Clinical guidelines for the management of HIV/AIDS in adults and adolescents ≥15 years

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CAPRISA ACC – DOH ETHEKWINI PROJECT
HIV DR RESEARCH PROJECTS
Overview

• HIV continuum of care
• ICDM
• What is NEW
• Co Infections
• ART adverse events
• Monitoring VL and DR
## Antiretroviral Agents Approved

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>NNRTIs</th>
<th>PIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>zidovudine (AZT)</td>
<td>nevirapine (NVP), efavirenz (EFV)</td>
<td>saquinavir (SQV)</td>
</tr>
<tr>
<td>didanosine (ddl)</td>
<td><em>Rilvipsirine</em> (RLP)</td>
<td>indinavir (IDV)</td>
</tr>
<tr>
<td>zalcitabine (ddC)</td>
<td>etravirine (ETV)</td>
<td>ritonavir (RTV)</td>
</tr>
<tr>
<td>stavudine (d4T)</td>
<td></td>
<td>nelfinavir (NFV)</td>
</tr>
<tr>
<td>lamivudine (3TC)</td>
<td>tenofovir DF (TDF)</td>
<td>lopinavir/ritonavir (LPV/r)</td>
</tr>
<tr>
<td>abacavir (ABC)</td>
<td></td>
<td>atazanavir (ATV)</td>
</tr>
<tr>
<td>emtricitabine (FTC)</td>
<td>enfuvirtide (ENF, T20)</td>
<td>fosamprenavir (FPV)</td>
</tr>
<tr>
<td>?TAF</td>
<td>Raltegravir (MK0518)</td>
<td>tipranavir (TPV)</td>
</tr>
<tr>
<td></td>
<td>Daltegravir</td>
<td>Darunavir (DRV)</td>
</tr>
</tbody>
</table>

### Nucleotide RTIs
- nelfinavir (NFV)

### Entry Inhibitors
- atazanavir (ATV)

### Integrase Inhibitors
- tipranavir (TPV)
KZN - ARV Update

- The Ethekwini district has 121 fixed facilities offering ART.
- As at end of Q4/2015-16, there were 346,966 clients (1 million in KZN).
- Out of 346,966 TROA, a total of 298,000 patients are on FDC (83%).
- District had a target of 104,459 ARV initiations and achieved 73,713 which was 71% of the target.
- Out of 73,713 total initiations, 70,616 were initiated on FDC which was 96%.
Integrated care of patients with chronic conditions

1. Fast-track treatment initiation counselling
2. Enhanced adherence counselling
3. Spaced fast-lane appointments
4. Adherence Clubs
5. Decentralised medicine delivery
6. Tracing and retention in care
7. Child and adolescent disclosure counselling
8. If child or adolescent living with HIV

Stable and adherent
Unstable and non-adherent
Missed appointments
### What is new in these guidelines 2015?

#### Eligibility
- UTT (All eligible regardless of CD4/WHO stage)
- Option B+

#### Regimens
- Use of FDCs for simplification
- Harmonised ART regimens
- Alternatives in second line for AEs
- Third line drugs

#### Labs
- Routine CrAg screening in CD4 <100 cells/mm³
- Use of VL for monitoring treatment
- TST for IPT eligibility and duration
## UTT Eligibility and Timing

<table>
<thead>
<tr>
<th>UTT (All eligible regardless of CD4/WHO stage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ All HIV+ children, adolescents and adults offered ART</td>
</tr>
<tr>
<td>➢ Pre-ART and wellness patients offered ART</td>
</tr>
<tr>
<td>➢ Assess willingness and readiness to start ART. If not ready continue wellness program and continuous counselling for ART.</td>
</tr>
<tr>
<td>➢ Baseline CD4 will still be done</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ART should be started within 2 weeks after the CD4 count is done</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fast track:</strong></td>
</tr>
<tr>
<td>HIV Stage 4</td>
</tr>
<tr>
<td>CD4 &lt;200 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Immediate Priority:</strong></td>
</tr>
<tr>
<td>HIV+ pregnant and breastfeeding women</td>
</tr>
<tr>
<td>HIV+ children and adolescents</td>
</tr>
<tr>
<td>HIV+ Adults with CD4&lt;350 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>TB/HIV co-infection:</strong></td>
</tr>
<tr>
<td>Start TB Rx first then ART within 2-8 weeks</td>
</tr>
<tr>
<td>If CD4&lt;50 initiate ART within 2 weeks of TB Rx</td>
</tr>
<tr>
<td><strong>Cryptococcal/TB meningitis:</strong></td>
</tr>
<tr>
<td>Defer ART for 4-6 weeks</td>
</tr>
</tbody>
</table>
Advanced disease

Low CD4 count <50
Different OIs with poor general medical condition and risk of high mortality –irrespective of CD4 count
CNS infections including CCM, Toxoplasmosis ,PML
Lung infections –PCP, severe PTB, Bacterial pneumonias
Extrapulmonary TB
HIV associated malignancies.
Dementia
Persistent diarrhoea
Renal failure
Cardiomyopathy
Life threatening ART adverse events
ICU admissions
Treatment failure –multiclass drug resistance
Acute OIs and Timing of ART

- Early ART outweighs risk
  - Esophageal candidiasis
  - Crypto/microsporidiosis
  - PML
  - KS
  - PCP
  - Serious bacterial infections
  - TB

- Early ART be beneficial or harmful
  - Toxoplasmosis
  - Tb meningitis

- Early ART is harmful
  - Crypto meningitis
Starting ART in patients with TB

• CD4 count ≤50 cells/μl: - after 2 weeks of TB treatment when it is clear that the patient’s TB symptoms are improving and that TB therapy is tolerated.

