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Southern African HIV Clinicians Society (SAHCS) Clinical Update, May 2022

Use of dolutegravir-based regimens for first- and second-line antiretroviral therapy.

Based on data from several recent trials, we now recommend that all patients >10 years old and >35 kg on tenofovir/emtricitabine (or lamivudine)/efavirenz (TEE/TLE) or NVP-based regimens be switched to tenofovir/lamivudine/dolutegravir (TLD) regardless of the viral load (VL) result. In addition, all patients >10 years old and >35 kg on a regimen of two nucleoside reverse transcriptase inhibitors (NRTI) with a boosted protease inhibitor (PI) (e.g., lopinavir/ritonavir (LPV/r) or atazanavir/ritonavir (ATV/r)) and a suppressed VL can be switched to TLD, regardless of prior resistance patterns or treatment history.

In 2019, the South African National Department of Health (NDoH) recommended that patients on non-nucleoside reverse transcriptase inhibitors (NNRTI)-based ART regimens be switched to dolutegravir (DTG)-based regimens, because of DTG's higher barrier to resistance and improved side effect profile, and rising pre-treatment NNRTI resistance in South Africa (1). However, this transition is happening more slowly than desired partly because a documented suppressed VL is required prior to switching from TEE/TLE to TLD.

Since this recommendation was first made, evidence from several trials (NADIA, VISEND and ARTIST) has been published or presented, that demonstrates that tenofovir with lamivudine can be safely and effectively recycled from a first- to a second-line regimen. Therefore, in patients with virological failure on a TEE or TLE regimen a single drug can be switched (efavirenz to dolutegravir i.e., TLD as second-line), resulting in virological suppression comparable to or better than alternative second-line options.

The NADIA trial included 464 patients at 7 sub-Saharan African sites. Patients with virological failure on a TDF/3TC/NNRTI-based regimen were randomised to either DTG or darunavir/ritonavir (DRV/r), and to either continue with tenofovir/lamivudine (TDF/3TC), or switch to zidovudine/lamivudine (AZT/3TC) (2,3). The 96-week data showed that recycling TDF/3TC was superior to switching to AZT/3TC, and that DTG was non-inferior to boosted darunavir (2,3). Fewer patients on TDF/3TC had VL >1000 copies/mL than those on AZT/3TC (14.3 vs 5.6%, p = 0.0002), and fewer patients on TLD developed dolutegravir resistance than those on AZT/3TC/DTG (3 vs 6 cases) (2,3).

The VISEND trial was a randomised, open-label, phase 3 non-inferiority trial performed in Zambia including 1201 patients on TEE (4). The subset of patients (n = 208) with virological failure (VL ≥ 1000 copies/mL) were randomised to receive either TLD, tenofovir alafenamide/emtricitabine/ dolutegravir (TAFED), AZT/3TC/LPV/r or AZT/3TC/ATV/r (4). At week 48, TLD or TAFED regimens demonstrated superiority in viral suppression compared to boosted protease inhibitor regimens with AZT/3TC (4).

The single-arm ARTIST study from South Africa has also provided reassuring data (5). Sixty patients were switched from TEE to second line TLD once they had two VL >1000 copies/mL (5). The 24 week data found 51 of 60 patients had a VL <50 copies/mL [85%, 95% confidence interval (CI) 73–93%], 6 had a viral load 50–100 copies/mL, 1 had viral load 100–1000 copies/mL, 1 had switched due to side effects and 1 missed the VL measurement (5). Of note, VL <50 copies/mL was achieved in 29 of 35 patients with pre-existing TDF plus 3TC resistance (5). No integrase resistance was found (5).

The DAWNING trial, a phase 3b open-label, parallel-group, non-inferiority active control trial, was conducted at 58 sites in 13 countries (6). Patients with confirmed first-line virological failure (VL ≥ 400 copies/mL after at least 6 months of an NNRTI and two NRTIs were randomised to receive either DTG (n=312) or ritonavir-boosted lopinavir (n=315) plus 2 NRTIs. At week 48, 261 (84%) of patients in the DTG group had achieved viral suppression (VL < 50 copies/mL) compared with 219 (70%) in the ritonavir-boosted lopinavir group. The safety profile in the DTG group was also favourable. In addition, rates of virological failure were lower in the DTG arm regardless of baseline NRTI resistance patterns and second-line background NRTI use.

Taking into consideration the above evidence, we recommend the following:

1. **Adults:**
   - ***Switching to TLD from a first-line regimen containing an NNRTI (EFV or NVP):***
     - All patients on TEE or TLE or NVP-based regimens can switch to TLD, regardless of VL (suppressed or unsuppressed) or regardless of whether there is a recent VL result.
     - Similarly, patients who were previously on an EFV- or NVP-based regimen and interrupted treatment can be restarted on TLD.
   - ***Switching to DTG from a second-line boosted PI-containing regimen:***
     - Patients on any two NRTIs + LPV/r or ATV/r who have a VL <50 copies/mL (in the last 6 months) can switch to TLD.
     - Patients on LPV/r or ATV/r-based regimens who have a VL >50 copies/mL should continue to be managed as per the current guidelines.

2. **Children and adolescents:**
   - ***>10 years and >35 kg:***
     - As for adults. Also:
     - Adolescent patients transitioning from ABC-based first-line regimens (NNRTI- or PI-based) can also be moved to TLD, regardless of VL.
   - ***20 kg – 35 kg:***
     - All patients on ABC/3TC/EFV who have a VL <50 copies/mL (in the last 6 months) can switch to ABC/ 3TC/DTG.
     - All patients on ABC/3TC/EFV who have VL >50 copies/mL and a regimen switch is necessary, should switch to AZT/3TC/DTG, with repeat VL at 3 months.
     - All patients on ABC/3TC + LPV/r or ATV/r who have a VL <50 copies/mL (in the last 6 months) can switch to ABC/3TC/DTG
     - Patients on LPV/r or ATV/r-based regimens who have a VL >50 copies/mL (in the last 6 months) should continue to be managed as per current NDoH guidelines.
   - ***<20 kg:***
     - These patients are currently not eligible for DTG 50 mg tablets, unless recommended by expert opinion.

Please note:

- These recommendations are made with the assumption that there are no contraindications to DTG or TLD.
- Patients with an unsuppressed viral load who switch to DTG should be considered for additional support to enhanced adherence, and to identify any other potential causes of the raised viral load (such as drug-drug interactions or poor drug absorption.)
- Terms such as ‘first-line’ and ‘second-line’ will become increasingly confusing and inaccurate. WHO is currently addressing this, and clinicians should take care with terminology during this transition period.

For more guidance, please contact:

- National HIV & TB Health Care Worker Hotline: 0800 212 506, SMS/Please Call Me/WhatsApp to 0718401572 or download the app here: http://onelink.to/hotline-app
- Right to Care Adult, Paediatric and Adolescent HIV Helpline: 082 352 6642

These recommendations are supported by the SAHCS Adult ART guidelines group and the SAHCS Paediatric and Adolescent Committee.

References

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