HIV Drug Resistance in KwaZulu-Natal, second line failure and third line ARVs

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Professor: University of KwaZulu-Natal, South Africa
Director: Southern African Treatment Resistance Network (SATuRN)
Question 1: Will drug resistance jeopardize the National HIV treatment?

A) Yes
B) Maybe
C) No
D) No idea
What is the SATuRN?

a network consisting of biomedical scientists, clinicians, epidemiologists and public health experts

SATuRN managed at the UKZN and the SA-MRC

CURRENT PARTNERS includes 24 partners in southern Africa (including CAPRISA ACC)


Collaborators & implementation sites info at www.bioafrica.net/saturn/
SATuRN Vision

Develop advanced yet affordable HIV & TB drug resistance diagnostics, implement it at primary health care clinics in resource limited settings and create a collaborative system for surveillance, research and capacity building.
HIV-1 drug resistance levels in KZN.

As part of CAPRISA ACC we summarize the current levels of HIV-1 drug resistance in KZN.

The data was collated from NHLS, StanfordHIVDB, CAPRISA and from published results from other cohorts in KZN (e.g. Africa Centre, Hlabisa).
Surveillance of Drug Resistance Mutations (SDRM) increasing in treatment naïve patients (i.e. Transmitted) in KZN

Hlabisa sub-district: No TDR was detected in 2010. 2011 and 2012 TDR levels were 4.7% and 7.1% respectively. Chiqs trend test p-value= 0.0024). Majority of the mutations were NNRTI (103, 106), which provide resistance to EFV. Only 0.3% (2/701) had K65R, which is the main mutation to TDF. Manasa ARHR 2016

KZN transmitted resistance: New data confirm an increase trend of transmitted drug resistance. New data include CAPRISA HIPSS (Umgungundlovu) 2014 (n=708) and 2015 (n=470). Unpublished data.
Trend by drug class:

Average percentage mutations by drug class

Year
Percentage
0,0 2,0 3,0 4,0 5,0 6,0 7,0 8,0 9,0 10,0 11,0 12,0 13,0 14,0 15,0 16,0 17,0 18,0 19,0 20,0
Drug class
PI
NRTI
NNRTI

Average percentage mutations by drug class
Question 2: Is transmission of drug resistance increasing?

A) Yes
B) No
• Concerns have been raised about potential transmission of K65R, main mutation affecting tenofovir regimens...

• Can this mutation be transmitted?
No fitness cost for K65R: Results show that K65R individuals have similar viral load as resistance naïve. There is the potential that K65R transmission of K65R can increase. Our recent data show this mutation at low frequency, but important to survey it as TDR levels are already high in KZN. *The TenoRes Study Group*. *Lancet Infectious Diseases*, 2016
Conclusion: Transmitted resistance

- Transmitted drug resistance seems to be increasing over time.
- KZN has the highest level of transmitted resistance in South Africa (> 10%).
- Still low levels of TDF transmitted resistance.
- Need to continue surveillance of transmitted resistance in KZN.
- Need to closely follow viral load monitoring for patients on 1\textsuperscript{st} line therapy as resistance may increase failure rates to first line therapy.
Surveillance of Drug Resistance Mutations (SDRM) in patients failing 1\textsuperscript{st} line ART

<table>
<thead>
<tr>
<th>Results</th>
<th>Adult* 2010-2013 (n=491)</th>
<th>Children* 2011-2012 (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion with any HIVDR mutation</td>
<td>82%</td>
<td>83%</td>
</tr>
<tr>
<td>Proportion with HIVDR to &gt;= 2 drugs</td>
<td>74%</td>
<td>71.8%</td>
</tr>
<tr>
<td>GSS for the standard second-line regimen was &lt;2, suggesting a significantly compromised standard regimen</td>
<td>17%</td>
<td>7%</td>
</tr>
<tr>
<td>Average time on therapy</td>
<td>47 months</td>
<td>39 months</td>
</tr>
<tr>
<td>Average time on failing regimen</td>
<td>27 months</td>
<td>20 months</td>
</tr>
</tbody>
</table>

- Approximately 15\% of Adults and 25\% of children have a viral load > 1,000 on failing regimen.

Question 4: Which of the factors are involved in the development of failure and drug resistance?

A) Adherence
B) Poor absorption
C) Toxicities
D) Social issues
E) All of the above.
Conclusion: 1\textsuperscript{st} line resistance

- The majority (> 80\%) of patients that FAIL first line therapy have drug resistance mutations.

