Review: What’s New?

2020 HIV Clinicians Society Adult ART Guidelines

Jeremy Nel
What’s new?

- New threshold for virological failure
- Recognition of new side-effects of EFV
- New isoniazid-preventative therapy guidelines
- Recommendation against routine CD4 monitoring once CD4 >200.
- Recommendation for low-dose prednisone as prophylaxis against paradoxical TB IRIS.
What’s new?

• The “dolutegravir era”
  • First line implications
  • Second line implications
  • Third line implications
  • Viral load interpretation
  • Resistance testing implications
  • Management of patients who return to care after defaulting
The journey
Diagnosis

• **Confirm HIV with two different methods** (at least one of which should be a lab-based test):
  • Rapid test + ELISA
  • Rapid test + viral load
  • ELISA + viral load

Undetectable viral load? Remember elite controllers (<1%) vs false positives.
Baseline tests

**TABLE 9: Summary of baseline investigations for antiretroviral therapy.**

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4⁺ count</td>
<td>If CD4⁺ count &lt; 200 cells/μL, then CPT is required and sCrAg testing needs to be performed.</td>
</tr>
<tr>
<td>Baseline VL</td>
<td>Can also serve as a confirmatory HIV test.</td>
</tr>
<tr>
<td>ALT</td>
<td>If raised, then will need workup and may influence ART regimen choice.</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Avoid TDF if CrCl &lt; 50 mL/min. Other NRTIs, except ABC, require dose adjustment if CrCl &lt; 50 mL/min.</td>
</tr>
<tr>
<td>HBsAg</td>
<td></td>
</tr>
<tr>
<td>Syphilis serology</td>
<td>Only required in patients with a CD4⁺ count &lt; 200 cells/μL. If sCrAg-positive, exclude CM by LP. See section on CM management for further details.</td>
</tr>
</tbody>
</table>

ABC, abacavir; ALT, alanine transaminase; CrCl, creatinine clearance rate; CM, cryptococcal meningitis; CPT, cotrimoxazole preventive therapy; HBsAg, hepatitis B surface antigen; LP, lumbar puncture; sCrAg, serum/plasma cryptococcal antigen; TDF, tenofovir disoproxil fumarate; VL, viral load.
Symptom screening

- **Tuberculosis (TB): cough, weight loss, fever, night sweats and a possible TB contact.**
  - If present: sputum Xpert; and if hospitalised or the CD4\(^+\) count is < 200 cells/\(\mu\)L → a urine LAM

- **Cryptococcal meningitis (CM): new-onset of headache**
  - Serum CrAg testing +/- LP if positive

- If the patient’s symptom screen is positive, defer ART until above results back. (But minimise delay!)
What regimen should I choose?

First line therapy
Preferred:

**TDF + 3TC + DTG** – as a fixed-dose combination: **TLD**

- *Remember*: if rifampicin given, DTG dosing needs to be increased to 50mg 12-hourly until 2 weeks after stopping rifampicin.
TABLE 13: Alternative initial ART regimens for the previously untreated patient.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Notes</th>
</tr>
</thead>
</table>
| TDF + 3TC (or FTC) + EFV | • EFV can be used at 600 mg nocte or 400 mg nocte  
• EFV 400 mg dose is associated with fewer side-effects and less LTFU\textsuperscript{22}  
• EFV 400 mg dose is not available in FDC combination in South Africa  
• There are insufficient data to recommend the EFV 400 mg dose in pregnant patients and patients receiving RIF although small-cohort studies have suggested that adequate concentrations are achieved in these patients\textsuperscript{65,66} |
| TDF + 3TC (or FTC) + RPV | • RPV cannot be used in patients receiving RIF  
• RPV should not be used in initial therapy when baseline VL is > 100 000 copies/mL |
| ABC + 3TC + DTG     | • International guidelines recommend HLA-B*5701 testing before prescribing ABC because a negative result rules out the risk of hypersensitivity reaction. However, this genotype is very rare in people of African descent and is thus probably not indicated.  
• In patients of non-African descent, HLA-B*5701 testing should be considered if ABC is to be used, though access to this test is limited in South Africa. |

