INTERESTING CLINICAL CASES: HIV diagnostic and treatment dilemmas

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Goals of the programme
(2013 SA ARV guidelines – public sector)

- Save lives and improve the quality of life of people living with HIV
- Achieve best health outcomes in the most cost-efficient manner
- Implement nurse-initiated treatment
- Decentralise service delivery to PHC facilities
- Integrate services for HIV, TB, MCH, SRH and wellness
- Diagnose HIV earlier
- Prevent HIV disease progression
- Avert AIDS-related deaths
- Retain patients on lifelong therapy
- Prevent new infections among children, adolescents, and adults
- Mitigate the impact of HIV and AIDS
<table>
<thead>
<tr>
<th>Year</th>
<th>Regimen 1</th>
<th>Regimen 2</th>
<th>Regimen 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>D4T/3TC/EFV or NVP</td>
<td>TDF/3TC/EFV or NVP</td>
<td>TDF/FTC/EFV (FDC)</td>
</tr>
<tr>
<td>2010</td>
<td>TDF/3TC/EFV or NVP</td>
<td>TDF/FTC/EFV (FDC)</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>TDF/FTC/EFV (FDC)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Contra-indication to TDF and AZT:
- use d4T or ABC

Baseline HIV VL
- No baseline HIV VL
### SA – first line ARV regimens (children)

<table>
<thead>
<tr>
<th>Year</th>
<th>&lt;3 years (or &gt;10 kg)</th>
<th>&gt;3 years (and &gt;10kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>D4T/3TC/LPV-r</td>
<td>D4T/3TC/EFV</td>
</tr>
<tr>
<td>2010</td>
<td>ABC/3TC/LPV-r</td>
<td>ABC/3TC/EFV</td>
</tr>
<tr>
<td>2013</td>
<td>ABC/3TC/LPV-r</td>
<td>ABC/3TC/EFV</td>
</tr>
</tbody>
</table>

NVP prophylaxis - for 6 weeks for children born to HIV infected mothers

Baseline HIV VL *** Baseline HIV VL *** Baseline HIV VL
### VL & CD4 Monitoring in Public Sector

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6mo</th>
<th>12mo</th>
<th>18mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>----</td>
<td>VL</td>
<td>VL</td>
<td>annually</td>
</tr>
<tr>
<td>CD4 count</td>
<td>----</td>
<td>CD4 count</td>
<td>----</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Children 5 – 15 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>VL</td>
<td>VL</td>
<td>VL</td>
<td>annually</td>
</tr>
<tr>
<td>CD4 count</td>
<td>----</td>
<td>CD4 count</td>
<td>----</td>
<td>annually</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Children &lt;5 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>VL</td>
<td>VL</td>
<td>VL</td>
<td>every 6 months</td>
</tr>
<tr>
<td>CD4 count</td>
<td>----</td>
<td>CD4 count</td>
<td>----</td>
<td>annually</td>
</tr>
</tbody>
</table>

2013 South African Antiretroviral Treatment Guidelines.
Ms HM – 20 month old child

- HAART since 7 weeks of age – ABC/3TC/LPVr

- HIV ELISA @ 18 months = NEGATIVE

- HIV PCR @ 19 months = NEGATIVE

- HIV VL @ 20 months = LDL (lower than detectable limit)

- Baseline test results @ 6 weeks
  - HIV ELISA - POSITIVE
  - PCR = POSITIVE
  - HIV VL = 311 705 copies/ml

**ISSUES**

- Significance of baseline tests
- Negative HIV ELISA ≥18 months
- Negative PCR
- ? Functional cure
NEGATIVE HIV ELISA IN CHILDREN 18 MONTHS OR OLDER

- Seroreversion in children infected with HIV-1 who are treated in the first months (esp. in ≤3 months) of life is not a rare event


