Introduction to the 2017 SA HIV Clinicians Society ART guidelines

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March 2018
First-line ART Strategies Roadshow

Thanks all at SAHCS, Michelle Moorhouse
Disclosures

• Speaker fees and honoraria from Gilead Sciences, AbbVie, Cipla, Mylan, Janssen, Gilead, Merck, Cipla, Mylan.

• Part of ART optimisation collaborations

• Funding from USAID, Unitaid and study drug donations from ViiV Healthcare and Gilead Sciences
## WHO guideline evolution

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>When to start</strong></td>
<td>CD4 ≤200</td>
<td>CD4 ≤200</td>
<td>CD4 ≤200</td>
<td>CD4 ≤350</td>
<td>CD4 ≤500</td>
<td><strong>Toward Treat All adolescents age band</strong></td>
</tr>
<tr>
<td></td>
<td>− Consider 350</td>
<td>− Regardless CD4</td>
<td>− Regardless CD4</td>
<td>− Regardless CD4</td>
<td>− CD4 ≤350 as priority</td>
<td></td>
</tr>
<tr>
<td></td>
<td>− CD4 ≤350 for tuberculosis (TB)</td>
<td>− CD4 ≤350 for TB and hepatitis B virus (HBV)</td>
<td>− CD4 ≤350 as priority for TB, HBV PW and SDC</td>
<td>− CD4 ≤350 as priority for PW and SDC</td>
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</tr>
</tbody>
</table>

### Earlier initiation

#### First-line ART
- 8 options
  - AZT preferred
- 4 options
  - AZT preferred
- 8 options
  - AZT or TDF preferred
  - d4T dose reduction
- 6 options and FDCs
  - AZT or TDF preferred
  - d4T phase out
- 1 preferred option and FDCs
  - TDF and EFV preferred across all populations
- **Continue with FDC and harmonisation across age bands**

#### Simpler treatment

#### Second-line ART
- Boosted and non-boosted PIs
- Boosted PIs
  - IDV/r LPV/r, SQV/r
- Boosted PI
  - ATV/r, DRV/r, FPV/r LPV/r, SQV/r
- Boosted PI
  - Heat stable FDC: ATV/r, LPV/r
- **Greater number of options**

#### Less toxic, more robust regimens

#### Third-line ART
- None
- None
- None
- DRV/r, RAL, ETR
- DRV/r, RAL, ETR
- Encourage HIV DR to guide

#### Viral load (VL) testing
- No
- No (desirable)
- Yes (tertiary centers)
- Yes (phase-in approach)
- Yes (preferred for monitoring, use of PoC, DBS)
- Support for scale up of VL using all technologies
Drug optimisation

Science evolved: smarter and better HIV treatment options are now available
PLWH on ART globally 2005-2015

19.5 million in 2016
HIV in South Africa, 2016

South Africa (2016)

- 7.1 million people living with HIV
- 18.9% adult HIV prevalence
- 270,000 new HIV infections
- 110,000 AIDS-related deaths
- 56% adults on antiretroviral treatment
- 55% children on antiretroviral treatment

Source: UNAIDS Data 2017

> 4 million on ART
The drugs rock

TDF + XTC + Efavirenz

AZT + 3TC + PI/r (LPV or ATV)

XTC, other nukes

Darunavir, Dolutegravir, Etravirine
Process for guideline development
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.
Evidence: TEMPRANO and START
Urgency to start ART

- **CD4 count < 200 cells/uL**
  - 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/uL**
  - Within 2 weeks
- **TB if CD4 count > 50 cells/uL**
  - 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 + XTC + EFV

ABC + RPV*
AZT + NVP
d4T + RAL**
First-line in 2017

TDF + XTC + EFV

ABC + DTG

AZT + RPV*

d4T
### What ART to start?

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>SAHIVSOC</th>
<th>SA NDoH</th>
<th>WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TDF + FTC/3TC ABC AZT Short term d4T</td>
<td>TDF + FTC/3TC ABC</td>
<td>TDF + FTC/3TC AZT ABC Short term d4T</td>
</tr>
<tr>
<td>Third drug</td>
<td>EFV DTG RPV</td>
<td>EFV NVP LPV/r</td>
<td>EFV EFV400 DTG</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></td>
<td>On AZT</td>
</tr>
<tr>
<td>ALT</td>
<td>✓</td>
<td>W 2, 4, 8 and 12</td>
<td></td>
<td>Only if on NVP</td>
</tr>
<tr>
<td>Creat Cl</td>
<td>✓</td>
<td>M3, 6 and 6-monthly</td>
<td></td>
<td>Also M1 and 2: high risk</td>
</tr>
<tr>
<td>TC and TG</td>
<td>Not routine</td>
<td>M3</td>
<td></td>
<td>On PI/r. Only reassess if other CV risk factors</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?

### NRTI combinations

<table>
<thead>
<tr>
<th>First line NRTI</th>
<th>Switch to</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT d4T</td>
<td>TDF</td>
</tr>
<tr>
<td>TDF ABC</td>
<td>AZT</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
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
Third-line regimen: principles

- Specific adherence counselling
- Add 3TC/FTC Other NRTIs
- No first generation NNRTIs
- Other drugs eg DTG, ETR
- PI/r with broadest resistance profile
- No double boosted PIs
- Role of MVC?

If VS not achieved, still benefit in continuing failing ART
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
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>nocte</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 suppression\textsuperscript{11}</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%
Conclusion

• CD4 count no longer a barrier to ART initiation
• Earlier ART benefits all HIV-infected individuals
  – Reduces risk of disease progression
  – Prevents onward transmission
• Benefits of early ART in RLS/LMIC
  – Reduced rates of incident TB
• IPT for all patients on ART
Save the Date

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