3TC, lamivudine; ABC, abacavir; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; LTFU, loss to follow-up; RIF, rifampicin; RPV, rilpivirine; TDF, tenofovir; VL, viral load.
Other scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Recommended regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal failure</td>
<td>3TC+ABC+DTG</td>
</tr>
<tr>
<td>DTG side-effects</td>
<td>TDF+FTC (or 3TC) + EFV (or RPV)</td>
</tr>
<tr>
<td>Pure red cell aplasia due to 3TC/FTC</td>
<td>TDF + DGT (can add AZT once Hb improves)</td>
</tr>
</tbody>
</table>
What about DTG + 3TC?

- GEMINI-1 and -2 trials: non-inferior to TDF+FTC+DTG.

- BUT:
  - Excluded patients with VL >500,000
  - Virological suppression in patients with CD4 <200: 79% (2 drugs) vs 93% (3 drugs).
Opportunistic infection prophylaxis
1. Cotrimoxazole prophylaxis

2. Cryptococcal antigen screening and pre-emptive treatment

3. TB preventative therapy
TABLE 29: Indications for isoniazid preventive therapy (provided there are no TB symptoms or contra-indications to INH)

<table>
<thead>
<tr>
<th>Patient category</th>
<th>IPT</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-pregnant, regardless of CD4⁺ count</td>
<td>Indicated</td>
<td>12 months</td>
</tr>
<tr>
<td>Pregnant women with CD4⁺ count &gt; 350 cells/μL</td>
<td>Not indicated</td>
<td>N/A</td>
</tr>
<tr>
<td>Pregnant women with CD4⁺ count &lt; 350 cells/μL (at high risk for TB)</td>
<td>Indicated</td>
<td>12 months</td>
</tr>
</tbody>
</table>

ART, antiretroviral therapy; CD4⁺, cluster of differentiation 4; IPT, isoniazid preventive therapy; N/A, not applicable; TB, tuberculosis.
Monitoring
**TABLE 19: Standard laboratory monitoring of patients after commencement of antiretroviral therapy.**

<table>
<thead>
<tr>
<th>Test†</th>
<th>When</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VL</strong></td>
<td><em>Baseline</em></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td><strong>Ongoing</strong></td>
<td></td>
</tr>
<tr>
<td><strong>CD4⁺ count</strong></td>
<td>Yes</td>
<td>6-monthly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>At virological/clinical failure</td>
</tr>
<tr>
<td><strong>FBC + differential count</strong></td>
<td>Yes</td>
<td>Monthly for the first 3 months, then at 6 months</td>
</tr>
<tr>
<td><strong>ALT</strong></td>
<td>Yes</td>
<td>At initiation</td>
</tr>
<tr>
<td><strong>CrCl</strong></td>
<td>Yes</td>
<td>At 3 months, 6 months and then 6-monthly</td>
</tr>
<tr>
<td><strong>TC and TG</strong></td>
<td>Not routinely</td>
<td>After 3 months on a PI-containing regimen</td>
</tr>
</tbody>
</table>

ALT, alanine transaminase; AZT, zidovudine; CrCl, creatinine clearance rate; FBC, full blood count; NVP, nevirapine; TC, total cholesterol; TG, triglycerides; VL, viral load.

† These tests should also be done when clinically indicated, based on the discretion of the clinician.
Baseline

If VL > 100,000 copies/mL, then RPV is contraindicated

3 months

If not virally suppressed, then should have minimum > 2 log₁₀ decrease; provide adherence counselling

6 months

VL < 50 copies/mL

VL > 50 copies/mL

12 months

VL < 50 copies/mL

VL > 50 copies/mL

Adherence counselling
Repeat VL in 2–3 months

Every 6–12 months

VL < 50 copies/mL

VL > 50 copies/mL
Virological failure: threshold of 50 copies/mL

Virological failure = \( VL > 50 \) copies/mL on two consecutive measurements, taken 2-3 months apart.
Low-level viraemia

Association with “virological failure” (however defined) is significant:

