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Bixlenvo™ (bictegravir/lenacapavir) Pharmacokinetics

This document is in response to your request for information regarding Bixlenvo™ (bictegravir/lenacapavir [BIC/LEN]) and its pharmacokinetics (PK).

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The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/BIXLENVO/BIXLENVO_pi; www.gilead.com/-/media/files/pdfs/medicines/hiv/SUNLENCA/SUNLENCA_pi.

Summary

Product Labeling[1]

BIC/LEN is indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current ARV regimen in those who are VS (HIV-1 RNA <50 c/mL) on a stable ARV regimen with no known or suspected resistance to the individual components of BIC/LEN.

The PK properties of BIC/LEN are provided in Table 1. The PK parameter estimates of the components of BIC/LEN following administration of the recommended BIC/LEN treatment regimen with or without food in adults with HIV-1 are provided in Table 2.

BIC/LEN PK Data From Clinical Studies

The PK of BIC and LEN were assessed using data from ARTISTRY-1 and ARTISTRY-2, two phase 3 studies that are evaluating the efficacy and safety of BIC/LEN in VS PWH.[2]

- With intensive PK sampling in ARTISTRY-1, the observed mean steady-state C_{trough} concentrations at dosing at up to 8 hours post-dose were approximately 26- to 30-fold >IQ1 of 162 ng/mL for BIC and approximately 21- to 29-fold above the IQ1 of 3.87 ng/mL for LEN. In ARTISTRY-1 and ARTISTRY-2, plasma C_{trough} BIC and LEN concentrations were above the IQ1 at Weeks 24, 36, and 48.[2]

A popPK analysis used data from 11 studies, including ARTISTRY-1 and ARTISTRY-2, to assess LEN exposure following ≤7 days of missed BIC/LEN maintenance doses, and 99.3% and 98% of virtual participants on BIC/LEN under fasted and fed conditions, respectively, were projected to have LEN plasma concentrations >IQ1. All 7 participants in ARTISTRY-1 and ARTISTRY-2 who missed >7 consecutive doses and underwent LEN reloading maintained virologic suppression at Week 48, the last available measure, or after LEN reloading.[3]

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Product Labeling[1]

Indications and Use

BIC/LEN is indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current ARV regimen in those who are VS (HIV-1 RNA <50 c/mL) on a stable ARV regimen with no known or suspected resistance to the individual components of BIC/LEN.

Dosage and Administration

Recommended dosage

The BIC/LEN dosing schedule in adults requires a two-day initiation regimen of BIC/LEN tablets plus LEN tablets taken orally, followed by a maintenance regimen of one tablet of BIC/LEN taken orally once daily. BIC/LEN must be taken with LEN during the two-day initiation period. BIC/LEN and LEN tablets may be taken with or without food.

Clinical Pharmacology

PK

The PK properties of BIC/LEN are provided in Table 1. The PK parameter estimates of the components of BIC/LEN following administration of the recommended BIC/LEN treatment regimen with or without food in adults with HIV-1 are provided in Table 2.

Table 1. PK Properties of the Components of BIC/LEN[1]

Parameter			BIC	LEN
Absorption	T_{max},[a] hours		2	4
	Effect of high-fat meal (relative to fasting)[b]	AUC ratio	1.12 (1.01, 1.25)	0.67 (0.53, 0.83)
		C_{max} ratio	1.16 (1.07, 1.26)	0.86 (0.67, 1.09)
Distribution	% bound to human plasma proteins		>99	>98.5
	Blood-to-plasma ratio		0.64[c]	0.5 to 0.7[d]
Elimination	$T_{1/2}$[a]		19.3 to 21 hours	10.6 to 11.5 days
Metabolism	Metabolic pathway(s)		CYP3A UGT1A1 (minor)	
Excretion	Major route of elimination		Metabolism	Excretion of unchanged drug into feces
	% of dose excreted in urine[e]		35	<1
	% of dose excreted in feces[e]		60.3	76

Abbreviations: ^{14}C=carbon-14; AUC=area under the concentration-time curve; $T_{1/2}$=elimination half-life; T_{max}=time required to reach maximum plasma concentration; UGT1A1=uridine diphosphate glucuronosyl transferase family 1 member A1.

[a]Median values presented following administration of BIC/LEN with or without food.

[b]Values refer to geometric mean ratio (high-fat meal/fasting) in PK parameters and (90% CI). A high-fat meal is approximately 800 kcal, 50% fat.