• CD4 count >50 cells/μl: - delayed until after the intensive phase of TB treatment (2 months) unless the patient has other serious HIV-related conditions (e.g. Kaposi’s sarcoma or HIV encephalopathy, persistent diarrhoea etc)

• TB meningitis (TBM) - Recommend starting ART 2 - 8 weeks after TBM diagnosis.

Starting ART in patients with other OIs

Cryptococcal meningitis (CM) - Recommend starting ART before 3-4 weeks after antifungal treatment (preferably amphotericin B-based) is started

Pneumocystis pneumonia / bacterial pneumonia /Toxoplasmosis - within 2 weeks of starting treatment for that infection.

Severe Kaposi’s sarcoma and lymphoma, - ART counselling should be expedited and ART should be started as soon as possible.
Starting ART in patients with PTB

- **CD4 ≤50**
  - ART within 2/52 of TB treatment
  - reduces AIDS progression & mortality

- **CD4 >50**  →  ART after intensive phase
  - Reduced shared toxicity
  - Reduce risk of IRIS

TB while on ART

On First-line regimen
- Continue ART with TB treatment.
- No change ART

On Second-line regimen:
- Double dose LPV/r
- Monitor ALT monthly.
- Reduce LPV/r to standard dose 2/52 after stopping TB treatment
Overview

• HIV continuum of care
• ICDM
• What is NEW
• Co Infections
• ART & adverse events
• Monitoring VL and DR
## First line regimen

<table>
<thead>
<tr>
<th>Who?</th>
<th>What?</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adults</td>
<td>TDF + FTC (or 3TC) + EFV (FDC preferred)</td>
<td>Replace EFV with NVP if significant psychiatric comorbidity or intolerance to EFV and where the neuropsychiatric toxicity of EFV may impair daily functioning, e.g. shift workers. Remember CD4 count restrictions for NVP. Evidence supports the efficacy and safety equivalence of 3TC and FTC.</td>
</tr>
<tr>
<td>• Pregnant and breastfeeding women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• TB co-infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• HBV co-infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• HIV-positive partner in serodiscordant couple</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Adolescents &gt;15 years and weighing &gt;40kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Adolescents &lt;40kg</td>
<td>ABC + 3TC + EFV</td>
<td>If adolescent’s weight &lt;40kg, align with paediatric regimen.</td>
</tr>
<tr>
<td>• HIV-positive partner in serodiscordant couple</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• TB co-infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pregnant women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Adolescents &gt;15 years and weighing &gt;40kg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Substituting contraindicated drugs in first line

<table>
<thead>
<tr>
<th>Contraindicated drug</th>
<th>Substitute</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV</td>
<td>TDF + FTC (or 3TC) + NVP</td>
<td>Replace EFV with NVP if significant psychiatric comorbidity or intolerance to EFV and where the neuropsychiatric toxicity of EFV may impair daily functioning, e.g. shift workers. Remember CD4 count restrictions for NVP</td>
</tr>
<tr>
<td>NVP</td>
<td>TDF + FTC (or 3TC) + LPV/r</td>
<td>Avoid NVP in women if CD4 count &gt;250 cells/mm$^3$, and men with CD4 count &gt;400 cells/mm$^3$</td>
</tr>
<tr>
<td>TDF</td>
<td>ABC + 3TC + EFV (or NVP)</td>
<td>Renal disease or the use of other nephrotoxic drugs, e.g. aminoglycosides MDR treatment</td>
</tr>
<tr>
<td>Currently on d4T</td>
<td>TDF + FTC (or 3TC) + EFV FDC preferred</td>
<td>d4T to be discontinued in all patients, even if well tolerated. If patient is not virally suppressed, consider switching to second line</td>
</tr>
</tbody>
</table>
Second-Line Regimen

- AZT/3TC/LPV/r

LPV/r  <->  ATV/r

TDF

AZT
ABC
D4T
Drugs for Third-line

- Lamivudine
- Tenofovir
- Raltegravir
- Boosted Darunavir
- Etravirine

Combinations
TDF/3TC/DAR
DAR/RAL/ETR
National 3\textsuperscript{rd}-line committee

- \(\sim n = 163\) patients
- Median age 40 years
- DRV/r +3TC/FTC+AZT/TDF ± RAL ± ETR
- Facility completes motivation form and submits to:
  - the Secretariat: Third Line ARV Peer Review Committee (PRC)
  - TLART@health.gov.za
Reintroducing ART after Interruption

- If defaulted - restart old regimen- VL after 3/12
  - Not suppressed - 2\textsuperscript{nd} line
- Multiple episodes of interruption
  - switch to 2\textsuperscript{nd} line
- Do genotypic resistance test while on ARV’s
## Monitoring at diagnosis/baseline