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Virological failure defn</th>
<th>aHR</th>
</tr>
</thead>
</table>
| ART-CC. AIDS 2015            | Europe, North America | 500 copies/mL           | 50-199: 1.38 (0.96-2.0)  
200-499: 3.97 (3.05-5.17) |
| Laprise et al. CID 2013      | Canada            | 1000 copies/mL          | 50-199: 1.90 (1.16-3.11)  
200-399: 1.60 (0.81-3.14)  
500-999: 4.16 (1.68-10.29) |
| Hermans et al. Lancet ID 2018| South Africa      | 1000 copies/mL          | 51-199: 2.0 (1.8-2.2)  
200-399: 3.6 (3.2-4.1)  
400-999: 5.5 (4.8-6.4)  |
Management of virological failure
Virological failure on DTG-based 1st line regimens

The typical virological failure criteria of “two VL measurements greater than a certain threshold despite an adherence intervention” are not appropriate for DTG-based regimens.

Rather, in patients started on a first-line DTG regimen, we recommend switching to second-line therapy only if there is demonstrated InSTI resistance.
So when is a resistance test indicated in patients on 1st-line DTG-based regimens?

- **VL >50 copies/mL for >2 years** (despite adherence interventions, 100% pharmacy refills and self-reported adherence) and the current VL is > 500 copies/mL (permitting a resistance test).

- **Others:**
  - DTG monotherapy for a period
  - Co-administration of a drug that interacts with DTG without necessary dose adjustment
  - The patient was infected while receiving PrEP
Patient on two NRTIs + DTG

VL every 6 months (can be reduced to 12-monthly if suppressed)

VL < 50 copies/mL
Continue regimen

VL > 50 copies/mL
Repeat VL in 3 months

If VL > 50 copies/mL, then consider resistance testing in the case of:
- DTG monotherapy
- Exposed to interacting drugs/drugs impairing absorption without necessary adjustment
- VL > 500 copies/mL for > 2 years despite 100% adherence assessment

Do not switch to second-line regimen unless resistance shown on resistance test

- Enhanced adherence counselling
- Address potential side-effects affecting adherence
What if the patient was on an NNRTI-based regimen?
What if the patient was on an NNRTI-based regimen?

If patient was on TDF (or ABC) + 3TC (or FTC) as first line:

→ AZT + 3TC + DTG

If patient was on AZT (or d4T) + 3TC first line:

→ need a resistance test result.

- If the virus is susceptible to TDF on resistance testing: → TDF + 3TC (or FTC) + DTG (provided: the patient has not potentially previously experienced virological failure on TDF and the patient did not previously experience TDF nephrotoxicity).
- If no fully active NRTI is available to accompany DTG → best to switch to PI-based second-line therapy with TDF + 3TC (or FTC).
And second line?

• When DTG is used in second-line therapy, there should be at least one fully active accompanying drug until further evidence is available.

• If the patient is failing an NNRTI regimen with 3TC/FTC + either TDF or ABC, then AZT + 3TC + DTG is the recommended second-line regimen.

• If the patient is failing other first-line regimens, then resistance testing is advised to decide on the choice of NRTIs in a DTG-based second-line regimen:
  • If no active NRTIs: boosted PI + two NRTI second-line regimens are effective even if there is resistance to both NRTIs in the regimen.

• We advise DRV/r 800 mg/100 mg once daily as the first choice PI for use in second-line therapy.
Patients failing NRTI + NNRTI:

<table>
<thead>
<tr>
<th>Failing first-line regimen</th>
<th>Advised second-line regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF + 3TC (or FTC) + NNRTI</td>
<td>AZT + 3TC + DTG*</td>
</tr>
<tr>
<td>AZT + 3TC + NNRTI</td>
<td>Resistance test: if fully active NRTI is available, then combine this with:</td>
</tr>
<tr>
<td></td>
<td>3TC (or FTC) + DTG; or TDF + FTC + DRV/r†</td>
</tr>
<tr>
<td>ABC + 3TC + NNRTI</td>
<td>AZT + 3TC + DTG*</td>
</tr>
</tbody>
</table>

†, Provided that the patient: has not potentially previously experienced virological failure on TDF; and did not previously experience TDF nephrotoxicity.

