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SAHCS Conference

Adult ART guidelines update
Disclosures

• Speaker fees and honoraria from Gilead Sciences, AbbVie, Cipla, Mylan, Aspen, Sanofi, Pfizer and Janssen

• Conference sponsorship from BD, Gilead, Janssen, Merck, Cipla and Mylan

• Part of ART optimisation collaborations

• Funding from USAID, Unitaid, SAMRC and study drug donations from ViiV Healthcare and Gilead Sciences for ART optimisation studies
Process for GL development
What prompts guideline updates?
Updated GL: underlying philosophy

• Affordability considered
• Only treatment and diagnostic options available in Southern Africa were considered
• Bridge gap between public and private sectors
• Intended to reflect “best practice”
We recommend initiation of lifelong ART for all patients diagnosed with HIV infection. The CD4 count and clinical stage of the patient should no longer be a consideration in the decision to start ART.

For patients who are asymptomatic with CD4 > 350 cells/μL, additional time (weeks to a few months) can be spent counselling and preparing the patient for lifelong ART with good adherence before starting. In those with CD4 < 350 cells/μL (and especially < 200 cells/μL), or with clinical indication for starting, there should not be undue delay.

Within ART programmes, it is important to factor in that the absolute benefit of ART is much greater at lower CD4 counts (there is a mortality benefit at CD4 < 350 cells/μL). Therefore, planners and clinicians should prioritise and fast-track those with low CD4 counts (especially < 200 cells/μL); this is particularly relevant where there are ART shortages or anticipated stock-outs.
Urgency to start ART

- CD4 count < 200 cells/μL
  - Within one week of adherence counselling (NB: exceptions)
- Same day as diagnosis or receiving CD4 count?
  - Less LTFU
  - Careful selection
- PCP and other OIs
  - Within 2 weeks

- TB if CD4 count < 50 cells/μL
  - Within 2 weeks
- TB if CD4 count > 50 cells/μL
  - Start 2-8 weeks
- CM
  - Defer 4-6 weeks
- TBM
  - Defer 4-8 weeks

# When to defer ART?

<table>
<thead>
<tr>
<th>Reason</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of CM</td>
<td>Defer ART for 4–6 weeks after start of antifungal treatment</td>
</tr>
<tr>
<td>Serum or plasma cryptococcal antigen positive</td>
<td>Defer ART for 2 weeks after start of antifungal treatment (if meningitis is excluded on LP then ART does not need to be deferred)</td>
</tr>
<tr>
<td>Diagnosis of TB meningitis or tuberculoma</td>
<td>Defer ART until 4–8 weeks after start of TB treatment</td>
</tr>
<tr>
<td>Diagnosis of TB at non-neurological site</td>
<td>Defer ART up to 2 weeks after start of TB treatment if CD4(^+) ≤ 50 cells/µL and up to 8 weeks if CD4(^+) &gt; 50 cells/µL</td>
</tr>
<tr>
<td>Headache</td>
<td>Investigate for meningitis before starting ART</td>
</tr>
<tr>
<td>TB symptoms (cough, night sweats, fever, recent weight loss)</td>
<td>Investigate for TB before starting ART</td>
</tr>
<tr>
<td>Significantly abnormal liver function tests (ALT &gt; 200 or jaundice)</td>
<td>Investigate and address the cause before starting ART, including other drugs causing DILI</td>
</tr>
</tbody>
</table>

CM, cryptococcal meningitis; ART, antiretroviral therapy; TB, tuberculosis; ALT, alanine transaminase; DILI, drug-induced liver injury; LP, lumbar puncture.
First-line in 2015

- TDF
- ABC
- ZDV
- d4T

+ XTC

+ EFV
- RPV*
- NVP
- RAL**
First-line in 2017

\[ \text{TDF} + \text{XTC} + \text{EFV} \]

\[ \text{ABC} + \text{ZDV} + \text{d4T} \]

\[ \text{DTG} + \text{RPV}* \]
What ART to start?