## SEROREVERSION IN A CORHOT OF 12 CHILDREN

### NEGATIVE HIV ELISA >18 MONTHS

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age at start of HAART (months)</th>
<th>Baseline HIV VL ($\log_{10}$ c/ml)</th>
<th>Time to LDL VL (months)</th>
<th>Duration of suppression (years)</th>
<th>Age tested for HIV ELISA in study (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C102</td>
<td>1.6</td>
<td>&gt;5.8</td>
<td>3</td>
<td>3.4</td>
<td>2.8</td>
</tr>
<tr>
<td>C103</td>
<td>1.8</td>
<td>5.7</td>
<td>2.9</td>
<td>5.6</td>
<td>5.1</td>
</tr>
<tr>
<td>C104</td>
<td>2.4</td>
<td>&gt;5.8</td>
<td>2.5</td>
<td>4.5</td>
<td>4.3</td>
</tr>
<tr>
<td>C107</td>
<td>3.8</td>
<td>&gt;5.8</td>
<td>2.3</td>
<td>0.7</td>
<td>0.71</td>
</tr>
<tr>
<td>C108</td>
<td>2.5</td>
<td>5.5</td>
<td>5.8</td>
<td>2.2</td>
<td>2</td>
</tr>
<tr>
<td>C109</td>
<td>1.4</td>
<td>5.6</td>
<td>1.9</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td>C110</td>
<td>1.7</td>
<td>&gt;5.8</td>
<td>1.9</td>
<td>5.1</td>
<td>4.8</td>
</tr>
<tr>
<td>C112</td>
<td>2</td>
<td>4.8</td>
<td>2.1</td>
<td>2.2</td>
<td>2.5</td>
</tr>
</tbody>
</table>

### POSITIVE HIV ELISA >18 MONTHS

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age at start of HAART (months)</th>
<th>Baseline HIV VL ($\log_{10}$ c/ml)</th>
<th>Time to LDL VL (months)</th>
<th>Duration of suppression (years)</th>
<th>Age tested for HIV ELISA in study (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C101</td>
<td>1.8</td>
<td>&gt;5.8</td>
<td>5.4</td>
<td>4.9</td>
<td>4.5</td>
</tr>
<tr>
<td>C105</td>
<td>3.4</td>
<td>&gt;5.8</td>
<td>3.2</td>
<td>2.4</td>
<td>2.6</td>
</tr>
<tr>
<td>C106</td>
<td>4.8</td>
<td>4.2</td>
<td>1.2</td>
<td>4.6</td>
<td>5</td>
</tr>
<tr>
<td>C111</td>
<td>0.6</td>
<td>4.9</td>
<td>3.3</td>
<td>1.4</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Ms HM – 20 month old baby

- HAART since 7 weeks of age
- HIV ELISA @ 18 months = NEGATIVE
- HIV PCR @ 19 months = NEGATIVE
- HIV VL @ 20 months = LDL (lower than detectable limit)
- Baseline test results @ 6 weeks
  - PCR = POSITIVE
  - HIV VL = 311 705 copies/ml

**ISSUES**
- Significance of baseline tests
- Negative ELISA at or after 18 months
- Negative PCR
- ? Functional cure
DETECTION LIMITS OF HIV MOLECULAR ASSAYS USED IN NHLS LABORATORIES

- Qualitative HIV PCR on DBS card (Roche CAP/CTM v2): 300 copies/mL
- Qualitative HIV PCR on whole blood (Roche CAP/CTM v2): 20 copies/mL
- Abbott HIV viral load assay (m2000): 40 copies/mL
- Roche HIV viral load assay (CAP/CTM v2): 20 copies/mL

Roche and Abbot HIV PCR & viral loads packages inserts.
Performance of HIV-1 DNA or HIV-1 RNA Tests for Early Diagnosis of Perinatal HIV-1 Infection during Anti-Retroviral Prophylaxis

- Screening for HIV by PCR was done at:
  - **birth** and at ages **1 month, 3 months, and 6 months**
  - Prophylaxis for 4 – 6 weeks: AZT or AZT + 3TC or 2 NRTIs + PI

**At 1 month**

- 30 infected infants with at least one positive PCR test at birth
  - 90% had a positive PCR result in both PCR tests at 1 month