<table>
<thead>
<tr>
<th>What?</th>
<th>Why?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirm HIV result with rapid antibody test if no test results are available</td>
<td>To confirm HIV-positive status in patients who present without proof of status</td>
</tr>
<tr>
<td>WHO clinical staging if HIV-positive</td>
<td>For ART fast tracking and OI management</td>
</tr>
<tr>
<td>Screen for TB symptoms using the TB screening tool</td>
<td>To identify TB suspects and refer for investigation; assess IPT eligibility</td>
</tr>
<tr>
<td>Screen for pregnancy or ask if planning to conceive</td>
<td>To identify women who need ART for PMTCT and offer family planning services</td>
</tr>
<tr>
<td>Screening for STIs</td>
<td>To identify and treat STIs</td>
</tr>
<tr>
<td>Blood pressure and glycosuria</td>
<td>Screen for comorbidities</td>
</tr>
<tr>
<td>Weight and height in adolescents</td>
<td>To determine which ARVs to use</td>
</tr>
</tbody>
</table>
## Monitoring at diagnosis/baseline

<table>
<thead>
<tr>
<th>What?</th>
<th>Why?</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 count</td>
<td>Identify prioritisation (CD4 &lt;350 cells/mm³) eligibility</td>
</tr>
<tr>
<td></td>
<td>Identify cotrimoxazole (CD4 &lt;200 cells/mm³) eligibility</td>
</tr>
<tr>
<td></td>
<td>Identify CrAg eligibility (CD4 &lt;100 cells/mm³)</td>
</tr>
<tr>
<td>Screen for HBV (HBsAg)</td>
<td>HBV co-infection management</td>
</tr>
<tr>
<td>CrAg test if CD4 &lt;100 cells/mm³</td>
<td>Assess if there is disseminated cryptococcal infection and fluconazole therapy is indicated</td>
</tr>
<tr>
<td>Creatinine if pt requires TDF</td>
<td>Assess renal sufficiency</td>
</tr>
<tr>
<td>ALT if pt requires NVP</td>
<td>Exclude liver disease</td>
</tr>
<tr>
<td>FBC if patient requires AZT</td>
<td>Detect anaemia or neutropenia</td>
</tr>
<tr>
<td>Fasting cholesterol and triglycerides if LPV/r required</td>
<td>Identify patients at risk of LPV/r related hyperlipidaemia. If &gt;6 mmol/L, give ATV/r instead of LPV/r</td>
</tr>
</tbody>
</table>
# Monitoring on ART

<table>
<thead>
<tr>
<th>What?</th>
<th>When?</th>
<th>Why?</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB screen</td>
<td>Every visit</td>
<td>TB infection / IPT eligibility</td>
</tr>
<tr>
<td>WHO staging</td>
<td>Every visit</td>
<td>New OIs</td>
</tr>
<tr>
<td>Ask about SEs</td>
<td>Every visit</td>
<td>ARV toxicity</td>
</tr>
<tr>
<td>CD4 count</td>
<td>At 12 months on ART</td>
<td>Immune response</td>
</tr>
<tr>
<td>Viral load</td>
<td>Months 6 and 12 on ART; then 12 monthly</td>
<td>Treatment failure / adherence problems</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Months 3, 6 and 12 if on TDF; then 12 monthly</td>
<td>TDF toxicity / renal impairment</td>
</tr>
<tr>
<td>FBC</td>
<td>Months 3 and 6 if on AZT; then 12 monthly</td>
<td>AZT toxicity</td>
</tr>
<tr>
<td>ALT</td>
<td>If on NVP and develops rash or symptoms of hepatitis</td>
<td>NVP toxicity</td>
</tr>
<tr>
<td>Fasting TC and TG</td>
<td>At month 3 if on LPV/r</td>
<td>LPV/r toxicity</td>
</tr>
</tbody>
</table>
**General management: Creatinine clearance**

<table>
<thead>
<tr>
<th>Serum creatinine gives indication of renal function, but poor indicator in some cases:</th>
<th>Calculate creatinine clearance:</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Elderly</td>
<td>– Age &gt;50 years</td>
</tr>
<tr>
<td>– Low body weight</td>
<td>– Weight &lt;50 kg</td>
</tr>
<tr>
<td>– Acute illness</td>
<td>– Serum creatinine &gt;100 umol/L</td>
</tr>
<tr>
<td></td>
<td>– Comorbidities that affect renal function (HPT; DM)</td>
</tr>
<tr>
<td></td>
<td>– Medications that may impair renal function</td>
</tr>
</tbody>
</table>

TDF can only be used in patients with creatinine clearance >50 mL/min and creatinine <100 umol/L

Don’t forget dose adjustment of certain ARVs when used in renal impairment
Don’t forget to readjust doses as renal impairment improves!
Overview

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PREVENTION AND MANAGEMENT OF OPPORTUNISTIC INFECTIONS
# Cotrimoxazole preventive therapy (CPT)