<table>
<thead>
<tr>
<th></th>
<th>SAHIVSOC</th>
<th>SA NDoH</th>
<th>WHO 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTIs</strong></td>
<td><strong>TDF + FTC/3TC</strong></td>
<td><strong>TDF + FTC/3TC</strong></td>
<td><strong>TDF + FTC/3TC</strong></td>
</tr>
<tr>
<td><strong>Recommended</strong></td>
<td>ABC</td>
<td>ABC</td>
<td>ABC</td>
</tr>
<tr>
<td><strong>Alternative</strong></td>
<td>ZDV</td>
<td>ZDV</td>
<td>ZDV</td>
</tr>
<tr>
<td><strong>Short term</strong></td>
<td>d4T</td>
<td>d4T</td>
<td>d4T</td>
</tr>
<tr>
<td><strong>Third drug</strong></td>
<td><strong>Recommended</strong></td>
<td><strong>Recommended</strong></td>
<td><strong>Recommended</strong></td>
</tr>
<tr>
<td><strong>EFV</strong></td>
<td><strong>DTG</strong></td>
<td><strong>EFV</strong></td>
<td><strong>DTG</strong></td>
</tr>
<tr>
<td><strong>RPV</strong></td>
<td><strong>NVP</strong></td>
<td><strong>LPV/r</strong></td>
<td><strong>NVP</strong></td>
</tr>
<tr>
<td><strong>LPV/r</strong></td>
<td></td>
<td></td>
<td><strong>LPV/r</strong></td>
</tr>
</tbody>
</table>

When to do a baseline resistance test

Baseline resistance test to guide first-line regimen choice only in the following situations:

• Pre-exposure prophylaxis (PrEP) received in the previous 6 months
• History of sexual exposure to a person with known drug resistant HIV or known to have failed an ART regimen

When to check VL

<table>
<thead>
<tr>
<th></th>
<th>SA Dept. Health</th>
<th>SA HIV Clin. Soc.</th>
<th>DHHS (USA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At initiation</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Before 6 months</td>
<td>X</td>
<td>3 months</td>
<td>At 2-8 weeks, then every 4-8 weeks until suppressed</td>
</tr>
<tr>
<td>6 months</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>12 months</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Thereafter</td>
<td>Every 12 months</td>
<td>Every 6 (-12) months</td>
<td>Every 3-6 months</td>
</tr>
</tbody>
</table>

**Why check viral loads before 6 months?**

- Enables early detection of virological failure (usually due to poor adherence), before resistance develops, or worsens.
- At 3 months, most patients will be virally suppressed, but a small group of people who started with a very high viral load may still have detectable viraemia... although they’ll still show at least a $2 \log_{10}$ drop from their initiation viral loads.
When to check CD4 count

• At baseline
  – Identify patients at risk of OIs to start appropriate OI prophylaxis

• Every 6 months until CD4 > 200 cells/uL
  – Can stop checking if CD4 > 200 cells/uL if VL suppressed (and remains suppressed)

• Virological or clinical failure

• If otherwise clinically indicated
Other monitoring?

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>When?</th>
<th>Ongoing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC</td>
<td>✓</td>
<td>M1, 2, 3, 6</td>
<td>On ZDV</td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>✓</td>
<td>W 2, 4, 8 and 12</td>
<td>Only if on NVP</td>
<td></td>
</tr>
<tr>
<td>Creat Cl</td>
<td>✓</td>
<td>M3, 6 and 6- monthly</td>
<td>Also M1 and 2: high risk</td>
<td></td>
</tr>
<tr>
<td>TC and TG</td>
<td>Not routine</td>
<td>M3</td>
<td>On PI/r. Only reassess if other CV risk factors</td>
<td></td>
</tr>
</tbody>
</table>

“This recommended routine monitoring ensures a standard level of care is given to patients on ART. However, it does not replace clinical judgement. These tests should also be carried out when clinically indicated, based on the discretion of the clinician.”

When to switch?

• Two VL > 1000 copies/mL
• 2-3 months apart
• At least 4 weeks adherence intervention in between

Low level viraemia (200 – 1000 copies/mL)
• Prolonged (> 1 year)
  OR
• With persistently low CD4 counts (< 100 cells/mm³)

Despite adherence interventions

Switch to which?

