KZN
Sunpath, AIDS 2012: n=33 2010-11 KZN
Sigaloff, ARHR 2012: n=43 2006-09 GP
Manasa, POne 2013: n=242 2010-2012 KZN

Orrell C et al, AVT 2006
Changing patterns within N/NNRTI drug class

Skhosana L et al, PLoS ONE 2015
Increase in resistance with time on failing regimen

<table>
<thead>
<tr>
<th>Time (T)</th>
<th>NRTI</th>
<th>NNRTI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>4</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>T1</td>
<td>5</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>T2</td>
<td>28</td>
<td>18</td>
<td>46</td>
</tr>
<tr>
<td>T3</td>
<td>40</td>
<td>26</td>
<td>62</td>
</tr>
</tbody>
</table>

Mulu et al PLoS ONE 2017
Increasing levels of PI resistance in sub-Saharan Africa

Stockdale A et al CID, 2017
Decreasing levels of Acquired HIVDR in UK
Global epidemiology of transmitted resistance
Relationship between ART coverage and TDR

Figure 3.5 Relationship between antiretroviral therapy coverage and prevalence of transmitted NNRTI drug resistance mutations

WHO HIVDR report 2012
Trends in transmitted resistance in sub-Saharan Africa

Sub-Saharan Africa

Overall

NRTI

NNRTI

PI

% Resistance

Years Since ART Scale-Up

Chi-square test p-value = 0.024

Chi-square test p-value = 0.043

Chi-square test p-value = 0.003

0%

2%

4%

6%

8%

10%

12%

2010

2011

2012

Rhee SY PLoS ONE 2015, Manasa J ARHR 2016
Drug resistance in high-income countries

Data suggest that 10–17% of ARV-naïve individuals treated in Australia, Japan, the United States of America and Europe are infected with virus resistant to at least one antiretroviral drug. These levels of drug resistance occurred early after antiretroviral therapy was introduced in many high-income countries in the late 1990s but have since plateaued. The proportion of people achieving treatment success (viral load suppression) has increased over time, thus reducing the emergence of acquired drug resistance and its subsequent transmission.
Effect of Transmitted Resistance on virologic response

![Graph showing the effect of transmitted resistance on virologic response. The graph compares patients with virological failure over time for different treatment groups: No TDR, TDR and fully-active cART, and TDR and resistant. The log-rank test is significant at p<0.0001.]}
Global epidemiology of pre-treatment resistance
Increasing levels of pre-treatment resistance

Fig. 2: Prevalence of pretreatment NNRTI resistance across studies, by calendar year

1. Component of the WHO-recommended first-line ART regimens

Levels of resistance detected amongst patients enrolled according to prior ART exposure

HIVDR:
- 37% in ART starters with prior exposure to ARVs
- 15% in ARV-naive
Predicted consequences of PDR

