Biktarvy® (BIC/FTC/TAF) Low-Level Viremia

This document is in response to your request for information regarding Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide [BIC/FTC/TAF]) and the occurrence of persistent low-level viremia (LLV) while taking BIC/FTC/TAF.

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Real-World Data on LLV in Patients Receiving BIC/FTC/TAF

Retrospective Cohort Study

Study design and demographics[1]

A single-center, retrospective cohort study was conducted among PWH aged ≥20 years who received HIV care in Taiwan between January 2016 and September 2021. Patients receiving stable ART with HIV-1 RNA <50 c/mL for ≥6 months before switching to BIC/FTC/TAF (BIC cohort; n=862) or DTG plus 1 to 2 NRTIs (DTG cohort; n=623) were included in the study (Table 1). Patients who had documented genotypic resistance to BIC or DTG, used DTG in combination with a PI or NNRTI at baseline, or did not have HIV-1 RNA VL results within one year of switching were excluded; however, patients with NRTI RAMs were allowed. There were 155 patients who met the inclusion criteria for, and were included in, both cohorts; however, a sensitivity analysis that excluded those patients was performed to avoid potential confounding.

The primary endpoint was the incidence rate of LLV (HIV-1 RNA 50–200 c/mL). Secondary endpoints included the incidence rates of VF (HIV-1 RNA ≥1000 c/mL) in each cohort and factors associated with the development of LLV and VF. Patients in both cohorts were followed from the day of the ART switch through Month 18 post-switch. In accordance with national HIV treatment guidelines on patients receiving a stable ART, VL and CD4 cell counts were assessed every 3 to 6 months.

Table 1. Baseline Demographics and Disease Characteristics (Chen et al)[1]

Key Demographics and Characteristics		BIC Cohort (n=862)	DTG Cohort (n=623)	*P*-Value
Age, mean (SD), years		39.9 (10.5)	41.2 (10.7)	0.02
Male sex, n (%)		841 (97.6)	597 (95.8)	0.06
VL at switch, median (IQR), log_{10} c/mL		1.3 (1.3–1.3)	1.3 (1.3–1.3)	-
Undetectable at <20 c/mL, n (%)		794 (92.1)	596 (95.7)	0.006
CD4 cell count at switch, mean (SD), cells/mm^3		688 (256)	673 (260)	0.31
Duration of viral suppression before switch, median (IQR), years		4.7 (2.8–7)	4.3 (2.5–6.7)	0.01
PWH with available genotypic resistance results, n (%)		493 (57.2)	244 (39.2)	-
PWH with any NRTI-associated RAM, n/N (%)		85/493 (17.2)	78/244 (32)	<0.001
PWH with M184I/V mutation, n/N (%)		43/493 (8.7)	49/244 (20.1)	<0.001
NRTI at switch, n (%)	ABC + 3TC	N/A	462 (74.2)	-
	TDF + FTC	N/A	141 (22.6)	-
	3TC alone	N/A	15 (2.4)	-
ARV agents before switch, n (%)	INSTI-based regimens	729 (84.6)	147 (23.6)	<0.001
	EVG	596 (69.1)	23 (3.7)	
	DTG	128 (14.8)	N/A	
	PI-based regimens	78 (9)	361 (57.9)	
	NNRTI-based regimens	55 (6.4)	115 (18.5)	
	RAL	5 (0.6)	124 (19.9)	
	BIC	N/A	0	

Abbreviations: 3TC=lamivudine; ABC=abacavir; ARV=antiretroviral; EVG=elvitegravir; RAL=raltegravir; TDF=tenofovir disoproxil fumarate.

Results

A total of 27 VL tests (1.7%) in the BIC cohort and 24 (1.2%) in the DTG cohort met the criteria for LLV (HIV-1 RNA 50–200 c/mL), with an incidence rate of 6.2 per 100 PYFU and 3.8 per 100 PYFU in the BIC and DTG cohorts, respectively (IRR, 1.63; 95% CI: 0.9–2.95; *P*=0.08). After adjusting for the differences in baseline demographics and disease characteristics between the two cohorts, the adjusted IRR for LLV was 1.27 (95% CI: 0.69–2.34; *P*=0.44).[1] In the sensitivity analysis, which excluded the 155 patients included in both cohorts, the incidence rate of LLV events was 6.7 per 100 PYFU in the BIC cohort and 3.8 per 100 PYFU in the DTG group (unadjusted IRR, 1.75; 95% CI: 0.95–3.22).[2]