**When to start**
- WHO stage 2, 3 and 4
- HIV/TB co-infection
- Reduces hospitalisation and morbidity
- Protects against PCP, toxoplasmosis, malaria and bacterial infections
- Benefit outweighs risk in pregnancy therefore continue in pregnant women
- Maculopapular rash most common SE. Continue or stop and restart for mild rash

**When to stop?**
- CD4 ≥ 350 on 2 occasions
- CD4 drops < 350
- ART fails
- New OI
- Neutropenia is rare SE. Routine FBC monitoring not required
- Can use dapsone 100 mg unless severe reaction (cross reactivity) Less cover

**When to restart**
- CD4 drops < 350
- ART fails
- New OI
- Do not delay ART in favour of cotrimoxazole initiation

**160/800 mg daily**
- (2 tablets)
- Monitor clinically at 3 monthly intervals

**Safety of CPT**
Isoniazid Preventive Therapy (IPT)

- Exclude active TB
- Confirm IPT eligibility
- TST to determine duration
- Start IPT and pyridoxine
- Monitor adherence and SEs
- Screen for TB at every visit
Exclude active TB

TB symptom screen

Investigate for TB if ≥1 symptoms

No TB, do not give IPT

Reassess for IPT eligibility after 3 months

<table>
<thead>
<tr>
<th>TB symptom screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current cough, any duration</td>
</tr>
<tr>
<td>Persistent fever &gt;2 weeks</td>
</tr>
<tr>
<td>Unexplained weight loss</td>
</tr>
<tr>
<td>Drenching night sweats</td>
</tr>
</tbody>
</table>
IPT eligibility

Who is eligible for IPT?

- All HIV-infected adults and adolescents with no signs or symptoms of active TB
- Pregnant/breastfeeding women
- Pre-ART patients
- Patients on ART
- Former TB patients

Who is not eligible for IPT?

- Confirmed or suspected active TB
- HIV-positive, TST-negative preART
- Active acute or chronic liver disease
- Symptoms of peripheral neuropathy
- History of adverse reaction to INH
- Excessive ETOH use
Cryptococcus

- Screen patients with CD4 count <100 cells/mm$^3$ for cryptococcal disease BEFORE initiating ART (CrAg)
  - Currently clinician initiated
- CrAg-positive indicates disseminated cryptococcal disease
  - Evaluate for symptoms/signs of meningitis

CrAg-positive

Evidence meningitis \[\rightarrow\] LP
CM confirmed \[\rightarrow\] Admit: IV antifungal x 2 weeks

No evidence meningitis \[\rightleftharpoons\] Offer LP if available
### Cryptococcus

#### Summary recommendations

<table>
<thead>
<tr>
<th>Clinical picture</th>
<th>Antifungal treatment</th>
<th>ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrAg-positive but no evidence of meningitis</td>
<td>Oral fluconazole (800mg/day x 2 weeks; standard consolidation and maintenance antifungal treatment)</td>
<td>Start after 2 weeks antifungal treatment</td>
</tr>
<tr>
<td>CrAg-positive with evidence of meningitis</td>
<td>IV antifungal treatment x 2 weeks; standard consolidation and maintenance antifungal treatment</td>
<td>Start after 4-6 weeks antifungal treatment</td>
</tr>
</tbody>
</table>

- **WOCBA:** if CrAg-positive, do pregnancy test before starting fluconazole (teratogenic)
- **All CrAg-positive PREGNANT women should be offered LP**
  - Discuss with expert before deciding management
- **Fluconazole may cause liver injury**
  - Monitor patients with evidence of liver disease carefully
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Adverse events

Life Threatening

- **Hypersensitivity reaction** (ABC, NVP)
- Pancreatitis (ddl, ddC, d4T)
- **Lactic acidosis** (NRTIs)
- **Hepatitis** (NNRTIs, PIs, d4T/ddI)
- SJS (NVP)

Acute/Early

- Gastrointestinal (ZDV, ddl, PIs)
- Jaundice (ATV, IDV)
- Renal stones (IDV)
- **Anemia, neutropenia** (ZDV)
- Asthenia (ZDV)
- **Central Nervous System** (EFV)
- Rash (NNRTIs)

Chronic/Long term

- **Peripheral Neuropathy** (ddC, d4T, ddl)
- Metabolic – glucose intolerance, lactate, lipids, fatty liver, osteoporosis (PIs, d4T, TDF)
- **Morphologic** – fat loss, fat gain (d4T, PIs?)
- Renal (TDF)
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Categories of HIV Viral Load per District in KZN

- ZULULAND
- UTHUNGULU
- UTHUKELA
- UMZINYATHI
- UMKHANYAKUDE
- UMGUNGUNDLOVU
- UGU
- SISONKE
- ILEMBE
- ETHEKWINI
- AMAJUBA

HIV VIRAL LOAD CATEGORY
- Undetectable
- 41 to 1000
- >1000
Goal of HAART

**Durable Viral Suppression**
Undetectable Levels

- Halt disease progression
- Immunological recovery
- Reduce OIs
- Prevent drug resistance
- Reduce viral transmission
Consequences of viraemia

- Poor immunological recovery - risk of recurrent OIs and increase mortality
- Increased risk of transmission of infection – poor prevention and control of the epidemic
- Risk of resistance to ART and need to change to more expensive regimens
- Increased risk of transmission of resistant virus
- Disease progression – increased risk of comorbidities viz. DM; HPT; IHD due to chronic immune activation with increasing age
Viral Load