- 17 infected infants with negative PCR results at birth
  - 76% had positive results in both PCR tests at 1 month

**At 3 Months** (prophylaxis had been stopped and HAART not initiated)
- the sensitivity of both assays was 100%.
MISSISSIPI BABY
Ms HM – 20 month old baby

- HAART since 7 weeks of age
- HIV ELISA @ 18 months = NEGATIVE
- HIV PCR @ 19 months = NEGATIVE
- HIV VL @ 20 months = LDL (lower than detectable limit)
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**ISSUES**
- Significance of baseline tests
- Negative ELISA at or after 18 months
- Negative PCR
- ? Functional cure
Born to an HIV infected mother who had no prenatal care, and not on ARVs

- HIV diagnosis established @ delivery (ELISA & WB)
- 24 hrs after delivery: HIV VL = 2423 copies/ml,
- 14 days later: CD4+ count = 644 cells/mm³

## FUNCTIONAL CURE IN A 30 MONTH OLD CHILD

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 DNA, at 30 hr</td>
<td>Positive</td>
<td>AZT</td>
</tr>
<tr>
<td>HIV-1 RNA, at 31 hr</td>
<td>19,812 copies/ml</td>
<td>AZT/3TC/NVP</td>
</tr>
<tr>
<td>HIV-1 RNA, at 6 days</td>
<td>2617 copies/ml</td>
<td>AZT/3TC/NVP</td>
</tr>
<tr>
<td>HIV-1 RNA, at 11 days</td>
<td>516 copies/ml</td>
<td>AZT/3TC/LPVr</td>
</tr>
<tr>
<td>HIV-1 RNA, at 19 days</td>
<td>265 copies/ml</td>
<td>AZT/3TC/LPVr</td>
</tr>
<tr>
<td>HIV-1 RNA, at 29 days</td>
<td>&lt;48 copies/ml</td>
<td>AZT/3TC/LPVr</td>
</tr>
<tr>
<td>CD4+ T-cell percentage, at 8 days</td>
<td>69%</td>
<td>AZT/3TC/LPVr</td>
</tr>
<tr>
<td>HIV-1 DNA, at 24 mo</td>
<td>Negative</td>
<td>None</td>
</tr>
<tr>
<td>HLA typing, at 26 mo</td>
<td>A3, A68, B7, B39, and Cw7</td>
<td>None</td>
</tr>
<tr>
<td>Mutation status in CCR5 delta32, at 26 mo</td>
<td>Nonmutated</td>
<td>None</td>
</tr>
</tbody>
</table>

FUNCTIONAL CURE IN A 30 MONTH OLD CHILD

- Proviral DNA detected on PBMCs resting CD4+ cells & monocyte-derived adherent cells from samples taken at 24 and 26 months (@ very low levels)

- Residual viremia in plasma = 1 copy/ml @ 24 months, and <2 copies/ml @ 26 months

- No recovery of infectious virus

FUNCTIONAL CURE IN A 30 MONTH OLD CHILD

- Controlled HIV-1 viremia for 12 months while not receiving ART
  - absence of rebound viremia,
  - undetectable replication-competent virus,
  - almost-complete disappearance of cell associated HIV-1 DNA, &
  - absence of HIV-1–specific immune responses while the child was not receiving ART

- Suggest that replication-competent HIV-1 reservoirs may not have been established or were markedly abated, if not extinguished

ONLY ONE MISSISSIPPI BABY SO FAR!
MECHANISMS OF NRTI RESISTANCE

- Impaired nucleotide analogue incorporation - e.g. M184V
- Excision of nucleoside analogue RT inhibitors
  - e.g. thymidine analogue mutations (TAMs)