<table>
<thead>
<tr>
<th>NRTI combinations</th>
<th>Switch to</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line NRTI</td>
<td></td>
</tr>
<tr>
<td>AZT</td>
<td>TDF</td>
</tr>
<tr>
<td>d4T</td>
<td></td>
</tr>
<tr>
<td>TDF</td>
<td>AZT</td>
</tr>
<tr>
<td>ABC</td>
<td></td>
</tr>
</tbody>
</table>

EARNEST trial suggested that NRTIs have important role in second-line with PI/r even when there is NRTI resistance present

Third drug options

<table>
<thead>
<tr>
<th>Preferred PI/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r</td>
</tr>
<tr>
<td>LPV/r</td>
</tr>
<tr>
<td>DRV/r*</td>
</tr>
</tbody>
</table>

* When 800/100mg daily available

Safety issues with PIs

**LPV/r**
- GI upset
- Lipids
- Hepatitis
- Dysglycaemia

**ATV/r**
- Jaundice
- Lipids (low potential)
- Renal stones
- Hepatitis

**DRV/r**
- Rash
- GI upset
- Hepatitis
DRV/r 800/100 mg once daily

Recently approved by MCC for the following indication:

• PREZISTA, in combination with low dose ritonavir (PREZISTA/rtv) and with other antiretroviral medicines, is indicated for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment experienced adult patients who are protease-inhibitor-naïve patients or after exclusion of darunavir resistance associated mutations (DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V).

• Genotypic or phenotypic testing should guide the use of PREZISTA/rtv.

• Ritonavir is used as a pharmacokinetic enhancer of darunavir.

• There is no information on the use of darunavir in combination with ritonavir in the paediatric population for the once daily dose.
SA HIV Clinicians Society Guidelines

• Currently recommends ATV/r 300/100 mg as preferred PI/r for second-line ART

• “When the appropriate dose tablet becomes available, the [DRV/r] 800/100 mg daily dose will be a feasible option in second-line ART, with fewer side effects than the twice-daily dosing”

• DRV/r 600/100 mg bid recommended in third-line ART
Using DRV/r 800/100 mg in second-line ART

• Patient failing first-line NNRTI- or InSTI-based regimen: switch to DRV/r 800/100 mg daily + 2NRTIs (sequence NRTIs as per guidelines)

• Patient on PI/r-based second-line regimen: check VL

• If VL LDL – can switch PI/r to DRV/r 800/100 mg daily. Retain same NRTI backbone

• If detectable VL, intensify adherence interventions and repeat VL in 2-3 months. If VL LDL, can switch PI/r to DRV/r 800/100 mg daily. If VL > 1000 copies/mL, resistance genotype is needed to determine if eligible for third-line ART
Failing NNRTI- or InSTI-based first-line ART

NNRTI/InSTI + 2NRTI

VL > 1000 copies/mL (confirmed)

DRV/r 800/100 mg daily + 2NRTI
On PI/r-based second-line ART

On PI/r + 2NRTI

Check VL

- VL LLDL
  - Switch PI/r to DRV/r 800/100 mg daily

- VL detectable
  - Intensify adherence
    - Repeat VL in 2-3 months
      - VL LLDL
      - VL > 1000 copies/mL
      - VL detectable

Genotype

VL detectable
Check VL
Patients failing on second-line ART

- Intensified adherence intervention
- PI > one year; not virologically suppressed
- Genotype on ART
- Documented PI resistance
- Third-line ART selected based on genotype and ART history

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

Add DTG

TDF/AZT > 29
AND
DRV ≥ 15
AND
ETR/RPV ≤ 29

Add ETR/RPV

DRV 400 mg is now available in SA

• Currently patients on DRV in third-line receive DRV/r 600/100 mg bid
• A small proportion of third-line patients have no DRV RAMs, and in such patients it may be possible to use DRV/r 800/100 mg daily instead of DRV/r 600/100 mg bid to, reducing pill burden, dosing frequency and side effects
• Patients initiating third-line ART: if DRV score (Stanford) is zero on all genotypes, may initiate DRV 800/100 mg daily
• Switching patients already on third-line: the patient’s VL must be LDL, AND the DRV score (Stanford) MUST be zero on all genotypes the patient has had done
Initiating third-line ART

- **PI/r + 2NRTI**
- **VL > 1000 copies/mL (confirmed)**
- **Genotype: PI/r score ≥ 15 AND DRV score ≤ 0**
- **DRV/r 800/100 mg once daily + 2NRTI ± DTG ± ETR**
On DRV/r based third-line ART (600/100 mg bid)