Plasma HIV RNA load is the most representative and sensitive laboratory test for monitoring:

- Response to antiretroviral therapy
- Failure of treatment from any cause
  1. Drug resistance
  2. Adherence
Virological failure – first warning sign

- CD4 Count
- Viral Load
- Virologic Failure
- Immunologic Failure
- Clinical Failure
- Drug Resistance

References:
- Losina E et al, 15th CROI 2008, #823
- Pillay D, et al. 14th CROI, Los Angeles 2007, #642
Factors that contribute to the Development of Resistance

- Poor Adherence
- Insufficient Drug Level
- Viral Replication in the Presence of Drug
- Resistant Virus
- Transmission

Factors include:
- Social/Personal Issues
- Regimen Issues
- Toxicities
- Poor Potency
- Wrong Dose
- Drug Interactions
- Poor Absorption
- Rapid Clearance
- Poor Activation
- Host Genetics
Virology failure (SA)

- HIV RNA >1000 check for:
  - Adherence
  - Tolerability
  - Dosing schedule
  - Drug interactions
- Repeat VL in 2 months
- Repeat VL >1000 change regimen
Adherence monitoring:

**Use the viral load.**
- WHO recommends **VL monitoring** with other adherence measures.
- Raised viral load indicates a risk of failure, so **DO** something.
- 56-68% can re-suppress with an adherence intervention.
Improving Viral Load Monitoring and Outcome
File and facility Audit
2 hospitals/3 CHCs/5 PHCs
Viral Load Testing and Suppression Rates

Viral Load Coverage in Adult and Paediatric patients

Viral Suppression Rates in Adults and Children

<table>
<thead>
<tr>
<th>Percentage</th>
<th>6 months</th>
<th>12 months</th>
<th>24 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral Load Conducted (Adults)</td>
<td>32.1% (546/1701)</td>
<td>25.9% (364/1403)</td>
<td>19.6% (10/51)</td>
</tr>
<tr>
<td>Viral Load Conducted (Peds)</td>
<td>29.3% (22/75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral Suppression (Adults)</td>
<td>88.8% (485/546)</td>
<td></td>
<td>89.8% (327/364)</td>
</tr>
<tr>
<td>Viral Suppression (Peds)</td>
<td>68.2% (15/22)</td>
<td></td>
<td>70.7% (7/10)</td>
</tr>
</tbody>
</table>
MAKING VL ROUTINE
**The Viral Load Cascade**

**Step 1:** Achieving Coverage of Viral Load Testing

- **Viral Load Test**

**Step 2:** Acting on the results

- **Low Viral Load Count**
  - Offer differentiated ART delivery for stable patients
- **High Viral Load Count**
  - Enhanced adherence counselling

**Step 3:** Switching to Second Line ART

- **Repeat Viral Load Test**
- **Low Viral Load Count**
- **High Viral Load Count**
<table>
<thead>
<tr>
<th>STEPS TO AN IDEAL ART SERVICE SITE</th>
</tr>
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<tbody>
<tr>
<td><strong>1. HAST Clinical Manager And VL Champ in each CHC/hospital and VLC in each ART site assisted by QA teams</strong></td>
</tr>
</tbody>
</table>
| 1. Terms of reference identified for overall supervision of process.  
2. Responsible for facility reports to DOH  
3. Manage exit plan with partners in 2018 so that M&E takes over. |
| **2. Make viral load monitoring routine** |
| 1. Increase demand by pt. education and HCW education  
2. Institute VL anniversary concept  
3. Implement gate keeping not to issue repeat scripts without VL |
| **3. Synergise data sources so that TIER.NET is optimally functional and totally reliable** |
| 1. Create a high VL register for 1st and 2nd line ART from all data sources – routine clinic VL records, NHLS weekly dashboard, TIER.NET records, pharmacy records, complete file audit of all active patients.  
2. Ensure that VL results are entered into clinical charts daily so that TIER.NET can be updated.  
3. Clean and update TIER.NET for recording and reporting –will improve after catch up phase  
4. Catch up phase to account for every patient every seen in clinic and not accounted for on TIER.NET.  
5. Finally depend on TIER reports only. |
| **4. Start VL priority clinic on specific day/ dedicated team working daily** |
| Trained EAC team work with trained doctor to manage complex VF in first line and all second line VF  
Ensure that all patients receive care by a MDT |
| **5. Support PHCs in the area** |
| VLC in each PHC to be mentored and supported by local CHC/hospital. Manage all first line VF and refer all second line VF  
Standardise referral forms for VF and data required for 3rd line ART |
CREATING DEMAND FOR VIRAL LOAD TESTING

• Programmes should invest in the training of counsellors and development of educational material to ensure quality patient education on VL,

• Funding for civil society organisations to support VL awareness campaigns should be integrated into national VL scale-up plans.
MY VIRAL LOAD IS UNDETECTABLE.