## Mutations associated with impaired nucleotide analogue incorporation

<table>
<thead>
<tr>
<th>Mutations</th>
<th>Nucleoside analogue</th>
</tr>
</thead>
<tbody>
<tr>
<td>K65R</td>
<td>Tenofovir</td>
</tr>
<tr>
<td></td>
<td>Didanosine</td>
</tr>
<tr>
<td></td>
<td>Abacavir</td>
</tr>
<tr>
<td></td>
<td>Lamivudine</td>
</tr>
<tr>
<td></td>
<td>Emtricitabine</td>
</tr>
<tr>
<td></td>
<td>Zalcitabine</td>
</tr>
<tr>
<td>K70E</td>
<td>Tenofovir</td>
</tr>
<tr>
<td>L74V</td>
<td>Abacavir</td>
</tr>
<tr>
<td></td>
<td>Didanosine</td>
</tr>
<tr>
<td>V75I</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>V75T</td>
<td>Stavudine</td>
</tr>
<tr>
<td>Q151M</td>
<td>Zidovudine</td>
</tr>
<tr>
<td></td>
<td>Stavudine</td>
</tr>
<tr>
<td></td>
<td>Didanosine</td>
</tr>
<tr>
<td></td>
<td>Zalcitabine</td>
</tr>
<tr>
<td></td>
<td>Abacavir</td>
</tr>
<tr>
<td>M184V</td>
<td>Lamivudine</td>
</tr>
<tr>
<td></td>
<td>Emtricitabine</td>
</tr>
<tr>
<td></td>
<td>Abacavir</td>
</tr>
</tbody>
</table>

THYMIDINE ANALOGUE MUTATION (TAM) PATHWAYS

- TAM-1 pathway - M41L, L210W and T215Y
  - confer higher levels of AZT resistance and are responsible for more extensive cross-resistance to other NRTIs

- TAM-2 pathway - D67N, K70R and K219E/Q, and sometimes T215F
  - resistance is usually limited to zidovudine and stavudine

Patterns of HIV-1 Drug Resistance on Failing First-Line ART in South Africa

226 patients virologically failing first-line regimens – included in this study.

Patterns of HIV-1 Drug Resistance on Failing First-Line ART in South Africa

226 patients virologically failing first-line regimens – included in this study.

Ms LC - 52 year old lady

- HIV infected, completed TB Rx in Dec 2010
- Diabetes and hypertension on treatment
  - Metformin, then later changed to insulin injection
  - Hydrochlorothiazide / adalat / atenolol / perindopril

- Nov 2010
  - Hb = 9.0 g/dl (12.1 – 16.3), ALT = 21 U/l (10 - 40), Cr = 93 µmol/l (49 – 90), eGFR >60; CD4 = 337 cells/mm³

- Jan 2011
  - HAART initiation at Tshwane ARV clinic = D4T/3TC/EFV
  - BP – 133/78
Ms LC - 52 year old lady

Lactate - Venous plasma: 0.5 – 2.2 mmol/l

ISSUES
- Side effect
- Poor follow up
- NNRTI half life
- DM & HPT
- Weak health care system

Cr = 64 µmol/l (49 – 90), eGFR >60
HIV VL = LDL, CD4 = 247
Ms LC - 52 year old lady

- **July 2012**
  - HIV VL = 9416, CD4 count = 222 cells/mm³
  - Glucose =15.2 (post-prandial), Triglycerides = 2.3, Cholesterol – 3.6
  - Hb = ↓ 10.3 g/dl, ALT = 18 U/l, Cr = 67 µmol/l (eGFR >60)

  **TDF/3TC/EFV**

- **Dec 2012**
  - HIV VL = LDL
  - Hb = ↓ 10.7 g/dl, Cr = 76 µmol/l (eGFR >60)

- **Oct 2013**
  - HIV VL = LDL, CD4 count = 519 cells/mm³
  - Hb = 11.3 g/dl, Cr = 87 µmol/l (eGFR = 59), ALT =17, Lactate =1.7
ISSUES

- Side effect
- Poor follow up
- NNRTI half life
- DM & HPT
- Weak health care system
Hyperlactataemia / lactic acidosis during ART

- Hyperlactataemia is defined as a mild-to-moderate increase in serum lactate concentration (2 – 5mmol/l), with normal pH value and bicarbonate level (pH≥7.35 and bicarbonate concentration ≥20mmol/l).