- Drug resistance testing for first line (or more surveys) do not seem necessary as the results are consistent.

- It is important that national guidelines are followed and patients failing 1\textsuperscript{st} line are switch to 2\textsuperscript{nd} line.

- It is worrisome that in many of the publications, patients keep failing 1\textsuperscript{st} line ART for a long time (ranging from 5.7 months to 42 months). This may be one of the reasons why transmitted resistance is on the increase. Furthermore, these patients harbor high level resistance, which may jeopardize 2\textsuperscript{nd} line ART.
Resistance to protease inhibitors

Classically occurs in an ordered stepwise process

High-level resistance requires accumulation of multiple mutations

Similar to thymidine analogue mutations with d4T/AZT
Resistance to lopinavir/ritonavir

- The accumulation of six or more mutations is associated with reduced virological response to LPVr

- Emerging evidence that specific mutations (I47A, V32I) are associated with high-level resistance

Source: IAS-USA mutation list [https://www.iasusa.org/](https://www.iasusa.org/)
## Resistance at second-line ART failure in South Africa

<table>
<thead>
<tr>
<th>Study author</th>
<th>N</th>
<th>Criteria for genotype</th>
<th>Duration on second-line ART (median)</th>
<th>Drug resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wallis</td>
<td>75</td>
<td>2 x VL &gt;5000</td>
<td>16 months</td>
<td>39% no major DRAM 7% major PI mutations</td>
</tr>
<tr>
<td>El-Khatib</td>
<td>35</td>
<td>1 x VL &gt;400</td>
<td>-</td>
<td>6% major PI mutations</td>
</tr>
<tr>
<td>van Zyl</td>
<td>33</td>
<td>1 x VL &gt;5000</td>
<td>-</td>
<td>85% no major DRAM 6% major PI mutations</td>
</tr>
<tr>
<td>Levison</td>
<td>33</td>
<td>2 x VL &gt;1000</td>
<td>10 months</td>
<td>67% no major DRAM No major PI mutations</td>
</tr>
<tr>
<td>Sigaloff</td>
<td>15</td>
<td>1 x VL &gt;1000</td>
<td>&gt;12 months</td>
<td>40% no major DRAM 7% major PI mutations</td>
</tr>
<tr>
<td>Berhanu</td>
<td>65</td>
<td>1 x VL &gt;400 then 1 x VL &gt;1000</td>
<td>-</td>
<td>18% no major DRAM 26% PI mutations</td>
</tr>
</tbody>
</table>

NHLS 2nd line: As part of CAPRISA ACC, we have analyzed the genotypes 195 produced in 2014 and 2015 by the NHLS in KZN. Drug resistance levels were 39% for major protease mutations (which patients need third line). These increase to 46% in minor mutations. Unpublished
Conclusion: 2nd line resistance

- The minority (< 40%) of patients that fail second line therapy have drug resistance mutations. However, preliminary results suggest that KZN has the highest level of second line resistance in South Africa (see dashboard).

- Drug resistance testing for second line necessary to guide management. Second line surveys also necessary given the small number of studies and samples for management.

- It is important that national guidelines are followed and patients 2nd line ART are provided with drug resistance testing and specialized management.
Figure 8: Algorithm for diagnosis of second-line treatment failure

1. **HIV RNA >1000 copies/ml on second-line ART for longer than one year**
   - Check for adherence, compliance, tolerability and drug-drug interaction and assess psychological issues

2. **Repeat VL after 6 months**
   - **VL ≤1000 copies/ml**
     - Continue second-line regimen
   - **VL >1000 copies/ml**
     - Specialist referral as needed

3. **Genotypic resistance testing**
   - Specialist decision regarding further management

Decentralizing
Third-line options

- **Darunavir**
  - Protease inhibitor

- **Etravirine**
  - NNRTI

- **Raltegravir**
  - (Dolutegravir)
  - Integrase inhibitor

- Other existing drugs
Algorithm for choosing 3rd line agents

Eligible for third line ART?
- PI score ≥15

DRV/r
- PLUS
- 3TC/FTC
- PLUS
- AZT/TDF (lowest score)

TDF/AZT (30-59)
- or
- DRV ≥15

TDF/AZT >29
- and
- DRV ≥15
- and
- ETR ≤29

- Potential low level resistance: >10 to <15
- Low level resistance: ≥15 to <30
- Intermediate level resistance: ≥30 to <60
- High level resistance: ≥60