I AM CONTROLLING THE VIRUS!
STEP 2

ACTING ON THE RESULT

LOW VIRAL LOAD

OFFER DIFFERENTIATED ART DELIVERY FOR STABLE PATIENTS

ENHANCED ADHERENCE COUNSELLING

REPEAT VIRAL LOAD TEST

HIGH VIRAL LOAD

LOW VIRAL LOAD COUNT

HIGH VIRAL LOAD

Enhanced Adherence Documented:

- NORMAL: 56%
- SWAZILAND: 82%

Repeat Viral Load Taken:

- CHICHUGUBE: 23%
- CHIRIWOLO: 71%
NHLS Track Care

Nurse or delegate or counselor

IALH

Data Capturer

VL Result Printout

Sample Log

Doctor

File in Patient Chart

Nurse or Phlebotomist

Patient Navigator

Data Capturer

HAST Flow Sheet in Patient Chart

Data Capturer

Tier.Net

First Line

Weekly Group Session

Second Line

Weekly Group Session

Clinical Manager or ARV Clinic Director

Daily Individual Session

Data Capturer

Doctor

Nurse for Care (Viral Load Champ)

Adherence Counseling

Suppressed Follow Up

Unsuppressed to Doctor
SWITCHING TO SECOND-LINE ART

LESSONS LEARNED

- Rates of switch to second-line ART remain low in most sites.
- Where patients are well or where adherence is not optimal, clinicians are reluctant to switch and ‘give more time’ for adherence support.
- The optimal duration to allow for suppression before switch is not clear but may depend on the first VL result.
- Factors that facilitated switch to second-line ART included:
  - Decentralisation of second-line initiation
  - Task-shifting of second-line initiation to non-physician cadres
  - M-health strategies to allow remote clinical decision support for switching.
- Ensuring second-line drugs are available where the patient is accessing their first-line therapy should be a priority.
- Ongoing adherence support following the switch to second-line ART is essential.
Resistance tests serve two purposes:

• \((i)\) a fully sensitive pattern may imply that the patient is not adhering to treatment or has completely interrupted ART; and

• \((ii)\) if resistance mutations are present, then the clinician, preferably together with an expert, can decide on the most appropriate second-line (and now third line) regimen.
HIVDR testing algorithm

VL >1000 copies/mL on PI-based ART >1 year

Adherence; compliance; tolerability; drug interactions; psychological issues

Repeat VL after 6 months

VL ≤1000 copies/mL
- Continue second-line

VL >1000 copies/mL
- Specialist referral
  - GENOTYPE
    - Specialist decision re further management
### Criteria for referral

<table>
<thead>
<tr>
<th>1. FIRST LINE VF- after counselling for two months, if the repeat VL 1000 copies/ml and now requires second line ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. The patient has multimorbidity – renal, cardiac, liver pathology</td>
</tr>
<tr>
<td>b. The patient needs TB treatment or review of Tb treatment</td>
</tr>
<tr>
<td>c. There are existing drug toxicities or concerns about drug interactions</td>
</tr>
<tr>
<td>d. The patient has been commenced on second line ART and continues to be intolerant of the drugs – vomiting etc</td>
</tr>
<tr>
<td>e. The patient has proven hyperlipidemia as per guidelines and requires another PI</td>
</tr>
<tr>
<td>f. All pts with complex psychosocial problems that need intervention by trained EAC teams</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. SECOND LINE VF- REFER FROM LOCAL CLINIC LINKED TO SITE</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. ALL patients that have 2 high viral loads (&gt;1000 copies/ml) 6 months apart after the high viral load done at 12 months review.</td>
</tr>
<tr>
<td>Pt A has a high VL at 6 months on second line ART – then has counselling and repeat VL 6 months later (12 months on ART) – NOW the pt will be seen 6 months later and have another VL (18 months on ART). If this VL is &gt;1000 copies/ml then refer this patient.</td>
</tr>
<tr>
<td>Patient A will then have EAC at the referral site by the team and another VL will be done 6 months later (24 months on ART). If that VL is high – a GRT will be ordered by the senior clinical advisor at the referral site</td>
</tr>
<tr>
<td>b. HBV positive patients that have renal failure</td>
</tr>
<tr>
<td>c. All pts on second line ART that have multimorbidities or drug toxicities</td>
</tr>
<tr>
<td>d. WITHIN A REFERRAL SITE ALL SECOND LINE ART PATIENTS WITH A HIGH VIRAL LOAD CAN BE REFERRED IMMEDIATELY FOR ONGOING MANAGEMENT and remain in the clinic till further discussions about the follow up are resolved.</td>
</tr>
</tbody>
</table>
Overview

- HIV continuum of care
- ICDM
- What is NEW
- Co Infections
- ART adverse events
- Monitoring VL and DR
Putting resistance in perspective

• Drug resistance depends on:
  – Adherence
  – Health systems
  – Potency of regimens

Evidence: Swiss cohort 11,084 patients on ART between 1999 and 2013
  – 56% resistance in patients initiating ART before 1999
    • dual/mono ART
  – 20% resistance in patients initiating ART between 1999 and 2006
    • early NNRTI or 1st generation boosted PI
  – 10% resistance in patients initiating ART after 2007

Scherrer et al. CID 2016
ART naïve survey

Are patients initiating treatment susceptible to the 1st line ART regimen?