- Lactic acidosis is defined as persistently and remarkably elevated serum lactate level (generally >5 mmol/l), associated with metabolic acidosis (pH <7.35 and bicarbonate concentration <20 mmol/l).

Hyperlactataemia / lactic acidosis during ART

Hyperlactataemia / lactic acidosis during ART

Hyperlactataemia / lactic acidosis during ART

- The mean time to developing lactic acidosis is 10–12 weeks after initiation of combination ART

- $d_4T > ddI = ZDV > TDF=ABC=3TC=FTC$


DHHS guidelines 2009.
ISSUES

- Side effects
- Poor follow up
- NNRTI half life - prolonged
- DM & HPT
- Weak health care system
Stopping rules for ARV therapy

- **Simultaneous stop**
  - for *half-life balanced regimens*: i.e. three short or long half-life drugs can be stopped simultaneously

- **Staggered stop**
  - for *unbalanced regimens*: i.e. the long half-life drug or drugs are discontinued before the short half-life drugs of the regimen

- **Replacement stop**
  - where the *drug with the long half-life* is replaced by a *drug with a short half-life and a high genetic barrier* for a short period of time; for example replacement of EFV with LPV/r; the correct length of LPV/r intake is unknown, but 4 weeks is probably advisable with this strategy

- **Protected stop**
  - when the *drugs are stopped simultaneously despite their different half-lives* and LPV/r is administered for 4 weeks; clinical data are being collected to investigate whether this strategy could be recommended

*British HIV Association guidelines 2008.*
### Risk of Resistance After Stopping NVP

<table>
<thead>
<tr>
<th>Country</th>
<th>Study</th>
<th>HIV Subtype</th>
<th>Time of Testing</th>
<th>Proportion with Resistant Virus (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zimbabwe</td>
<td>HPTN023</td>
<td>C</td>
<td>2</td>
<td>75%</td>
</tr>
<tr>
<td>Malawi</td>
<td>NVAZ</td>
<td>C</td>
<td>8</td>
<td>69%</td>
</tr>
<tr>
<td>South Africa</td>
<td>SAINT</td>
<td>C</td>
<td>2</td>
<td>67%</td>
</tr>
<tr>
<td>South Africa</td>
<td>TOPS</td>
<td>C</td>
<td>2-6</td>
<td>57%</td>
</tr>
<tr>
<td>Botswana</td>
<td>MASHI</td>
<td>C</td>
<td>4</td>
<td>45%</td>
</tr>
<tr>
<td>South Africa</td>
<td>NVP-R</td>
<td>C</td>
<td>7</td>
<td>39%</td>
</tr>
<tr>
<td>Ivory Coast</td>
<td>Ditrame</td>
<td>CRF, A</td>
<td>4</td>
<td>33%</td>
</tr>
<tr>
<td>Zambia</td>
<td>NCT00204308</td>
<td>C</td>
<td>6</td>
<td>30%</td>
</tr>
<tr>
<td>Uganda</td>
<td>HIVNET 012</td>
<td>A, D</td>
<td>6</td>
<td>25%</td>
</tr>
<tr>
<td>Thailand</td>
<td>PHPT2</td>
<td>E, B</td>
<td>2</td>
<td>18%</td>
</tr>
<tr>
<td>USA/France</td>
<td>PACTG316</td>
<td>B</td>
<td>6</td>
<td>15%</td>
</tr>
<tr>
<td>Zambia</td>
<td>NCT00204308</td>
<td>C</td>
<td>6</td>
<td>14%</td>
</tr>
<tr>
<td>South Africa</td>
<td>TOPS</td>
<td>C</td>
<td>2-6</td>
<td>9%</td>
</tr>
</tbody>
</table>

Graph showing the proportion of resistant virus for each study with different treatments.

Response to Antiretroviral Therapy after a Single, Peripartum Dose of Nevirapine

- Women who received a single dose of nevirapine to prevent perinatal transmission of HIV-1 had higher rates of virologic failure with subsequent nevirapine-based antiretroviral therapy than did women without previous exposure to nevirapine.