- Check VL
- LDL
- Check all previous genotypes
- DRV score ≤ 0 (Stanford)
- Switch DRV/r to 800/100 mg
  - Retain rest of third-line regimen
### What about TB? Drug interactions

<table>
<thead>
<tr>
<th>Class</th>
<th>ART drug</th>
<th>Interaction</th>
<th>Dose of ART drug with rifampicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>All in class</td>
<td>No significant pharmacokinetic interactions</td>
<td>No dose adjustment required.</td>
</tr>
<tr>
<td>NNRTI</td>
<td>EFV</td>
<td>Mild reduction in EFV concentrations. In some patients on TB treatment, EFV concentrations may increase</td>
<td>No dose adjustment required (600 mg <em>nocete</em>).</td>
</tr>
<tr>
<td></td>
<td>NVP</td>
<td>Moderate reduction in NVP concentrations with increased risk of virological failure compared with EFV</td>
<td>Use standard dosing, but omit the lead-in dose phase and start 200 mg NVP 12-hourly.</td>
</tr>
<tr>
<td></td>
<td>ETR and RPV</td>
<td>Marked reduction in concentrations</td>
<td>Do not prescribe concomitantly with rifampicin.</td>
</tr>
<tr>
<td>PI</td>
<td>LPV/r</td>
<td>LPV plasma concentrations significantly decreased</td>
<td>The preferable strategy is to double the dose of LPV/r to 800/200 mg 12-hourly. Alternatively, add 300 mg RTV 12-hourly to standard dose of two tablets of LPV/r 12-hourly. There is an increased risk of hepatotoxicity with these strategies. These dose adjustments can be made gradually over 1–2 weeks†.</td>
</tr>
<tr>
<td></td>
<td>All other PIs</td>
<td>Marked reduction in PI concentrations</td>
<td>Do not prescribe concomitantly.</td>
</tr>
<tr>
<td>INSTI</td>
<td>RAL</td>
<td>Reduction in concentrations, but a clinical trial showed that standard dosing results in adequate virological suppression31</td>
<td>No dose adjustment required (i.e. RAL 400 mg 12-hourly).</td>
</tr>
<tr>
<td></td>
<td>DTG</td>
<td>Significant reduction in concentrations</td>
<td>Dosing frequency increased to 50 mg 12-hourly.</td>
</tr>
</tbody>
</table>
What about IPT?

<table>
<thead>
<tr>
<th>TST</th>
<th>Pre-ART</th>
<th>On ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not done</td>
<td>6 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Negative</td>
<td>Not indicated</td>
<td>12 months</td>
</tr>
<tr>
<td>Positive</td>
<td>At least 36 months</td>
<td>At least 36 months</td>
</tr>
</tbody>
</table>

- TEMPRANO: separate randomisation to 6 months of IPT
  - addition of IPT to ART - provided added protection against active TB disease
  - Benefit to patients with relatively high CD4 counts

- Khayelitsha study: placebo controlled
  - 12 months of IPT to patients on ART
  - reduced TB incidence by 37%

NEJM 2015
Guidance for DTG in first-line ART

<table>
<thead>
<tr>
<th>Population</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women* on effective contraception or not of childbearing potential</td>
<td>DTG-based first-line ART is recommended</td>
</tr>
<tr>
<td>All pregnant (from eight weeks after conception) and breastfeeding women</td>
<td>DTG-based first-line ART is recommended</td>
</tr>
<tr>
<td>WOCP** who want to become pregnant or have no effective contraception</td>
<td>Counsel about risks and benefits of DTG- versus EFV-based ART. Offer choice of both treatments. Document discussion, preferably along with consent from those women opting for DTG-based ART</td>
</tr>
<tr>
<td>Confirmed pregnancy &lt;8/40</td>
<td>DTG-based first-line ART is recommended</td>
</tr>
</tbody>
</table>

* Women includes adolescent girls  
** Women of childbearing potential

“A woman-centred approach should be adopted: healthcare providers should give women information and options to allow for informed choices about using lifelong ART regimens.”

Final thoughts
Acknowledgements