Overview

- Definition of treatment failure
- Extent of the problem
- Why do patients fail?
- HIV resistance 101
- First line failures
- Second line failures
- Choosing a third line regimen
Treatment failure definitions

• Clinical:

New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition) after 6 months of effective treatment

• Immunological:

CD4 count falls to the baseline (or below) or Persistent CD4 levels below 100 cells/mm3

• Virological:

“Treatment failure in adults and children, including infants, is defined by a persistently detectable viral load exceeding 1000 copies/ml (that is, 2 consecutive viral load measurements within a 2-month interval, with adherence support between measurements) after at least six months of using ARV drugs”

(Who and SA DOH 2015)
1st line regimen VL monitoring:

<table>
<thead>
<tr>
<th>Viral Load (VL)</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOTE: Always check hepatitis B before stopping TDF. If patient has chronic hepatitis B, stopping TDF may lead to a fatal hepatitis flare. If hepatitis B positive, TDF should be continued as a 4th drug in the second-line regimen</td>
<td></td>
</tr>
</tbody>
</table>
| <400 copies/mL        | • VL monitoring according to duration of ART and routine adherence support  
                        | • Continue routine VL monitoring as it may be 12 monthly depending on how long patient is on treatment |
| 400-1000 copies/mL    | • Assess and manage adherence carefully                                   
                        | • Repeat VL in 6 months and manage accordingly                             |
| >1000 copies/mL       | • Adherence assessment and intense adherence support                       
                        | • Repeat VL in 2 months and check HBV status and Hb, if not already done  
                        | • If <1000 copies/mL, repeat in 6 months and then reassess               
                        | • If >1000 copies/mL and adherence issues addressed, switch to second line therapy after checking HBV status and Hb |
## Second-line regimen

<table>
<thead>
<tr>
<th>First-line virological failure</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failing on a TDF-based first-line regimen</td>
<td>AZT + 3TC + LPV/r</td>
</tr>
<tr>
<td></td>
<td>AZT + TDF + 3TC + LPV/r (If HBV co-infected)</td>
</tr>
<tr>
<td>Failing on a d4T or AZT-based first line regimen</td>
<td>TDF + 3TC (or FTC) + LPV/r</td>
</tr>
<tr>
<td>Dyslipidaemia (total cholesterol &gt;6 mmol/L) or diarrhoea associated with LPV/r</td>
<td>Switch LPV/r to ATV/r</td>
</tr>
<tr>
<td>Anaemia and renal failure</td>
<td>Switch to ABC</td>
</tr>
</tbody>
</table>
Impact of Viral load monitoring

- Reduces unnecessary switching on clinical/CD4 criteria
- Reduces delay in switching from a failing regimen, and resistant mutation accumulation

<table>
<thead>
<tr>
<th></th>
<th>AZT resistance</th>
<th>TDF resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No VL</td>
<td>60%</td>
<td>50%</td>
</tr>
<tr>
<td>VL monitoring</td>
<td>10%</td>
<td>30%</td>
</tr>
</tbody>
</table>

(De Luca et al. JID 2013)
Extent of the problem in South Africa

Figure 5: Total patients on antiretroviral therapy by reporting source and calendar period

(Sanac-NSP Report 2014)
Table 8: Viral load testing and suppression in adults and children on ART in South Africa by duration of follow-up and financial year of outcome reporting²

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th></th>
<th>Children</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients remaining on ART</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>42 370</td>
<td>115 839</td>
<td>3 535</td>
<td>5 537</td>
</tr>
<tr>
<td>5 years</td>
<td>3 273</td>
<td>11 622</td>
<td>329</td>
<td>1 469</td>
</tr>
<tr>
<td>Viral load done</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>42.0%</td>
<td>37.6%</td>
<td>40.1%</td>
<td>36.6%</td>
</tr>
<tr>
<td>5 years</td>
<td>56.3%</td>
<td>37.2%</td>
<td>55.6%</td>
<td>35.8%</td>
</tr>
<tr>
<td>Viral load &lt;400 copies/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 years</td>
<td>83.7%</td>
<td>77.4%</td>
<td>77.2%</td>
<td>62.3%</td>
</tr>
<tr>
<td>5 years</td>
<td>87.9%</td>
<td>74.0%</td>
<td>79.4%</td>
<td>69.9%</td>
</tr>
</tbody>
</table>

(Sanac-NSP report 2014)
SA retention in ART care

Figure 18: Adult remaining in care by year started ART (cohort)

Percentage adults remaining on ART by duration

Seven-year experience of a primary care antiretroviral treatment programme in Khayelitsha, South Africa

Andrew Boulle\textsuperscript{a}, Gilles Van Cutsem\textsuperscript{a,b}, Katherine Hilderbrand\textsuperscript{a,b}, Carol Cragg\textsuperscript{c}, Musaed Abrahams\textsuperscript{b}, Shaheed Mathee\textsuperscript{c}, Nathan Ford\textsuperscript{a,b}, Louise Knight\textsuperscript{b}, Meg Osler\textsuperscript{a}, Jonny Myers\textsuperscript{a}, Eric Goemaere\textsuperscript{b}, David Coetzee\textsuperscript{a} and Gary Maartens\textsuperscript{d}
Virological failure and switching to second-line