*, If patient has chronic hepatitis B then continue TDF, in addition, in the second line regimen
What if the patient is suppressed on 2\textsuperscript{nd} line?

**TABLE 17:** Switching from a boosted PI to DTG in second-line antiretroviral therapy when the viral load is < 50 copies/mL.†

<table>
<thead>
<tr>
<th>First- and second-line regimen: prior ART</th>
<th>Second-line options</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line TDF + 3TC (or FTC) + NNRTI and second-line AZT + 3TC + PI/r</td>
<td>• Can continue same regimen or switch to AZT + 3TC + DTG</td>
</tr>
</tbody>
</table>
| First-line AZT (or d4T) + 3TC + NNRTI and second line TDF + FTC + PI/r | • Preferably stay on the same regimen  
• If resistance testing was performed at first-line failure and showed full susceptibility to TDF, then can switch to TDF + 3TC (or FTC) + DTG  
• If no resistance test was performed, but there is intolerance to all boosted PIs, then consider switching to TDF + 3TC (or FTC) + DTG with close virological monitoring (3-monthly) for the first year |

†, Note: ABC is interchangeable with TDF in this table.
**PIs: order of preference**

1. **DRV/r 800/100 mg daily**
   - Once daily
   - Better tolerated than LPV/r
   - High genetic barrier to resistance
   - Can consider 400/100 if suppressed on a PI & no previous PI failure

2. **ATV/r 300/100 mg daily**
   - Once daily
   - Better tolerated than LPV/r
   - Hyperbilirubinaemia
   - Not as robust virologically
   - Drug interactions with drugs that affect stomach acidity

3. **LPV/r 400/100 mg twice daily**
   - Coformulated with RTV
   - Worst SE profile of the PIs
   - Can be given with TB treatment (if double-dosed)
WORST PATIENT AWARD

In recognition of the successful completion of the requisites and on nomination of League of doctors on the 20th of June in the year 2017 by virtue of their authority, hereby confers upon Annie Hollis the Worst Patient Award with all the honors, rights, and privileges thereto pertaining.

Signature of the graduate
League of doctors

www.diploma-degree.com
N° 0000001235612
2nd-line:
Avoid resistance tests before ~2 years

UNLESS:

- Patient not prescribed LPV/r double dosing with concurrent RIF use
- Patient who has been taking an incorrectly low dose of medication.
**TABLE 18:** Third-line regimen recommended for the majority of patients failing protease inhibitor-based second-line therapy.

<table>
<thead>
<tr>
<th>Regimen Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF 300 mg daily, 3TC 300 mg daily, DTG 50 mg daily (given as TLD) plus</td>
<td>DRV/r 600 mg/100 mg twice daily</td>
</tr>
</tbody>
</table>

3TC, lamivudine; DTG, dolutegravir; DRV/r, ritonavir-boosted darunavir; TDF, tenofovir disoproxil fumarate; TLD, tenofovir disoproxil fumarate + lamivudine + dolutegravir fixed-dose combination.
WORST PATIENT
EVER
Patients who return after stopping ART
OK, then what?

DTG-based
- Same regimen

PI-based
- Same regimen OR AZT+3TC+DTG (if applicable)

NNRTI
- It's complicated...
Returning after stopping NNRTI-based therapy

- Multiple episodes of disengaging $\rightarrow$ switch to DTG or PI-based regimen (with appropriate NRTI backbone)
- AIDS-defining condition / extremely low CD4 $\rightarrow$ switch
- Very adherent prior to disengaging, with suppressed VL $\rightarrow$ same regimen (check VL at 3 months) or TLD
But Wait... There's MORE!
Authors: Jeremy Nel, Sipho Dlamini, Graeme Meintjes (Chairpersons), John Black, Rosie Burton, Natasha Davies, Eric Hefer, Gary Maartens, Pheto Mangena, Moeketsi Mathe, Michelle Moorhouse, Yunus Moosa, Muhangwi Mulaudzi, Jennifer Nash, Thandekile Nkonyane, Wolfgang Preiser, Mohammed Rassool, David Stead, Helen van der Plas, Cloete van Vuuren, Francois Venter, Joana Woods (Authors)