In a multivariate regression analysis, the duration of viral suppression before switching (aOR per 1-year increase, 0.87; 95% CI: 0.77–0.99) and VL at switch (aOR per 1 c/mL increase, 1.08; 95% CI: 1.03–1.13) were significantly associated with the development of LLV events. There was no statistically significant association between the choice of core agent (ie, BIC vs DTG) and the development of a LLV event (aOR, 1.41; 95% CI: 0.77–2.59).[1]

Over the course of the study, 3 patients in the BIC cohort and 6 patients in the DTG cohort experienced VF with HIV-1 RNA levels between 1240 and 156,000 c/mL; incidence rates were 0.69 per 100 PYFU and 0.95 per 100 PYFU, respectively (unadjusted IRR, 0.72; 95% CI: 0.12–3.39).[1] The incidence rate of VF in the sensitivity analysis was 0.83 per 100 PYFU in the BIC cohort and 0.95 per 100 PYFU in the DTG cohort (unadjusted IRR, 0.87; 95% CI: 0.14–4.09).[2] Genotypic resistance testing had been performed in 3 patients who had VF, and no RAMs to NRTIs or INSTIs were detected. Eight of the 9 patients who experienced VF continued the same ART and were subsequently resuppressed. None of the factors included in the analysis, including the core agent and the development of LLV events, were associated with subsequent VF.[1]

A subgroup analysis was conducted among patients with available genotypic resistance data before switch to assess the association of preexisting NRTI RAMs and the occurrence of LLV events. The incidence rate of LLV was 5.3 per 100 PYFU among the 124 patients with a GSS <2 to their NRTI regimens and 5.1 per 100 PYFU among the 613 patients who were receiving fully active NRTIs with a GSS of 2 (IRR, 1.04; 95% CI: 0.31–2.85; *P*=0.89). There was no significant difference between subgroups in the incidence rates of VF: GSS <2, 1.1 per 100 PYFU; GSS of 2, 0.8 per 100 PYFU (IRR, 1.39; 95% CI: 0.03–17.3; *P*=0.37). The incidence rate of LLV events among the 92 patients with archived M184V mutation before switch was 6 per 100 PYFU, compared with 5 per 100 PYFU among the 645 patients without an M184V mutation (IRR, 1.21; 95% CI: 0.3–3.58; *P*=0.69).[1]

Safety data were not reported.

Guidelines on LLV and VF

The US Department of Health and Human Services recommendations regarding VF, including persistent LLV, in treatment-experienced adults and adolescents infected with HIV-1 can be accessed using the following link: https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/virologic-failure?view=full.

References

1. Chen GJ, Sun HY, Chen LY, et al. Low-level viraemia and virologic failure among people living with HIV who received maintenance therapy with co-formulated bictegravir, emtricitabine and tenofovir alafenamide versus dolutegravir-based regimens. *Int J Antimicrob Agents.* 2022;60(3):106631.
2. Chen GJ, Sun HY, Chen LY, et al. Low-level viraemia and virologic failure among people living with HIV who received maintenance therapy with co-formulated bictegravir, emtricitabine and tenofovir alafenamide versus dolutegravir-based regimens.[Supplement]. *Int J Antimicrob Agents.* 2022;60(3):1-5.

Abbreviations

ART=antiretroviral therapy
aOR=adjusted odds ratio
BIC=bictegravir
c/mL=copies/mL
CD4=cluster of differentiation 4
DTG=dolutegravir
IRR=incidence rate ratio
FTC=emtricitabine
GSS=genotypic susceptibility score
INSTI=integrase strand transfer inhibitor
LLV=low-level viremia
NNRTI=non-nucleos(t)ide reverse transcriptase inhibitor
NRTI=nucleos(t)ide reverse transcriptase inhibitor
OR=odds ratio
PI=protease inhibitor
PWH=people with HIV
PYFU=person-years of follow-up
RAM=resistance-associated mutation
TAF=tenofovir alafenamide
VF=virologic failure
VL=viral load

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Biktarvy US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi.

Follow-Up

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FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🖱 www.accessdata.fda.gov/scripts/medwatch

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