Add RAL/DTG
Add ETR
DRV - Darunavir (Prezista®)

• Highly potent protease inhibitor
• Dose 600mg bd + ritonavir 100mg bd
• Retains activity in the presence of resistance to other protease inhibitors (e.g. LPV/r and ATV/r)
• Drug interaction with rifampicin
• Important adverse effects: diarrhoea, rash, hepatitis
RAL - Raltegravir (Isentress®)

- Integrase inhibitor
- Dose 400mg bd
- Potential drug interaction with rifampicin
- Important adverse effects: rash, hepatitis
- New drug class so should not be any resistance at baseline
Dolutegravir

- Integrase inhibitor
- Dose 50mg daily
- Potential drug interaction with rifampicin (↓DTG levels)
- Needs to be adequately evaluated in patients on treatment for TB (INSPIRING study)
- Important adverse effects: insomnia and headache
- Mean rise in Cr of ~10µmol/L due to inhibition of tubular secretion and does not affect GFR
- New drug class – no resistance at baseline
Etravirine (Intalence®)

- Next-generation NNRTI
- Dose 200mg bd
- Retains activity in the presence of resistance to EFV/NVP
- Potential drug interaction with rifampicin
- Important adverse effects: rash
Source: Department of Health ARV tender 2015-2018
KwaZulu-Natal, preliminary results in comparison with other provinces:

- **KZN has the highest transmitted resistance (> 10%)**
- **KZN has high level 1\textsuperscript{st} line resistance (79%) in patients failing ART. Other provinces have levels > 90%**.
- **KZN has the highest level (>20%) of 2\textsuperscript{nd} line resistance in patients failing ART. Other provinces have lower level.**
Conclusion:

- The preliminary results suggest that KZN has the highest level of transmitted resistance (i.e. 1/10 of patients starting ART are likely to be resistance to first line regimen).

- Individuals on 1st fail for long, which may cause the increase in transmitted resistance.

- Preliminary results suggest that KZN has the highest level of second line resistance in South Africa. It is important to note that new surveys and more data is necessary to confirm these results.

- National drug guidelines are appropriate (genotypes for second line failure and pregnant women). However, there is a need to effectively implement viral load monitoring and appropriate switching patients. Need to increase surveillance.
Next Steps SATuRN and CAPRISA ACC

Training:
- Large SATuRN and CAPRISA workshop (400 clinicians and nurses) as part of AWACC, ICC, 8-9 Oct. 2016.
- Publish HIV & TB Drug Resistance and Clinical Management case book

Operational research:
- Implementation of national guidelines for drug resistance testing system in KZN
- Develop and apply a surveillance protocol for transmitted and second line resistance.
- Keep populating the dashboard with new data
- Publish manuscripts on the results of the analysis
- Provision of quaternary reports to CAPRISA ACC and provincial NDoH
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NHLS Tygerberg/Stellenbosch Univ.

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CAPRISA ACC CDC program
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SATuRN newsletter
www.bioafrica.net/saturn
# Summary of studies on HIV-1 primary resistance in KwaZulu Natal