[c]In vitro blood-to-plasma concentration ratio of BIC.

[d]Values reflect the blood-to-plasma ratio of LEN following a single dose of IV administration of ^{14}C LEN through 336 hours postdose.

[e]Dosing in mass balance studies: single dose oral administration of ^{14}C BIC 100 mg, and single dose IV administration of ^{14}C LEN 20 mg.

Table 2. PK Parameter Estimates[a] of BIC and LEN Following Oral Administration of the BIC/LEN Recommended Treatment Regimen With or Without Food in Adults With HIV-1[1]

Parameter, Mean (%CV)	Initiation Regimen[a,b]	Maintenance Regimen[c]	
	LEN	BIC	LEN
C_{max}, ng/mL	95.7 (186)	8600 (29)	99.3 (171)
AUC_T, ng*h/mL	2080 (182)	154,000 (33.3)	2360 (178)
C_{trough},ng/mL	86.5 (185)	4660 (39.8)	96.6 (174)

[a]Empirical Bayes estimate derived PK parameters from popPK analyses.
[b]Exposures corresponding to Day 2 of the recommended treatment regimen (N=806).
[c]Steady-state exposures from popPK analyses in ARTISTRY-1 and ARTISTRY-2 (N=754).

BIC/LEN PK Data From Clinical Studies

ARTISTRY-1 and ARTISTRY-2: Phase 3 Studies

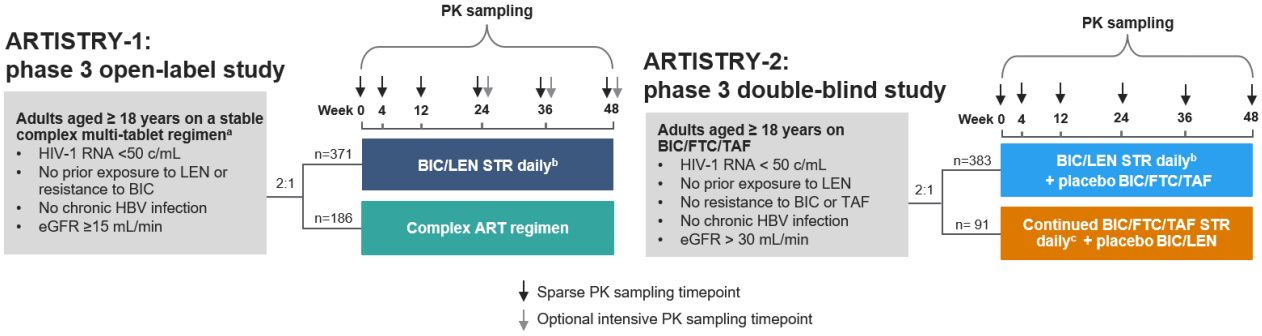
ARTISTRY-1 is an ongoing, randomized, multicenter, open-label, phase 2/3 study (NCT05502341) that is evaluating the efficacy and safety of switching to BIC/LEN vs continuing their ART regimen in PWH who were receiving a complex ART regimen.[4,5]

ARTISTRY-2 is an ongoing, randomized, multicenter, double-blind, active-controlled, phase 3 study (NCT06333808) that is evaluating the efficacy and safety of switching from BIC/FTC/TAF to STR BIC/LEN 75 mg/50 mg vs continuing BIC/FTC/TAF in VS PWH. After the randomized period, participants could continue in the open-label extension phase and receive BIC/LEN.[6]

Study designs and demographics[2]

An analysis was conducted to describe the PK of BIC and LEN to support the observed safety and efficacy of BIC/LEN in the ARTISTRY studies. In both studies, sparse PK blood samples were collected pre- and/or post-dose from participants in the BIC/LEN groups at specified weekly intervals from baseline through Week 48 (Figure 1). In addition, intensive PK sampling was conducted in a subset of participants in the BIC/LEN group of ARTISTRY-1 at a steady-state visit at Week 24, 36, or 48 (Figure 1). Concentrations of BIC and LEN were determined using bioanalytical assays.