Cumulative proportion with virological failure or on second-line

Duration on ART in years

- Virological failure
- Starting second-line
Loss to follow-up by year of ART initiation

Cumulative proportion lost to follow-up

Duration on ART in years

logrank p<0.001
And the Eastern Cape?
Inter district comparison for VLD/VLS at 6 months

6 month viral load done and viral suppressed of patients started ART in April - June 2013
(tests done in Oct - Dec 2013)

Eastern Cape 2013 Apr-Jun

<table>
<thead>
<tr>
<th>District</th>
<th>ART at 6 months - Adult VLD rate 6 mm</th>
<th>ART at 6 months - Adult VLS rate 6 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Nzo DM</td>
<td>50.5</td>
<td>85.0</td>
</tr>
<tr>
<td>Amathole DM</td>
<td>44.4</td>
<td>90.6</td>
</tr>
<tr>
<td>C Hani DM</td>
<td>71.8</td>
<td>80.1</td>
</tr>
<tr>
<td>Cacadu DM</td>
<td>87.0</td>
<td>34.4</td>
</tr>
<tr>
<td>Joe Gqabi DM</td>
<td>27.7</td>
<td>78.2</td>
</tr>
<tr>
<td>N Mandela Bay MM</td>
<td>66.7</td>
<td>9.9</td>
</tr>
</tbody>
</table>
Inter-district comparison of Adult LTF, by duration

Adults started ART in 2012, Lost to follow-up by duration
Lost to follow-up at 3, 6, 12 months on treatment, by district

- A Nzo DM
- Amathole DM
- Buffalo City MM
- C Hani DM
- Cacadu DM
- Joe Gqabi DM
- N Mandela Bay MM
- O Tambo DM

Eastern Cape

Analysis done on Phase 6 facilities only
Why do patients fail?

- Primary resistance
- Poor adherence
- Drug interactions
- Malabsorption
- Systems failures (stock outs etc)
Transmitted drug resistance in South Africa: 2000-2010

(Manasa J et al. AIDS Res Hum Retroviruses. 2012)
Adherence check list

- Inadequate treatment literacy
- Side effects
- Depression/ other psych disease
- Poverty & food insecurity
- Substance use
- Social problems
- Work related issues
Drug interactions

Substrates: NNRTI’s, PI’s

Integrase inhibitors

Cytochrome P450

Inducers: Rifampicin, Anti-convulsants
Why do patients fail?

- Primary resistance
- Poor adherence
- Drug interactions
- Malabsorption
- Systems failures (stock outs etc)
HIV resistance 101
Poor adherence → Incomplete viral suppression → Viral Replication → Selection of resistant mutants
Key factors predisposing to resistance developing

- High rate of HIV production and turnover
  - 1 to 10 billion / day
- Reverse Transcriptase is error prone
  - +/- 3 mutations for each viral genome transcribed
- Mutations exist at all alleles in the HIV genome
- Highly heterogenous pool of viruses differing by one or more mutations
- Drug resistant mutants precede the introduction of drugs and are selected out if replication continues in presence of drug
Figure 2: HIV life cycle showing the sites of action of different classes of antiretroviral drugs
Adapted from Walker and colleagues.\textsuperscript{36} by permission of Elsevier.
Reverse transcriptase enzyme inhibition:

**NRTI's:**

- ‘false’ drug nucleosides inserted into DNA, blocking further polymerization

**NNRTI's:**
Mutations:

- **Base substitutions**
  - eg. M184V

- **Insertions**

![Diagram](image)
Susceptible virus (Wild type)

Virus resistant to 3TC (has M184V mutation)

3TC MONOTHERAPY
Susceptible virus (WT)

Resistant to 3TC

Resistant to Efavirenz

Single D4T mutation

HAART with therapeutic levels (>95% adherence)

Viral suppression (VL < 50 copies/ml)
Susceptible virus (WT)

Resistant to 3TC

Resistant to Efavirenz

Single D4T mutation

HAART with subtherapeutic levels (Adherence 60-90%)

Mutations to 3TC and Efavirenz

Partial suppression and selects out virus with resistance mutation(s)
Genotyping

- Sequence RT and protease (and integrase) genes to detect resistance mutations

- Mutation detected if
  - VL > 1000 copies/ml (failing ART)
  - >20% of virus population carries mutation
NRTI resistance

2 main pathways

- Thymidine analogue mutations (TAMS)
  - Selected by: d4T, AZT
  - Resistance to: d4T, AZT, ABC, TDF
  - Sensitizes to: TDF, ABC, ddI, AZT

- K65R
  - TDF, ABC, d4T
  - TDF, ABC, ddI, AZT
• At first genotype (1 year after VF): median 3 TAMs

• Thereafter TAMs accumulated at a rate of 1/4.3 years

(JID, 2009)
M184V/I

• Single mutation high level resistance to 3TC and FTC

• Reduces viral fitness by 1/3

• Slows selection of TAMs

• When it occurs with TAMs:
  • Increases susceptibility to AZT, d4T and TDF
  • Increased resistance to ddl and ABC

• Also resensitizes to TDF in presence of K65R
Abacavir

- Selects for:
  - L74V: compromises ABC & ddl
  - Y115F: compromises ABC
  - K65R: compromises TDF, ABC, ddl