<table>
<thead>
<tr>
<th>Study year</th>
<th>Province</th>
<th>Study participants</th>
<th>Facility/ Region</th>
<th>N</th>
<th>CD4 cells/mm(^3)</th>
<th>PI resistance (%)</th>
<th>NRTI resistance (%)</th>
<th>NNRTI resistance (%)</th>
<th>Any drug resistance mutation (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>KwaZulu-Natal</td>
<td>Treatment naïve patients</td>
<td>Durban, Ulundi, Hlabisa, Tongaat and Phoenix.</td>
<td>72</td>
<td>N/A</td>
<td>0.0</td>
<td>0.0</td>
<td>2.8</td>
<td>2.8</td>
<td>Gordon et al., (2003)</td>
</tr>
<tr>
<td>2005</td>
<td>KwaZulu-Natal</td>
<td>ANC Survey</td>
<td>ANC clinics in KZN</td>
<td>40</td>
<td>≤200</td>
<td>ND</td>
<td>0.0</td>
<td>2.5</td>
<td>2.5</td>
<td>Hunt et al., (2012)</td>
</tr>
<tr>
<td>2007</td>
<td>KwaZulu-Natal</td>
<td>ANC Survey</td>
<td>ANC clinics in KZN</td>
<td>35</td>
<td>≤200</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>Hunt et al., (2012)</td>
</tr>
<tr>
<td>2008*</td>
<td>KwaZulu-Natal</td>
<td>ANC Survey</td>
<td>ANC clinics in KZN</td>
<td>37</td>
<td>≤200</td>
<td>2.9</td>
<td>5.4</td>
<td>8.1</td>
<td>13.5</td>
<td>Hunt et al., (2012)</td>
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<tr>
<td>2008</td>
<td>KwaZulu-Natal</td>
<td>Treatment naïve patients</td>
<td>Durban</td>
<td>405</td>
<td>≤200</td>
<td>1.5</td>
<td>1.8</td>
<td>1.8</td>
<td>4.4</td>
<td>Matthews et al., (2008)</td>
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<tr>
<td>2009</td>
<td>KwaZulu-Natal</td>
<td>ANC Survey</td>
<td>ANC clinics in KZN</td>
<td>48</td>
<td>≤200</td>
<td>0.0</td>
<td>2.2</td>
<td>6.5</td>
<td>6.2</td>
<td>Hunt et al., (2012)</td>
</tr>
<tr>
<td>2009</td>
<td>KwaZulu-Natal</td>
<td>ANC Survey</td>
<td>Folweni, Hlengi- sizwe, Inanda Community Health Centre, Kwadabeka and Kwamashu clinic</td>
<td>56</td>
<td>≤200</td>
<td>1.8</td>
<td>0.0</td>
<td>1.8</td>
<td>3.6</td>
<td>Parboosing et al., (2011)</td>
</tr>
<tr>
<td>2010</td>
<td>KwaZulu-Natal</td>
<td>HIV surveillance</td>
<td>Hlabisa subdistrict</td>
<td>72</td>
<td>≤350</td>
<td>0.0</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>Manasa et al., (2012)</td>
</tr>
<tr>
<td>2010</td>
<td>KwaZulu-Natal</td>
<td>HIV surveillance</td>
<td>uMkhanyakude</td>
<td>67</td>
<td>≤350</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>Manasa et al., (2016)</td>
</tr>
<tr>
<td>2011</td>
<td>KwaZulu-Natal</td>
<td>HIV surveillance</td>
<td>uMkhanyakude</td>
<td>381</td>
<td>≤350</td>
<td>0.6</td>
<td>1.3</td>
<td>4.5</td>
<td>5.2</td>
<td>Manasa et al., (2016)</td>
</tr>
<tr>
<td>2012</td>
<td>KwaZulu-Natal</td>
<td>HIV surveillance</td>
<td>uMkhanyakude</td>
<td>253</td>
<td>≤350</td>
<td>0.0</td>
<td>2.0</td>
<td>6.0</td>
<td>7.1</td>
<td>Manasa et al., (2016)</td>
</tr>
<tr>
<td>2014</td>
<td>KwaZulu-Natal</td>
<td>HIV surveillance</td>
<td>Umngungundlovu</td>
<td>708</td>
<td>≤500</td>
<td>0.6</td>
<td>4.1</td>
<td>11.9</td>
<td>13.7</td>
<td>N/A</td>
</tr>
<tr>
<td>2015</td>
<td>KwaZulu-Natal</td>
<td>HIV surveillance</td>
<td>Umngungundlovu</td>
<td>470</td>
<td>≤500</td>
<td>1.9</td>
<td>6.4</td>
<td>9.4</td>
<td>14.3</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* conducted as ANC survey, but the number of participants analyzed was insufficient to classify TDR based on the WHO method.
Question 3: Will individuals with resistance to 1/3 drugs on fixed dose combination suppress on ART?

A) Yes
B) No
C) More research need to see the long term effects
D) A & C
Summary of studies on HIV-1 resistance in patients failing 1st line ART KwaZulu Natal