- However, this applied only when nevirapine-based antiretroviral therapy was initiated within 6 months after receipt of a single, peripartum dose of nevirapine.

Viral kinetics after HAART interruption

HIV VL was detectable (>50 copies/ml) on:

- day 7 - in 5 patients
- day 14 – in 8 patients, &
- day 28 - in 18 patients (90%)

- In 2 patients HIV VL remained undetectable for 4 weeks

Ms PP – 35 year old

HIV VL (copies/ml)

CD4 count (cells/mm³)

Rx initiation
D4T/3TC/NVP

TDF/3TC/NVP

VL = LDL

1957

443

249

398

109

Ms PP – 35 year old

ISSUES

- Low level viraemia
- Poor follow up
- Single drug substitution
- ?Partner status
Ms PP – 35 year old

- Good adherence
- No clinical problems
- Partner - HIV positive on HAART (Mamelodi day hospital)
- ARV drug resistance testing – (VL was 1200 during resistance testing – April 2014)
Ms PP’s ARV RESISTANCE RESULTS

- Sequence includes PR: codons: 16 - 99
- Sequence includes RT: codons: 1 - 445
  - There are no insertions or deletions

- Subtype and % similarity to closest reference isolate:
  - 1. PR: C (94.0%)
  - 2. RT: C (94.1%)
Mr PP’s ARV RESISTANCE RESULTS

- **NRTI Resistance Mutations:**
  - M184V

- **NNRTI Resistance Mutations:**
  - A98G, K103N, V108I

- **Other Mutations:**
### Mr PP’s ARV RESISTANCE RESULTS

<table>
<thead>
<tr>
<th>Nucleoside RTI</th>
<th>Non-Nucleoside RTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3TC</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>ABC</td>
<td>Low-level resistance</td>
</tr>
<tr>
<td>AZT</td>
<td>Susceptible</td>
</tr>
<tr>
<td>D4T</td>
<td>Susceptible</td>
</tr>
<tr>
<td>DDI</td>
<td>Potential low level resistance</td>
</tr>
<tr>
<td>FTC</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>TDF</td>
<td>Susceptible</td>
</tr>
</tbody>
</table>
Mr PP’s ARV RESISTANCE RESULTS

- **PI Major Resistance Mutations**: None
- **PI Minor Resistance Mutations**: T74S
- **Other Mutations**: L19T, E35D, M36I, R41K, K45R, H69K, L89M, I93LV

**Protease Inhibitors**
- atazanavir/r (ATV/r) Susceptible
- darunavir/r (DRV/r) Susceptible
- fosamprenavir/r (FPV/r) Susceptible
- indinavir/r (IDV/r) Susceptible
- lopinavir/r (LPV/r) Susceptible
- nelfinavir (NFV) low-level resistance
- saquinavir/r (SQV/r) Susceptible
- tipranavir/r (TPV/r) Susceptible
Ms PP – 35 year old

HIV VL (copies/ml)

CD4 count (cells/mm$^3$)

Rx initiation
D4T/3TC/NVP
TDF/3TC/NVP

VL = LDL

TDF/3TC/LPVr – April 2014
ASSESSMENT OF TREATMENT FAILURE

- Clinical assessment
- Immunological assessment, e.g. CD4 count
- Virological assessment, e.g. HIV VL
The value of clinical and immunological monitoring of ARVs

- Consequent immunologic failure and clinical events after initiation of HAART generally occur 6 months to 2 years after virologic failure.

The value of clinical and immunological monitoring of ARVs

<table>
<thead>
<tr>
<th>Reasons for treatment failure</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical failure</td>
<td>46</td>
</tr>
<tr>
<td>Decrease in CD4 cell count to less than or equal to baseline value</td>
<td>2</td>
</tr>
<tr>
<td>50% Decrease in CD4 cell count from peak value</td>
<td>37</td>
</tr>
<tr>
<td>Persistent CD4 cell count &lt;100 cells/μL</td>
<td>15</td>
</tr>
<tr>
<td>&gt;1 Major mutation with drug resistance to NRTIs</td>
<td>90</td>
</tr>
<tr>
<td>&gt;1 Major mutation with drug resistance to NNRTIs</td>
<td>65</td>
</tr>
<tr>
<td>≥2 major NNRTI and/or NRTI mutations</td>
<td>88</td>
</tr>
<tr>
<td>No NRTI or NNRTI mutations</td>
<td>5</td>
</tr>
</tbody>
</table>

