Title: A review of the evidence for dolutegravir (DTG)-lamivudine (3TC) (Dovato) as initial therapy for the treatment of HIV infection in adults

Issue Statement

The BC-CfE Administration 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), for the treatment of HIV infection in adults in the context of initial therapy (or as a switch from a virologically successful regimen, reviewed in a separate document). 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 contains the following wording with respect to two-drug antiretroviral regimens:

In Section II, What to Start With:
A. Recommendations, recommendation 12 (p. 12) reads:
"Two-drug ARV regimens are not generally recommended for initial therapy at this time (B-II). "

B. Discussion of the Evidence, iv. Two-drug ARV regimens (p. 21-22), goes on to read:

"A number of two-drug ARV regimens have been investigated as initial therapy for treatment-naïve individuals [1], but only the fixed-dose combination dolutegravir-lamivudine has been approved by Health Canada [in August 2019] for this indication [2]. In the two identically designed Phase 3 GEMINI studies, a total of 1441 treatment-naïve patients were randomized to receive either once-daily dolutegravir and lamivudine or a once-daily standard three-drug regimen of dolutegravir and emtricitabine-tenofovir DF. In both trials, the two-drug regimen was non-inferior to the three-drug regimen in terms of virologic efficacy at weeks 48 [2] and 96 [3, 4]. Fewer patients reported drug-related adverse events in the two-drug regimen group.

"Dolutegravir-rilpivirine is available as a fixed-dose combination and is approved by Health Canada only for maintenance therapy in patients who are already virologically suppressed; it is not recommended for initial treatment [5]. **Two-drug regimens** are under investigation for the treatment of ARV-naïve patients (see results below) but **are not generally recommended for initial therapy at this time, due to lack of sufficient long-term efficacy data (B-II).**"

The finding that there was a "lack of sufficient long-term efficacy data" to recommend DTG-3TC as initial therapy was made at a time when the 48-week data for the Gemini studies (comparing DTG + 3TC with DTG + emtricitabine-tenofovir DF) had been published [6, as referenced in the Dovato Product Monograph] and the 96-week Gemini data had been

presented at IAS 2019 and ID Week 2019 [3, 4]. After the BC-CfE guidelines document was finalized, the week 96 Gemini data were published in JAIDS [7]. This is the final report of the randomized, double-blind phase of the Gemini studies. An open-label, randomized phase is continuing to 148 weeks, but no data beyond 96 weeks have been published or presented at this time.

Key Clinical Question(s)

Does the CDET consider the publication of the 96-week Gemini data to constitute "sufficient long-term efficacy data" meriting a change in the recommendation for this specific two-drug regimen, dolutegravir-lamivudine?

Findings

The published week 96 Gemini data [7] are consistent with those from the 2019 IAS and ID Week presentations [3,4] cited in the Dec 2019 CfE guideline document. Among 1433 ART-naïve participants in Gemini-1 and Gemini-2, viral load (VL) was<50 copies/mL at week 96 in 86.0% (616/716) of those randomized to receive DTG+3TC and 89.5% (642/717) of those randomized to DTG + emtricitabine-tenofovir DF (FTC-TDF). The 2-drug regimen met the criteria for non-inferiority to the standard 3-drug regimen (-10% margin by Snapshot algorithm). No treatment-emergent resistance was observed among participants who met confirmed virologic withdrawal criteria in either arm. Drug-related adverse events were observed less frequently with DTG + 3TC (9.6%) than with DTG + FTC-TDF (25.0%) [7].

The double-blind phase of the studies will be followed by an open-label phase from week 96 to 148. No data for the use of DTG-3TC as initial therapy beyond 96 weeks are currently available.

Of note, based on the week 96 Gemini data, the most recent guidelines from the US Department of Health and Human Services (DHHS, Jan 2020)[8] and the European AIDS Clinical Society (EACS, Nov 2019)[9] recommend DTG-3TC as an initial regimen, *except for* individuals with pre-treatment VL >500,000 copies/mL or active hepatitis B virus (HBV) coinfection. DTG-3TC is not sufficient treatment for HBV.

