Title: Bictegravir 50mg/emtricitabine 200mg/tenofovir alafenamide 25mg (Biktarvy®) with other antiretrovirals

Issue Statement

Bictegravir 50mg/emtricitabine 200mg/tenofovir alafenamide 25mg (Biktarvy®) is approved by Health Canada for use as a complete regimen for the treatment of HIV-1 infection in adults with no known resistance to the components of the product [Biktarvy® Product Monograph {PM}]. Coadministration of Biktarvy® in combination with other antiretroviral agents is therefore off-label. However, we recognize that such use may be considered under specific circumstances, e.g. in patients with multidrug-resistant HIV-1 who require a multi-class antiretroviral regimen to achieve or maintain virologic suppression. The BC-CfE has received a number of requests for Biktarvy® in combination with other antiretrovirals; therefore, we require a consistent, evidence-based approach to handle such prescriptions.

Background

Biktarvy® is a three-drug fixed-dose combination containing bictegravir 50mg, emtricitabine 200mg, and tenofovir alafenamide 25mg [Biktarvy® PM]. Because Biktarvy® was developed as a complete single-tablet regimen, little information is available regarding its use with concomitant antiretrovirals. The potential safety and efficacy of such regimens could be impacted by drug-drug interactions between the component drugs of Biktarvy® and the concomitant antiretrovirals. The pharmacokinetic properties of tenofovir alafenamide (TAF) and bictegravir are reviewed below. Emtricitabine (FTC) is not expected to contribute significantly to drug-drug interactions with protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs) [University Health Network {UHN}/Toronto General Hospital {TGH}; Liverpool HIV Drug Interactions website {Liverpool}].

Two fixed-dose combinations of FTC and TAF are available and approved by Health Canada [Descovy® PM]:

- FTC/TAF 200/25 mg is recommended when used in combination with NNRTIs, unboosted integrase inhibitors, or unboosted atazanavir.
- FTC/TAF 200/10 mg is recommended when used in combination with a pharmacokinetic booster (ritonavir or cobicistat).

TAF is a substrate of P-gp, BCRP, OATP1B1 and OATP1B3 transporters. It is minimally metabolized by CYP3A [TGH/UHN]. The lower (10 mg) dose of TAF is used in regimens also containing ritonavir or cobicistat to account for the P-gp inhibitory effects of the latter agents, which result in increasing serum tenofovir levels. However, TAF dose adjustment is not possible with the bictegravir/FTC/TAF fixed-dose combination. Since bictegravir is not available in Canada as a single entity, health care providers wishing to prescribe bictegravir with a boosted PI must use the 25 mg dose of TAF in Biktarvy®.

Bictegravir is primarily eliminated by hepatic metabolism, with similar contribution by CYP3A and UGT1A1. Drugs which are strong CYP3A4 and UGT1A1 inducers (e.g. efavirenz, nevirapine, etravirine) can substantially decrease plasma concentrations of bictegravir. Drugs which are strong CYP3A4 and UGT1A1 inhibitors (e.g. atazanavir) may significantly increase bictegravir plasma concentrations [TGH/UHN].

Key Clinical Question(s)

Is coadministration of Biktarvy® with PIs or NNRTIs likely to result in drug-drug interactions that could affect the safety and/or efficacy of either Biktarvy® or the coadministered drug?

Findings

Pharmacokinetic interaction data for Biktarvy® with boosted PIs

In 15 HIV-uninfected volunteers, bictegravir 75 mg + darunavir 800mg/cobicistat 150mg increased bictegravir area under the concentration-time curve (AUC) by 74%, peak concentration (Cmax) by 52%, and trough concentration (Cmin) by 111% [Zhang]. A comparable increase in bictegravir exposure is anticipated when coadministered with darunavir/ritonavir. This change could affect the safety profile of bictegravir; however, Phase 2 data indicate good safety and tolerability of bictegravir across a wide range of plasma exposures [Gallant]. Therefore, this magnitude of change is unlikely to be clinically significant [UHN/TGH].

In 15 HIV-uninfected volunteers, bictegravir 75 mg single dose + atazanavir 300mg/cobicistat 150mg or atazanavir 400mg alone increased bictegravir AUC by 306% and 315%, respectively [Zhang]. A similar magnitude of increase is expected to occur with atazanavir/ritonavir. Coadministration of Biktarvy® with boosted or unboosted atazanavir is not recommended [UHN/TGH; Liverpool].

TAF 10 mg once daily + darunavir/ritonavir 800/100 mg once daily increased tenofovir AUC by 105% and Cmax by 142% [Lawson]. TAF 25 mg (the dose in Biktarvy®) + darunavir/cobicistat increased tenofovir AUC by 224%, increased tenofovir Cmax by 216%, and increased tenofovir Cmin by 221% [Descovy® PM]. These changes could affect the safety profile of TAF. On the other hand, TAF has a favourable clinical safety profile based on a large clinical data set [Gupta]. Caution is recommended when TAF is coadministered with darunavir/cobicistat or darunavir/ritonavir [UHN/TGH; Liverpool].