MANAGEMENT OF VIROLOGICAL FAILURE
(2013 SA ARV guidelines – public sector)

- If plasma HIV RNA >1000 copies/ml
  - check for adherence, compliance, tolerability and drug-drug interaction and assess psychological issues

- Repeat VL test 2 months later

- If plasma VL confirmed >1000 copies
  - change regime to second line therapy

The South African Antiretroviral Treatment Guidelines 2013
Detection Virologic Failure (other guidelines)

- **SA HIV Clinicians Society guidelines (private sector)**
  - HIV viral load of >1000 copies/ml in 2 measurements taken 1 - 3 months apart

- **2013 WHO guidelines**
  - HIV viral load of >1000 copies/ml based on two consecutive viral load measurements after 3 months

- **2014 DHHS guidelines (USA)**
  - the inability to achieve or maintain suppression of viral replication to an HIV RNA level <200 copies/ml

- **2013 British HIV Association guidelines**
  - a single VL >400 copies/ml should be investigated further, as it is indicative of virological failure
Drug resistance at low viraemia in HIV-1-infected patients with antiretroviral combination therapy

Soo Aleman\textsuperscript{a}, Karin Söderbärg\textsuperscript{b}, Ubaldo Visco-Comandini\textsuperscript{c}, Gisela Sitbon\textsuperscript{b} and Anders Sönnerborg\textsuperscript{a,d}

- **Conclusion**: Low viraemia after virological treatment failure can select for virus with several new drug resistance mutations, despite a concomitant increase in CD4 T cell counts.

- This serial accumulation of mutations is likely to exhaust future drug options.

ISSUES

- Low level viraemia
- Poor follow up
- Single drug substitution
- ?Partner status
Mr PS – husband to Ms PP

- Baseline CD4 count = 11 cells/mm³

- June 2013 - HAART initiation (TDF/3TC/EFV)

- March 2014 – HIV VL = 9387
  - CD4 count = 8 cells/mm³

- 27 May 2014 😊
  - diarrhoea since he started ARVs – wakes him up at 3 – 4 a.m. daily
  - only loose stools in the morning, but fine later in the day
  - adherence assessment – good
  - ARV resistance testing - pending
Mr PS – husband to Ms PP

**ISSUES**
- Side effect
- Poor follow up
- Weak health care system
- Partners treated at different sites
# Tenofovir Adverse Effects

<table>
<thead>
<tr>
<th>Category</th>
<th>FTC + TDF + EFV&lt;sup&gt;b&lt;/sup&gt;</th>
<th>AZT/3TC + EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N = 257</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>General Disorders and Administration Site Condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinusitis</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Upper respiratory tract infections</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Truvada package insert. Revised December 2013
Pharmacokinetics and Tolerability of Tenofovir

- The most frequently reported AE was diarrhea, which occurred in 3 subjects (21%), 2 cases of which were considered by the investigator as possibly related to the study medication.

Ms PW

HIV VL (copies/ml)

CD4 count (cells/mm$^3$)

- Rx initiation D4T/3TC/NVP
- Pap smear - Keratinising HSIL – LLETZ done the same year

- TDF/3TC/NVP
HUMAN PAPILLOMA VIRUS (HPV) = causes CERVICAL CANCER

• ~510,000 new cases of invasive cervical cancer / year
  ~80% occurs in the developing world

Per 100,000 population

- <9.4
- <16.8
- <25.8
- <33.4
- <87.3
2013 SA HIV MANAGEMENT GUIDELINES

Patients with CD4 above 350, Not yet eligible for ART

- CD4 testing 6-monthly, HIV reduction counselling, INH prophylaxis for TB
- Provide counselling on nutrition and contraceptive & do annual pap smear

2013 WHO HIV MANAGEMENT GUIDELINES

- Cervical cancer screening leads to early detection of precancerous and cancerous cervical lesions that will prevent serious morbidity and mortality.
- Thus, all women with HIV should be screened for cervical cancer regardless of age

2010 SA guidelines for cervical cancer screening

- The national policy on cervical screening allows for 3 smears in a woman’s lifetime taken at 10 year intervals from 30 years of age.

