

Title: A review of the evidence for dolutegravir (DTG)-lamivudine (3TC) (Dovato) for treatment changes in HIV positive adults with suppressed HIV-1 RNA viral load.

Issue Statement

The BC-CfE has requested that the CDET perform an updated review of the evidence for the use of the two-drug antiretroviral regimen, dolutegravir (DTG)-lamivudine (3TC), in adults with HIV infection and suppressed viral load (VL) when a change/switch of the ongoing antiretroviral therapy (ART) is being considered, either for treatment simplification or to reduce toxicities of the ART regimen.

The purpose of the review is to determine whether any changes need to be made to the recommendations contained in the most recent version of the BC-CfE therapeutic guidelines document, dated December 2019.

Background

The current (December 2019) version of the BC-CfE therapeutic guidelines has recommendations for changing to two-drug regimens in patients with ongoing viral suppression, based on the available data at the time. Since then more robust data have become available for one of those two- drug regimen options, DTG-3TC.

Present recommendations

Recommendation #6, page 39:

“In patients with no prior virologic failure, no documented HIV-1 RNA resistance, no HBV co-infection, and viral suppression for longer than 6 months, clinicians may consider switching from three-drug regimen to one of the following recommended two-drug regimens:

dolutegravir/rilpivirine (A-I), a boosted PI/lamivudine (A-II), or dolutegravir/lamivudine (A-II).”

Discussion of evidence, page 41:

“Switching to regimens containing two ARV drugs can be considered, particularly to reduce NRTI-related bone, kidney, and cardiovascular complications. **In patients with no prior virologic failure, no documented HIV-1 RNA resistance, no HBV co-infection, and viral suppression for longer than 6 months, clinicians may consider switching from three-drug**

regimen to one of the following recommended two-drug regimens: dolutegravir/rilpivirine (A-I), or a boosted PI/lamivudine (A-II), or dolutegravir/lamivudine (A-II). Randomized controlled trials found that among patients who are virologically suppressed and have no previous drug resistance, switching to dolutegravir/rilpivirine [7], dolutegravir/lamivudine, or a boosted PI (lopinavir, atazanavir, or darunavir)/lamivudine has been shown to be non-inferior to three-drug regimens in maintaining virologic suppression [13-18]. However, this strategy should be avoided in patients co-infected with HBV.”

Key Clinical Questions

Is there new evidence that will favour changing from a standard three-drug regimen to a two-drug regimen of DTG-3TC in virologically-suppressed adults with HIV infection?

If the current recommendations should be changed, what should be the new recommendations be for switching virologically-suppressed patients to DTG-3TC?

Findings

Changing ART in virologically-suppressed adults to a two-drug regimen could be considered in the following situations [1]:

- To simplify a regimen by reducing pill burden and/or dosing frequency
- To enhance tolerability and/or decrease short- or long-term toxicity
- To prevent or mitigate drug-drug interactions
- To eliminate food or fluid requirements
- To reduce costs

A switch from a standard three-drug regimen to DTG plus 3TC as maintenance strategy in patients with virologic suppression has been examined in a large randomized clinical trial (TANGO), in two small clinical trials, and in observational studies with good success.

Previously-reviewed studies (cited in the Dec. 2019 version of the BC-CfE guidelines) showed maintenance of viral suppression after a switch to DTG/3TC among individuals on first-line ART that contained three or more antiretrovirals. Those studies included the single-arm, open label ANRS 167 LAMIDOL trial, including 104 individuals switched from a first-line triple drug regimen to DTG plus 3TC [2]. In this small study, 97% maintained virologic suppression at 48 weeks after switching to DTG plus 3TC. There were three virological

failures (VF), but neither the M184V nor INSTI mutations were identified. The other study previously reviewed is the ASPIRE trial, an open label randomized multicenter 48-week study that compared a switch to DTG plus 3TC with continuation of current three-drug ART in patients with VL < 50 copies/ml for over one year [3]. In this small study (45 patients in each arm), there was 91% and 89 % suppression (VL <50 copies/mL at week 48) in the DTG+3TC and the three-drug arms, respectively. There was one VF in the DTG+3TC arm but there was no evidence of NRTI or INSTI resistance.