- PASER: 2579 participants, 5.5% had pretreatment drug resistance.
- PDR was associated with increased risk of regimen switch (aHR 3.80 p=0.005)
- PDR was not associated with mortality (aHR 0.75 p=0.617) or new AIDS events (aHR 1.06 p=0.807)
- VL monitoring can improve the accuracy of failure detection and efficiency of switching practices
Pre-treatment resistance in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Median year of sampling</th>
<th>PDR Prevalence (95% CI)</th>
<th>Number of children with PDR</th>
<th>Total number of children tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMTCT exposed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zeh2013</td>
<td>Kenya</td>
<td>2003</td>
<td>66.01 (64.70, 68.80)</td>
<td>36</td>
<td>24</td>
</tr>
<tr>
<td>Towre2010</td>
<td>Uganda</td>
<td>2004</td>
<td>6.68 (4.94, 7.22)</td>
<td>2</td>
<td>35</td>
</tr>
<tr>
<td>Hunt2011</td>
<td>South Africa</td>
<td>2005</td>
<td>33.45 (25.91, 40.89)</td>
<td>80</td>
<td>355</td>
</tr>
<tr>
<td>Vos2000</td>
<td>South Africa</td>
<td>2007</td>
<td>9.68 (2.22, 21.30)</td>
<td>3</td>
<td>35</td>
</tr>
<tr>
<td>Fokom2011</td>
<td>Cameroon</td>
<td>2009</td>
<td>85.36 (81.75, 89.21)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Kitya2016</td>
<td>Uganda</td>
<td>2010</td>
<td>36.63 (14.96, 61.66)</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Kebe2014</td>
<td>Senegal</td>
<td>2010</td>
<td>53.58 (28.16, 76.09)</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Shao2014</td>
<td>Tanzania</td>
<td>2011</td>
<td>28.72 (18.62, 42.34)</td>
<td>13</td>
<td>46</td>
</tr>
<tr>
<td>Kuhn2014</td>
<td>South Africa</td>
<td>2011</td>
<td>59.94 (52.16, 67.47)</td>
<td>53</td>
<td>155</td>
</tr>
<tr>
<td>Crowell2015</td>
<td>Mali</td>
<td>2012</td>
<td>75.38 (62.70, 82.32)</td>
<td>99</td>
<td>123</td>
</tr>
<tr>
<td>Souza2016</td>
<td>Togo</td>
<td>2013</td>
<td>42.68 (31.62, 59.12)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
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<td></td>
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<tr>
<td>PMTCT unexposed</td>
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<tr>
<td>Towre2010</td>
<td>Uganda</td>
<td>2004</td>
<td>0.63 (0.57, 1.57)</td>
<td>0</td>
<td>39</td>
</tr>
<tr>
<td>Vos2000</td>
<td>South Africa</td>
<td>2007</td>
<td>2.86 (2.34, 22.70)</td>
<td>0</td>
<td>8</td>
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<tr>
<td>Fokom2011</td>
<td>Cameroon</td>
<td>2007</td>
<td>10.05 (3.27, 21.67)</td>
<td>4</td>
<td>41</td>
</tr>
<tr>
<td>Kitya2016</td>
<td>Uganda</td>
<td>2010</td>
<td>3.56 (1.11, 11.50)</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>Kebe2014</td>
<td>Senegal</td>
<td>2010</td>
<td>7.90 (4.80, 11.70)</td>
<td>18</td>
<td>233</td>
</tr>
<tr>
<td>Kuhn2014</td>
<td>South Africa</td>
<td>2011</td>
<td>11.25 (4.39, 31.18)</td>
<td>1</td>
<td>12</td>
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<tr>
<td>BoermelBoender2016</td>
<td>Nigeria</td>
<td>2012</td>
<td>34.87 (24.62, 57.67)</td>
<td>36</td>
<td>75</td>
</tr>
<tr>
<td>Crowell2015</td>
<td>Mali</td>
<td>2012</td>
<td>16.26 (9.16, 24.92)</td>
<td>13</td>
<td>82</td>
</tr>
<tr>
<td>Souza2016</td>
<td>Togo</td>
<td>2013</td>
<td>19.77 (13.50, 26.92)</td>
<td>26</td>
<td>133</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
<td>37.37 (15.32, 43.68)</td>
<td>11</td>
<td>41</td>
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NOTE: Weight are from random-effects analysis
Modelling the impact of increasing level of HIVDR

Table 1: Projected impact of HIV drug resistance on AIDS deaths, new infections and ART costs in sub-Saharan Africa (pretreatment HIVDR > 10% in Fast-Track countries) during 2016–2020 and 2016–2030, assuming the use of NNRTI-based regimen in first-line ART.

<table>
<thead>
<tr>
<th></th>
<th>AIDS deaths</th>
<th>New HIV infections</th>
<th>ART costs</th>
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<tbody>
<tr>
<td>Amount attributable to HIVDR</td>
<td>135,000</td>
<td>890,000</td>
<td>105,000</td>
</tr>
<tr>
<td>Percentage attributable to HIVDR</td>
<td>5.7%</td>
<td>16%</td>
<td>3.5%</td>
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<tr>
<td></td>
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<tr>
<td></td>
<td>US$ 0.65 billion</td>
<td>US$ 6.5 billion</td>
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<td></td>
<td>2.0%</td>
<td>7.7%</td>
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Global action plan and response
WHO Global Action Plan on HIV Drug Resistance

• Prevention and response
  – Adherence
  – Appropriate prescribing and no stock-out
  – Maximise RIC
• Monitoring and surveillance
  – Expand VL testing
  – Periodic surveys
  – Routine data
• Research and innovation
  – Service delivery interventions
  – Maximum PH benefit
• Laboratory capacity
• Governance and enabling mechanisms
  – Country ownership
  – Sustainable funding
Conclusions

• Rates of pre-treatment resistance are increasing significantly in many LMIC regions
  – Predicted to compromise international efforts to achieve 90% virological suppression targets
• Efforts to improve retention in care and maintain VS are essential
  – VL testing scale up
• New formulations should be considered
• DR can be minimised and prevented
Acknowledgements

• National Institute for Communicable Diseases Centre for HIV and STIs
• NICD Germs staff
• National HIV Drug Resistance Working Group and Steering Group
• National Health Laboratory Service
• WHO ResNet
• Centers for Disease Control