<table>
<thead>
<tr>
<th>Study Period</th>
<th>Site</th>
<th>Criteria for failure</th>
<th>N</th>
<th>Median Duration of ART (months)</th>
<th>ART Regimen (%)</th>
<th>≥1 DRM (%)</th>
<th>NNRTI (%)</th>
<th>M184V (%)</th>
<th>Any TAM (%)</th>
<th>TAM ≥3 (%)</th>
<th>K65R (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dec 2010 – Mar 2012</td>
<td>Hlabisa (17 rural clinics)</td>
<td>1 × VL &gt;1000</td>
<td>222</td>
<td>42</td>
<td>d4T/3TC/EFV (51) d4T/3TC/NVP (24) AZT/3TC/EFV (8) TDF/3TC/EFV (11) Other (6)</td>
<td>88.0</td>
<td>83.0</td>
<td>78.0</td>
<td>40.0</td>
<td>16.0</td>
<td>8.0</td>
<td>Manasa et al. [34]</td>
</tr>
<tr>
<td>Sep 2010 to Mar 2011</td>
<td>Urban clinic</td>
<td>1 × VL &gt;1000</td>
<td>33</td>
<td>5.7</td>
<td>TDF/3TC/EFV (89)</td>
<td>&gt;97.0</td>
<td>97.0</td>
<td>27.3</td>
<td>15.2</td>
<td>NR</td>
<td>70.0</td>
<td>Sunpath et al. [33]</td>
</tr>
<tr>
<td>NR</td>
<td>Durban (urban hospital)</td>
<td>1 × VL &gt;5000</td>
<td>43</td>
<td>28</td>
<td>d4T/3TC/EFV (51) AZT/3TC/EFV (29) AZT/3TC/NVP (9) Other (10)</td>
<td>95.0</td>
<td>95.0</td>
<td>87.0</td>
<td>55.0</td>
<td>NR</td>
<td>NR</td>
<td>Singh et al. [32]</td>
</tr>
<tr>
<td>Aug 2004 to Aug 2008</td>
<td>Urban Clinics</td>
<td>1 × VL &gt;1000</td>
<td>141</td>
<td>NR</td>
<td>D4T/3TC/EFV (43) D4T/3TC/NVP (6) AZT/3TC/EFV (27) AZT/3TC/NVP (12) OTHER (11)</td>
<td>88.5</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>5.0</td>
<td>Murphy et al. [31]</td>
</tr>
<tr>
<td>Jan 2005 – Aug 2008</td>
<td>Durban (two urban hospitals)</td>
<td>1 × VL &gt;1000</td>
<td>115</td>
<td>10.8</td>
<td>d4T/3TC/EFV (49) d4T/3TC/NVP (5) AZT/3TC/EFV (26) AZT/3TC/NVP (11) Other (6)</td>
<td>83.5</td>
<td>78.3</td>
<td>64.3</td>
<td>32.2</td>
<td>13.0</td>
<td>2.6</td>
<td>Marconi et al. [30]</td>
</tr>
</tbody>
</table>
## Summary of studies on HIV-1 resistance in patients failing 2nd line ART in KwaZulu-Natal

<table>
<thead>
<tr>
<th>Study year</th>
<th>Province</th>
<th>Study participants</th>
<th>PI resistance (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>KwaZulu-Natal</td>
<td>Treatment naïve patients</td>
<td>0.0</td>
<td>Gordon et al., (2003)</td>
</tr>
<tr>
<td>2008</td>
<td>KwaZulu-Natal</td>
<td>Treatment naïve patients</td>
<td>2.2</td>
<td>Matthews et al., (2008)</td>
</tr>
<tr>
<td>2009</td>
<td>KwaZulu-Natal</td>
<td>ANC Survey</td>
<td>1.8</td>
<td>Parboosing et al., (2011)</td>
</tr>
<tr>
<td>2011</td>
<td>KwaZulu-Natal</td>
<td>HIV surveillance</td>
<td>0.6</td>
<td>Manasa et al., (2016)</td>
</tr>
<tr>
<td>2014</td>
<td>KwaZulu-Natal</td>
<td>Patients second-line therapy</td>
<td>5.8</td>
<td>Pillay et al., (2014)</td>
</tr>
<tr>
<td>2014</td>
<td>KwaZulu-Natal</td>
<td>HIV surveillance</td>
<td>0.6</td>
<td>N/A</td>
</tr>
<tr>
<td>2015</td>
<td>KwaZulu-Natal</td>
<td>HIV surveillance</td>
<td>2.4</td>
<td>N/A</td>
</tr>
<tr>
<td>2015</td>
<td>KwaZulu-Natal</td>
<td>Patients failing second-line therapy</td>
<td>39.0</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Summary of resistance over time (National, n=13,140 genotypes)

Blue: Majority patients fail first line with resistance

Green: Increasing trends of Transmitted resistance (*2013 no data)

Red: minority of patients On 2nd line with resistance