The newer data, not available at the time of writing the Dec. 2019 guidelines, includes the following two studies.

TANGO is an open-label, phase three randomized study that enrolled participants who were on their first ART regimen with VL <50 copies/mL for ≥ 6 months with a 3- or 4-drug TAF- based regimen (TDF to TAF switches were allowed > 3 months before screening) [4]. Participants were randomized to switch to open label DTG plus 3TC (n = 369) or to continue their TAF-based triple therapy (n = 372). Screening regimens included: boosted PI (7%), INSTI (80%) or NNRTI (13%) plus TAF/FTC, equally distributed in both arms. The participants had no history of virologic failure or evidence of resistance to DTG or 3TC and did not have HBV coinfection. Over 90% of the participants were males, and over 80% white. Baseline CD4 cell count was >500 cells/mm³ in 70% of participants. At week 48, switching to DTG plus 3TC was non-inferior to continuing on the current regimen, with 93% of participants in both arms maintaining VL <50 copies/mL. In a *post hoc* analysis, proviral DNA genotyping was conducted retrospectively on baseline whole blood samples. Preexisting archived M184V/I (all detected as mixtures with wild-type) was observed in 4/322 participants in the DTG/3TC group and 3/321 in the TAF-based regimen group. All 7 participants maintained VL <50 copies/mL at all on-treatment time points through week 48. There was a higher proportion of participants who withdrew because of adverse events (AEs) in the DTG/3TC group (n = 13 [3.5%] vs n = 2 [0.5%]). In the DTG/3TC group, AEs that led to withdrawal in ≥ 2 participants were anxiety (n = 3; 0.8%), insomnia (n = 3; 0.8%), weight increase (n = 2; 0.5%), and fatigue (n = 2; 0.5%). Shifts in lipids at week 48 were broadly favorable after switching to DTG/3TC. In addition,

insulin resistance, as measured by HOMA-IR, improved significantly after switching to DTG/3TC. Results from analyses of bone, renal, and inflammation biomarkers were inconclusive.

In an Italian retrospective, observational study, 556 HIV-infected patients on combination ART with plasma VL <50 c/ml were switched to DTG plus 3TC for clinical reasons [5]. Interestingly, this group of patients were more treatment-experienced, had a median of 15.4 years since HIV diagnosis and 11.5 years on ART, and 14% had previous AIDS-defining conditions. Furthermore, 40% had experienced at least one VF before the switch and of those 70% experienced more than one VF with a median of 2 VF. Amongst those with previous VF, 41% had failed TDF, 76% 3TC, 72 % NNRTIs and 4% INSTI (raltegravir or elvitegravir). The median CD4 cell count was 668 cell/mm³ and M184 V mutation was present in 8% of the study participants. At 22 months follow up, there were 12 VF, representing 1.2 VF per 100 PYFU. The presence of previous M184V mutation alone was not predictive of VF, although it was associated with VF among participants who had a shorter time of virological suppression prior to baseline (<88 months).The authors concluded that there was an estimated probability of maintaining viral suppression of 96.5% at 144 weeks of follow up [5].

In summary, we reviewed two new studies including one large randomized controlled trial and a retrospective observational study, in addition to the two smaller studies (previously reviewed in the Treatment Guidelines), where virologically-suppressed individuals switched from standard three-drug ART regimens to DTG+3TC. Of note, in all these studies individuals infected with Hepatitis B (HBV) were excluded. Furthermore, in most of these studies the participants were males (>80%), had high CD4 cell counts, were virologically suppressed for over 6 months at the time of the switch, and had no previously documented genotypic resistance.