Pharmacokinetic interaction data for Biktarvy® with NNRTIs

No data are available for coadministration of Biktarvy® with NNRTIs. Etravirine, efavirenz, and nevirapine are inducers of CYP3A4 and are expected to significantly decrease bictegravir exposure; therefore, coadministration of Biktarvy® with etravirine, efavirenz, or nevirapine is not recommended [UHN/TGH; Liverpool].

Coadministration of Biktarvy® with rilpivirine or doravirine would be possible from a pharmacokinetic standpoint [UHN/TGH; Liverpool].

Summary of Recommendations from HIV Drug Interaction Databases

Drug(s) coadministered with Biktarvy®	Liverpool	Toronto	Major drug interaction effect
Darunavir/cobicistat1	CAUTION	CAUTION	↑ tenofovir (and bictegravir)
Darunavir/ritonavir1	CAUTION	CAUTION	↑ tenofovir (and bictegravir)
Atazanavir1	NOT RECOMMENDED	NOT RECOMMENDED	↑↑ bictegravir
Atazanavir/cobicistat1	NOT RECOMMENDED	NOT RECOMMENDED	↑↑ bictegravir
Atazanavir/ritonavir2	NOT RECOMMENDED	NOT RECOMMENDED	↑↑ bictegravir
Efavirenz3	NOT RECOMMENDED	NOT RECOMMENDED	↓ bictegravir
Nevirapine3	NOT RECOMMENDED	NOT RECOMMENDED	↓ bictegravir
Etravirine3	NOT RECOMMENDED	NOT RECOMMENDED	↓ bictegravir
Rilpivirine3	CAUTION	OK	None expected
Doravirine3	CAUTION	OK	None expected

↑ increase in plasma drug levels; ↑↑ large increase in plasma drug levels; ↓ decrease in plasma drug levels

1. Based on pharmacokinetic (PK) data in healthy volunteers.
2. Extrapolation of healthy volunteer PK data for atazanavir/cobicistat and atazanavir alone.
3. Based on known PK properties of the NNRTIs; no clinical PK data available.

Clinical data for Biktarvy® + boosted darunavir

Available clinical information regarding Biktarvy® + boosted darunavir is limited to a retrospective cohort reported at a conference in November 2019 [Hill]. Forty-five highly treatment-experienced patients received Biktarvy® + darunavir/cobicistat and 1 received darunavir/ritonavir for 24-48 weeks (mean 312 days); 31/46 (67%) had resistance to ≥2 antiretroviral drug classes. Viral suppression (<200 copies/mL) was maintained at 24 weeks in 25/26 (96%) patients who were suppressed at baseline, and achieved in 12/17 (70.6%) of those who were not suppressed at baseline. Plasma drug levels were not measured. The authors concluded that the regimen was "safe and well-tolerated with no significant safety concerns", although 4 patients (8.7%) discontinued the regimen due to side effects: 1 rash, 1 diarrhea, 2 unspecified.

Guidance/Recommendations

Coadministration of Biktarvy® with darunavir/cobicistat, darunavir/ritonavir, doravirine, or rilpivirine is off-label, but may be considered an option in selected patients who require treatment with a multi-class antiretroviral regimen, and for whom more well-established regimens are not appropriate. Close monitoring of viral load, renal function, and potentially

bone health is advised due to limited clinical data supporting the safety or efficacy of these regimens.

Coadministration of Biktarvy® with atazanavir (with or without ritonavir), etravirine, efavirenz, or nevirapine is not recommended due to clinically significant drug interactions which could affect the safety or efficacy of the regimen.

References

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Appendix 1: Review Methodology

Type of literature reviewed

HIV Drug Interaction websites

Databases used

Liverpool HIV Drug Interactions website, https://www.hiv-druginteractions.org.

UHN/Toronto General Hospital HIV/HCV Drug Therapy Guide, https://hivclinic.ca/wp-content/plugins/php/app.php.

Search terms

Bictegravir, tenofovir alafenamide, emtricitabine

Inclusion criteria

All

Appendix 2: EACS Poster

Hill L, Momper J, Abulhosn K, Ballard C, Young M. Efficacy and Safety of Bictegravir/Emtricitabine/Tenofovir Alafenamide in Combination with Boosted Darunavir in Treatment Experienced Patients with HIV. 17th European AIDS Conference. November 6-9, 2019. Basel, Switzerland. Poster #PE2/56.