CLINICAL ARTICLE

Outcome of loop electrosurgical excision for HIV-positive women in a low-resource outpatient setting

Chumnan Kietpeerakool *, Prapaporn Suprasert, Jatupol Srisomboon

Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand
## Abnormal cervical cytology following LEEP/LLETZ in 6 HIV-infected women

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>25</td>
<td>35</td>
<td>40</td>
<td>35</td>
<td>41</td>
<td>30</td>
</tr>
<tr>
<td><strong>Time interval, mo</strong></td>
<td>8</td>
<td>8</td>
<td>9</td>
<td>4</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td><strong>Integrated HAART</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>CD4 count at 1st LEEP</strong></td>
<td>53</td>
<td>450</td>
<td>370</td>
<td>323</td>
<td>449</td>
<td>201</td>
</tr>
<tr>
<td><strong>First histologic result</strong></td>
<td>CIN 2,3</td>
<td>CIN 2,3</td>
<td>CIN 1</td>
<td>CIN 2,3</td>
<td>CIN 1,2,3</td>
<td>CIN 2,3</td>
</tr>
<tr>
<td><strong>Margin involvement</strong></td>
<td>Endo</td>
<td>Ecto</td>
<td>Ecto/endo</td>
<td>Ecto</td>
<td>Ecto</td>
<td>Endo</td>
</tr>
<tr>
<td><strong>Lesion grades at involved margins</strong></td>
<td>CIN 2,3</td>
<td>CIN 2,3</td>
<td>Negative</td>
<td>CIN 2,3</td>
<td>CIN 1</td>
<td>CIN 1</td>
</tr>
<tr>
<td><strong>Cytologic type</strong></td>
<td>ASC-H</td>
<td>LSIL</td>
<td>ASC-US</td>
<td>ASC-H</td>
<td>ASC-US</td>
<td>LSIL</td>
</tr>
<tr>
<td><strong>Second histologic result</strong></td>
<td>Chronic cervicitis</td>
<td>not done</td>
<td>CIN 1</td>
<td>Chronic cervicitis</td>
<td>not done</td>
<td>CIN 1</td>
</tr>
</tbody>
</table>

OUTCOMES OF LLETZ OR LEEP IN HIV-INFECTED WOMEN

- HIV-infected women have a higher risk of resection margin involvement after cervical conization, which may reflect a more extensive lesion.

- Margin involvement after conization has been found to be an independent predictor for persistent or recurrent disease.

- Severe immunosuppression (CD4 cell count <200 cells/μL) may be a predictor of margin involvement.

The median time between LLETZ and first follow-up Pap smear was short - at 122 days.

Persistent cytological abnormalities occurred in 49% of our patients after LLETZ.
2013 WHO guidelines for screening and treatment of precancerous cervical lesions in HIV+ women

If screening with cytology & followed by colposcopy (with or without biopsy)

- Normal cytology – rescreen within 3 years

- ASCUS or greater & colposcopy negative - rescreen within 3 years

- ASCUS or greater & colposcopy positive (no biopsy) – cryotherapy or LLETZ
  - post-treatment follow up at 1 year

- ASCUS or greater & colposcopy positive (biopsy)
  - CIN 2+ - cryotherapy or LLETZ – post-treatment follow up @1 year
  - CIN 1 or less – rescreen within 3 years
SUMMARY

- Infant diagnosis in the era of PMTCT and early HAART
- LDL – main goal of HAART
- ARV resistance testing – not part of SA guidelines yet (limited access through research labs)
- Side effects of ARVs
- Think beyond guidelines sometimes