After switching to DTG+3TC, viral suppression was maintained in >90 % of participants at 48 weeks in these studies, except for the Italian observational study

where they found 12 VF, representing 1.2 VF per 100 PYFU, mainly in patients who had previously documented 184V mutations.

Of note, in British Columbia screening for 3TC and DTG resistance in virologically-suppressed patients should be done by reviewing historic resistance results from plasma RNA samples and not by performing additional resistance testing from proviral DNA. There is little evidence suggesting that screening for resistance by proviral DNA in virologically-suppressed patients in general (not specific to DTG and 3TC) is predictive of treatment outcome [6,7].

Guidance/Recommendations

Switching to a DTG-3TC regimen is an acceptable option for individuals who have no evidence of resistance to either drug (A-I), and when the following conditions are met:

- Absence of hepatitis B chronic infection
- No previous virologic failure to NRTIs or INSTIs
- Having a VL of <40 copies/ml for over 6 months

DTG-3TC should be avoided in individuals who are pregnant and within 12 weeks post-conception; who are of childbearing potential and planning to become pregnant; or who are of childbearing potential, sexually active, and not using effective contraception.

References

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Revised December 2019
2. Joly V, Burdet C, Landman R, et al. Dolutegravir and lamivudine maintenance therapy in HIV-1 virologically suppressed patients: results of the ANRS 167 trial (LAMIDOL). *J Antimicrob Chemother.* 2019;74(3):739-745. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30476165>.
3. Taiwo BO, Marconi VC, Berzins B, et al. Dolutegravir plus lamivudine maintains human immunodeficiency virus-1 suppression through Week 48 in a pilot randomized trial. *Clin Infect Dis.* 2018;66(11):1794-1797. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29293895>.
4. van Wyk J, Ajana F, Bisshop F, De Wit S, Osiyemi O, Portilla Sogorb J, Routy JP, Wyen C, Ait-Khaled M, Nascimento M, Pappa K, Wang R, Wright J, Tenorio A, Wynne B, Aboud M, Gartland M, Smith K. Efficacy and Safety of Switching to Dolutegravir/Lamivudine Fixed-Dose 2-Drug Regimen vs Continuing a Tenofovir Alafenamide–Based 3- or 4-Drug Regimen for Maintenance of Virologic Suppression in Adults Living With Human Immunodeficiency Virus Type 1: Phase 3, Randomized, Noninferiority TANGO Study. *Clinical Infectious Diseases*, ciz1243, <https://doi.org/10.1093/cid/ciz1243>
5. Baldin G, Ciccullo A, Rusconi S, Capetti A, Sterrantino G, Colafigli M, d'Ettore G, Giacometti A, Cossu MV, Borghetti A, Gennari W, Mussini C, Borghi V, DiGiambenedetto S. Long-term data on the efficacy and tolerability of lamivudine plus dolutegravir as a switch strategy in a multi-centre cohort of HIV-1-infected, virologically suppressed patients. *International Journal of Antimicrobial Agents*, 54, (2019):728-734
6. Boukli N, Boyd A, Collot M, Meynard JL, Girard PM, Morand-Joubert, Utility of HIV-1 DNA genotype in determining antiretroviral resistance in patients with low or undetectable HIV RNA viral loads, *J Antimicrob Chemother*, 73;11 (2018):3129-3136
7. Dauwe K, Staelens D, Vancoillie L, Mortier V, Verhofstede C. Deep Sequencing of HIV-1 RNA and DNA in Newly Diagnosed Patients with Baseline Drug Resistance Showed No Indications for Hidden Resistance and Is Biased by Strong Interference of Hypermutation. *J Clin Microbiol*, 54;6 (2016);1605-1615

Appendix 1: Review Methodology

Type of literature reviewed

Peer-reviewed publications and major conference abstracts

Databases used

Updated Dovato data requested and received April 9-10, 2020 from Mike McKimm, Medical Science Liaison at ViiV Healthcare

Search terms

Dolutegravir and lamivudine

Inclusion criteria

Antiretroviral switch studies in HIV positive adults with virologic suppression