Appendix 2: EACS POSTER

UC San Diego Health

Efficacy and Safety of Bictegravir/Emtricitabine/Tenofovir Alafenamide in Combination with Boosted Darunavir in Treatment Experienced Patients with HIV

Lucas Hill[1], Jeremiah Momper[1], Kari Abulhosn[1], Craig Ballard[1], Maile Young[1]
[1] University of California San Diego

Background

- Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) has been studied in treatment naïve people living with HIV (PLWH) and in switch therapy in suppressed patients[1,2]
- Minimal data using B/F/TAF in treatment experienced PLWH with antiretroviral (ARV) resistance
- Boosted darunavir (DRV), commonly used in treatment experienced PLWH inhibits CYP3A4 and p-glycoprotein
- Bictegravir is a substrate of CYP3A4 and TAF of p-glycoprotein and combination with boosted DRV may introduce drug interactions.[3]

Objective

- To evaluate the safety and efficacy of B/F/TAF in combination with boosted DRV in a real-world cohort

Methods

- Retrospective cohort analysis of patients started on B/F/TAF in combination with boosted darunavir between 2/2018 and 6/2019 followed for a minimum of 24 weeks and up to 48 weeks

Results

Safety and Tolerability

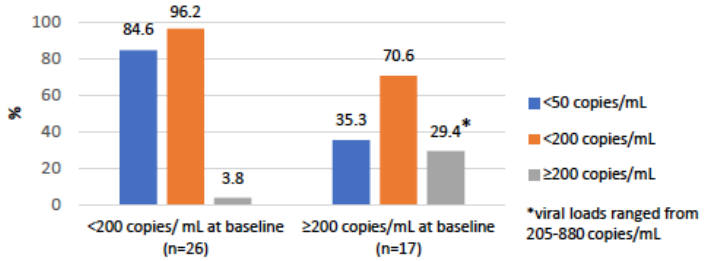
- 46 patients met criteria, of which 7 discontinued the regimen
- Mean time to discontinuation was 176 days
- Reasons for discontinuation included side effects of diarrhea (1) and rash (1), drug interaction (2), ongoing low level viremia (2), and simplification (1)
- No significant changes in weight or BMI over study period including patients not on INSTI at baseline (8)

Results

Table 1: Demographics, virologic, and treatment/resistance history for study population (n=46)

Mean Age (95% CI)	52 (49-55)
Gender (%)	
Male	36 (78.3)
Female	8 (17.4)
Transgender	2 (4.3)
Race (%)	
White	28 (60.9)
Black	5 (10.9)
Asian	1 (2.2)
Other	12 (26.1)
Ethnicity (%)	
Hispanic	16 (34.8)
Non-Hispanic	30 (65.2)
Pharmacokinetic enhancer (%)	
Cobicistat	45 (97.8)
Ritonavir	1 (2.2)
ARVs in prior regimen (mean, 95%CI)	3.9 (3.7-4.1)
VL<50 copies/mL at time of switch (%)	27 (58.7)
VL <200 copies/mL at time of switch (%)	29 (63.0)
CD4+ T-cell count (cells/mm3) (mean, 95% CI)	416 (337-495)
Number of previous ARVs (mean, 95% CI)	10.7 (9.5-11.8)
Number of ARV class resistance (%)	
Unknown	5 (10.9)
0	4 (8.7)
1	6 (13.0)
2	18 (39.1)
3	12 (26.1)
4	1 (2.2)
Documented integrase inhibitor resistance (%)	4 (8.7)
Reason for regimen change (%)	
Side effects	4 (8.7)
Poor adherence/resistance	17 (37.0)
Low level/ongoing viremia	5 (10.9)
Regimen simplification	18 (39.1)
Drug interaction	2 (4.3)
Follow up time (days) (mean, 95% CI)	312 (280-345)

Figure 1: Week 24 virologic outcomes



- All patients with INSTI resistance maintained (2) or achieved (2) VL <50 copies/mL

Figure 2: Change in mean serum creatinine over time

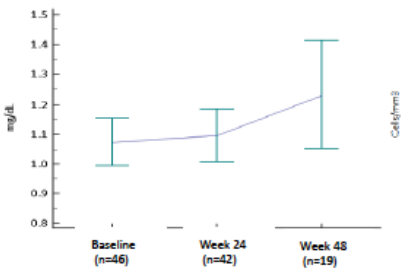
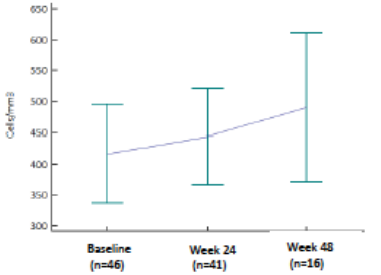


Figure 3: Change in mean CD4 count over time



Conclusion

- In a highly treatment experienced population in which 67% of patients had resistance to at least 2 antiretroviral classes B/F/TAF in combination with boosted DRV was efficacious in maintaining viral suppression as well as achieving viral suppression in 70.6% of those not previously suppressed
- B/F/TAF with boosted DRV was well tolerated with no significant safety concerns

References

[1] Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection: a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Lancet. 2017;390:2063-2072..
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