- Specimens collected from 45 health care facilities, in 34 districts and all 9 provinces
- Sample size of 336 calculated, using PPS sampling
- 277 sequences included in analysis (82.4% of target)
- 25 out of 277 patients presented with ≥ 1 surveillance drug resistance mutation (SDRM, WHO 2009)

- Prevalence of SDRM 9.0% (95% CI: 6.1-13.0%)
  - NNRTI mutations most common, n=23
  - NRTI mutations, n=7
  - PI mutations, n=2
  - In 4 patients ≥ 4 SDRMs detected, which might indicate they were not truly ART-naïve

Steegen K et al, IAS 2015: TUPEB232
ART naïve survey: Conclusion

- Although routine VL monitoring is available in South Africa, effort in earlier management of VL is important.

- Regular assessment of pre-treatment drug resistance levels in all regions are recommended.
1st-line failure survey: results

- 3.7% of patients presented with wild-type virus (indication for non-adherence)

- Most common NNRTI mutations:
  - K103N (48.8%), V106M (34.9%), Y181C (26.2%), G190A (21.7%)

- Most common NRTI mutations:
  - M184V/I (82.7%), K65R (45.8%)
  - K65R in TDF-exposed patients: 57.5%
  - ≥ 1 TAM: 27.2%
  - ≥ 3 TAMs: 6.4%
ART-experienced survey

Are patients who fail 1st line treatment susceptible to the 2nd line ART regimen?

- Specimens collected from 91 health care facilities, in 37 districts and 8 provinces (excl NC).
- 793 sequences included in analysis (88.1% of target 900)
- VL 4.7log cp/ml
- Median time on ART: 36 months
- 3.7% of patients presented with wild-type virus (indication for non-adherence)

- Most common NNRTI mutations: K103N (48 (21.7%)
- Most common NRTI mutations: M184V/I (82.7%), K65R (45.8%)
- K65R in TDF-exposed patients: 57.5%

Steegen K et al, IAS 2015: TUPEB238
Resistance mutations among 1\textsuperscript{st}-line failures in SA

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
It’s all about context

• **TenoRes study:**
  – Prevalence of TDF resistance was highest in Sub-Saharan Africa (57%) → K65R and subtype C
  – Only 20% in Europe → mainly subtype B and more frequent VL monitoring
  – Prevalence detected in patients failing ART

 6-11% of South Africans on ART (assuming 3.2 million people on ART with 10-20% failure rate)
Global epidemiology of drug resistance after failure of WHO recommended first-line regimens for adult HIV-1 infection: a multicentre retrospective cohort study

- 1926 patients from 36 countries with treatment failure between 1998 and 2015.
- Prevalence of tenofovir resistance was highest in sub-Saharan Africa (370/654 [57%]).
- Pre-ART CD4 cell count was the covariate most strongly associated with the development of tenofovir resistance (odds ratio [OR] 1.50, 95% CI 1.27–1.77 for CD4 cell count <100 cells per μL).

*Lancet Infect Dis* 2016
1\textsuperscript{st}-line failure survey: results

- 1/3 patients retain full susceptibility to 2\textsuperscript{nd}-generation NNRTIs
  - ETR: 36.3%
  - RPV: 27.1%

- Cross-resistance of NRTIs was often observed but,
  - 82.6% of all patients remained susceptible to AZT
  - 92.0% of TDF-exposed patients remained susceptible to AZT
Assessment of Second-Line Antiretroviral Regimens for HIV Therapy in Africa


Paton NI et al, NEJM 2014

Trial design (1)

HIV positive adolescents / adults (n=1200)
1st line NNRTI-based regimen >12m; >90% adherence last 1m
Failure by WHO (2010) clinical, CD4 (VL-confirmed) or VL criteria

RANDOMIZE

PI + 2-3 NRTIs (NRTIs according to local standard of care)

PI + RAL (12 wk induction)

PI (Monotherapy)

FOLLOW-UP FOR 144 WEEKS

Primary outcome at week 96:
Good HIV disease control – defined as all of:
- Alive and no new WHO4 events from 0-96 weeks AND
- CD4 cell count > 250 cells/mm³ at 96 weeks AND
- VL<10,000 c/ml OR >10,000 c/ml without PI res. mutations at 96 weeks

VL suppression at 96 weeks

<table>
<thead>
<tr>
<th>PI/RAL vs PI/NRTI</th>
<th>P=0.36</th>
<th>P=0.87</th>
<th>P=0.97</th>
<th>P=0.88</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pimono+ vs PI/NRTI</td>
<td>P=0.002</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Resihtance at 96 weeks (predicted in whole population)

<table>
<thead>
<tr>
<th>TDF/ZDV/ABC/ddi</th>
<th>RAL</th>
<th>LPV</th>
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<tbody>
<tr>
<td>% of randomized patients with intermediate/high level resistance</td>
<td></td>
<td></td>
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</tbody>
</table>

Note: assuming susceptible if VL<1000 c/ml at week 96; and using inverse probability weighting for VL>1000 c/ml with missing genotype at week 96 based on those with observed genotypes

*One patient in RAL/PI with intermediate/high level resistance to TDF had moved to 3TC TDF ALV at week 4 due to rash
Studies have shown that residual activity of NRTI-backbone in combination with PI is sufficient to suppress virus in most patients when switched to 2nd-line (Paton 2014, Boyd 2013, Sigaloff 2012).