Regarding the VL issue, a screening VL >500,000 copies/mL was an exclusion criterion for the Gemini studies, but a small number of participants (N=28, 2%) had a VL >500,000 copies/mL at the baseline visit [6, 7]. Among these, the proportion with VL<50 copies/mL at week 96 favoured the 3-drug regimen: 80% (12/15) with DTG + TDF-FTC vs. 69% (9/13) with DTG + 3TC [7], but the N is too small to reach a definite conclusion regarding the efficacy of DTG + 3TC at very high VL. Among Gemini participants with baseline VL >100,000 copies/mL, results did not differ by treatment arm: 86% (132/153) with 3 drugs vs. 84% (117/140) with 2 drugs had VL<50 copies/mL at 96 weeks [7].

The DHHS [8] also recommends against the use of DTG-3TC for individuals who will initiate antiretroviral therapy (ART) before results of HIV genotypic testing for reverse transcriptase are available. This is consistent with the statement in the Canadian Product Monograph, "Dovato is not recommended for patients with any known or suspected viral

resistance to dolutegravir or lamivudine "[2]. Major resistance mutations were exclusionary for the Gemini studies [6, 7].

The EACS guidelines [9] contain a further recommendation that the use of DTG-3TC be limited to individuals with CD4 >200 cells/mm3. A relatively small number (N=118, 8%) of participants in the Gemini studies had a CD4 count ≤200 cells/mm3 at baseline [6, 7]. Among them, the proportion with VL<50 copies/mL at week 96 again favoured the 3-drug regimen: 87% (48/55) with DTG + TDF-FTC vs. 68% (43/63) with DTG-3TC [7]. This is presumably the justification for the EACS proviso regarding CD4, but the Gemini authors state that the lower response rate among those with lower CD4 counts in the 2-drug arm "was primarily due to non-treatment related reasons" [7]. Reasons unrelated to study treatment (e.g. non-treatment related adverse event, protocol violation, lost to follow-up, withdrew consent) were given for 14 of 20 non-responders in the 2-drug arm, and 6 of 7 non-responders in the 3-drug arm. In the low CD4 subgroup, the rates of VL<50 copies/mL at week 96 in the treatment-related discontinuation = failure analysis were 96.2% (3 drugs) and 92.6% (2 drugs) [7]. The DHHS guidelines [8] do not restrict DTG-3TC use by CD4 cell count.

Another relevant proviso to the use of DTG-3TC would be with respect to its use in people of child-bearing potential. The current BC-CfE guidelines (p. 55) state:

"We recommend against the use of dolutegravir (DTG) for individuals:

a. Who are pregnant and within 12 weeks post-conception (A-II);

b. Who are of childbearing potential and planning to become pregnant (A-II); or

c. Who are of childbearing potential, sexually active, and not using effective contraception (A-III). "

Guidance/Recommendations

Recommendation

DTG-3TC is an acceptable option for first line therapy for ARV naive individuals (A-I) when the following conditions are met:

- HIV drug resistance test must be performed and show no evidence of resistance to DTG or 3TC
- Baseline VL is <500,000 copies/mL, and baseline CD4 count is >200 cells/mm3
- Absence of hepatitis B chronic infection

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

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2. Dovato Product Monograph. ViiV Healthcare, Laval, Quebec. 2019 August 22.
3. Cahn P, Sierra Madero J, Arribas J, et al. Durable efficacy of dolutegravir (DTG) plus lamivudine (3TC) in antiretroviral treatment-naïve adults with HIV-1 infection - 96-week results from the GEMINI studies. Presented at the 10th International AIDS Conference on HIV Science (IAS 2019), 21-24th July 2019, Mexico City, Mexico. Abstract WEAB0404LB.
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5. Juluca Product Monograph. ViiV Healthcare, Laval, Quebec. 2018 August 27.
6. Cahn P, Madero JS, Arribas JR, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naïve adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. *Lancet* 2018. http://dx.doi.org/10.1016/S0140-6736(18)32462-0
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9. European AIDS Clinical Society (EACS). Guidelines version 10.0. November 2019. Available at: https://www.eacsociety.org/files/2019_guidelines-10.0_final.pdf.

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

CROI 2020 abstract database (the only major HIV conference since the previous iteration of the guidelines)

Search terms

Dolutegravir and lamivudine

Inclusion criteria

Studies in antiretroviral treatment-naïve adults