The more mutations are seen, the more likely the patient is to suppress provided good adherence.

**Empirical switch to standard 2nd-line without drug resistance testing is still ok**

**Regimens recommended in South Africa for 1st and 2nd-line are still suitable**
• Similar rates of adverse events in NRTI group compared to other groups
• Recycling of NRTI’s not harmful
  – this has also been confirmed in the SECOND-LINE study
• Algorithmic NRTI drug selection and appropriate adherence measures are likely to achieve optimal outcomes in standardized PI/NRTI second-line therapy in RLS
• Resistance testing to select NRTIs is of little value.
Role of resistance testing in South Africa

- Public Health monitoring: surveys
- Patient monitoring
  - HIVDR testing at 1\textsuperscript{st}-line not required (EARNEST and Second-Line studies)
  - HIVDR testing at 2\textsuperscript{nd}-line required
    - Identify patients that are not adherent
    - Identify patients with PI-mutations to tailor 3\textsuperscript{rd}-line regimen
    - Uptake of HIVDR at 2\textsuperscript{nd}-line failure very slow
  - HIVDR testing in pregnant women on PI-regimen
  - HIVDR testing in infants who’s mother was exposed to Pis

- Expand VL monitoring to identify failure early and act on VL results\(>1000\) copies/ml
Acknowledgements

- The Epicentre team led by Cherie Cawood
- The 11 facilities that participated in the File and Facility Audit
- The CAPRISA ACC Statistics & Data Management Team
- Dr Henry Sunpath (eThekwini District Specialist Clinical Team Leader)

This project was supported by the Grant or Cooperative Agreement Number U2G GH001142, funded by the Centers for Disease Control and Prevention. Its contents are solely the responsibility of the presenter(s) and do not necessarily represent the official views of the U.S. Centers for Disease Control and Prevention or the U.S. Department of Health and Human Services
Partners

• Harvard Medical School
• Emory University
• SA HIV clinicians Society
• MEDICATE –AIDS T/A AWACC
Questions
Current regimens in SA

- TDF + FTC/3TC + EFV
- AZT + 3TC + PI<sub>(LPV/r or ATV/r)</sub>
- DRV/r + RAL + ETR
- 3TC/FTC, other NRTIs
Alternatives for current regimens?

- Dolutegravir (DTG)
- Tenofovir alafenamide fumerate (TAF)
- EFV 400 mg once daily
- Two-drug combinations
  - DRV/r+RAL
  - LPV/r+3TC

Vitoria et al. JIAS 2016
Issues with current 1\textsuperscript{st}-line

- **TDF**
- **FTC/3TC**
- **EFV**

- Cost driver
- Side effects (and size) driver
- Low barrier to resistance
Can TAF replace TDF?

- Low dose (10mg with ritonavir or cobicistat OR 25mg unboosted) → small pill size and cheap
- No difference in efficacy at 48 and 96 weeks between TDF and TAF
- No difference in risk of treatment related resistance (K65R in subtype C?)
- Slightly better safety profile than TDF (10 or 25mg vs 300mg)
- Current studies included TAF/FTC/DRV/cobi or TAF/FTC/EVG/cobi → too expensive for RLS
- Rifampicin interaction!
- RHI plans a study on TAF, including pregnant women

Wohl et al. JAIDS 2016
Mills et al. JAIDS 2015
Sax et al. JAIDS 2014
Is Dolutegravir the wonder drug?

- Similar VL suppression rates compared to EFV-regimens, but fewer adverse events (SINGLE study)
- No documented case of resistance when used as 1st-line
  - Resistance is possible when previously exposed to other INIs
- Potential to be low-cost and co-formulated
- No FDC yet
- Minimal toxicity but neurotoxicity might be concern
- Limited data in pregnant women
  - Planned studies: RHI and NIH (NCT02245022)
  - Increased Metformin levels with DTG
- Limited data in patients on rifampicin (double dose DTG required?)
  - Planned studies: RHI and NIH (NCT02178592)
- Limited data on long term use with TDF/FTC, no data with TAF/FTC
- Minimal toxicity but neurotoxicity might be concern

References:
- Walmsley et al. CROI 2014, poster 543
- Wainberg and Mesplede, JIAS 2015
- Dooley et al. JAIDS 2013
Acknowledgements

• National HIV Drug Resistance Working Group and Steering Group including all members and affiliates
• National Health Laboratory Service
• National Institute for Communicable Diseases
11th Annual Workshop on Advanced Clinical Care (AWACC) – AIDS 07& 08 September 2017-Durban.

Dr. Henry Sunpath – MEDICATE –AIDS NPC
Prof. Yunus Moosa - ID Unit - Nelson Mandela School of Medicine, UKZN
Prof. Raj Gandhi - ID Unit - Mass General Hospital – Harvard Medical School
Prof Tulio de Oliveira –SATURN (Southern African Treatment Resistance Network)

Elangeni Tsogo Sun in Durban

To view programme and register visit www.awacc.org