Figure 1. ARTISTRY-1 and ARTISTRY-2: Study Designs and PK Sampling[2]



Abbreviations: NNRTI=non-nucleos(t)ide reverse transcriptase inhibitor; NRTI=nucleos(t)ide reverse transcriptase inhibitor; PI=protease inhibitor.
[a]Participants were on a complex ART regimen due to ARV resistance, intolerance, drug-drug interactions, or contraindications to existing STRs. A complex multi-tablet regimen was defined as a regimen that contained any of the following: a boosted PI or NNRTI plus ≥1 other third agent from a class other than NRTI, or

≥2 pills/day, or requiring dosing more than daily, or parenteral agent(s) (excluding a complete long-acting injectable regimen) as well as oral agents.
[b]BIC/LEN 75/50 mg, with oral loading dose of LEN 600 mg on Days 1 and 2 of treatment.
[c]Participants were given placebo to match oral LEN on Days 1 and 2 of treatment.

Table 3. ARTISTRY-1 and ARTISTRY-2: Baseline Demographics and Disease Characteristics of BIC/LEN Participants With Sparse PK Data[2]

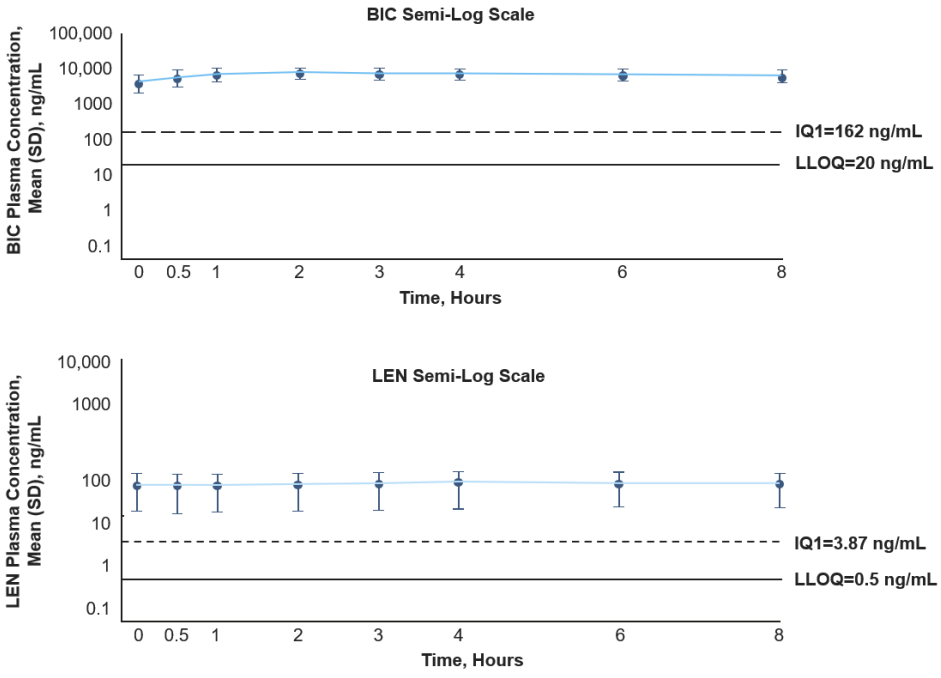
Key Demographics and Characteristics	ARTISTRY-1 (n=371)	ARTISTRY-2 (n=383)
Age, median (Q1, Q3), years	60 (55, 66)	47 (38, 58)
Male sex at birth, %	82.7	82
Body weight, median (Q1, Q3), kg	79.6 (68.7, 90)	81.1 (71.8, 92.8)
BMI, median (Q1, Q3), kg/m^2	26.1 (23.1, 29.9)	26.8 (24.2, 30.3)
$CrCl_{CG}$, median (Q1, Q3), mL/min	82.9 (66.4, 103.2)	101.4 (83.9, 117)
Prior ARV medications, median (Q1, Q3), n	7 (3, 14)	Not available

Abbreviations: CG=Cockcroft-Gault; Q=quartile.

PK data[2]

The observed mean steady-state C_{trough} concentrations at dosing and at all assessed time points thereafter were approximately 26- to 30-fold above the IQ1 of 162 ng/mL for BIC and approximately 21- to 29-fold above the IQ1 of 3.87 ng/mL for LEN (Figure 2).

Figure 2. ARTISTRY-1: BIC and LEN Concentration-Time Profiles[2]



Abbreviation: LLOQ=lower level of quantitation.
Note: Intensive serial PK sampling collection was performed at Week 24, 36, or 48. Mean concentration values that were ≤LLOQ are not shown in the figure.

The steady-state BIC and LEN PK data from ARTISTRY-1 and ARTISTRY-2 are presented in Table 4.

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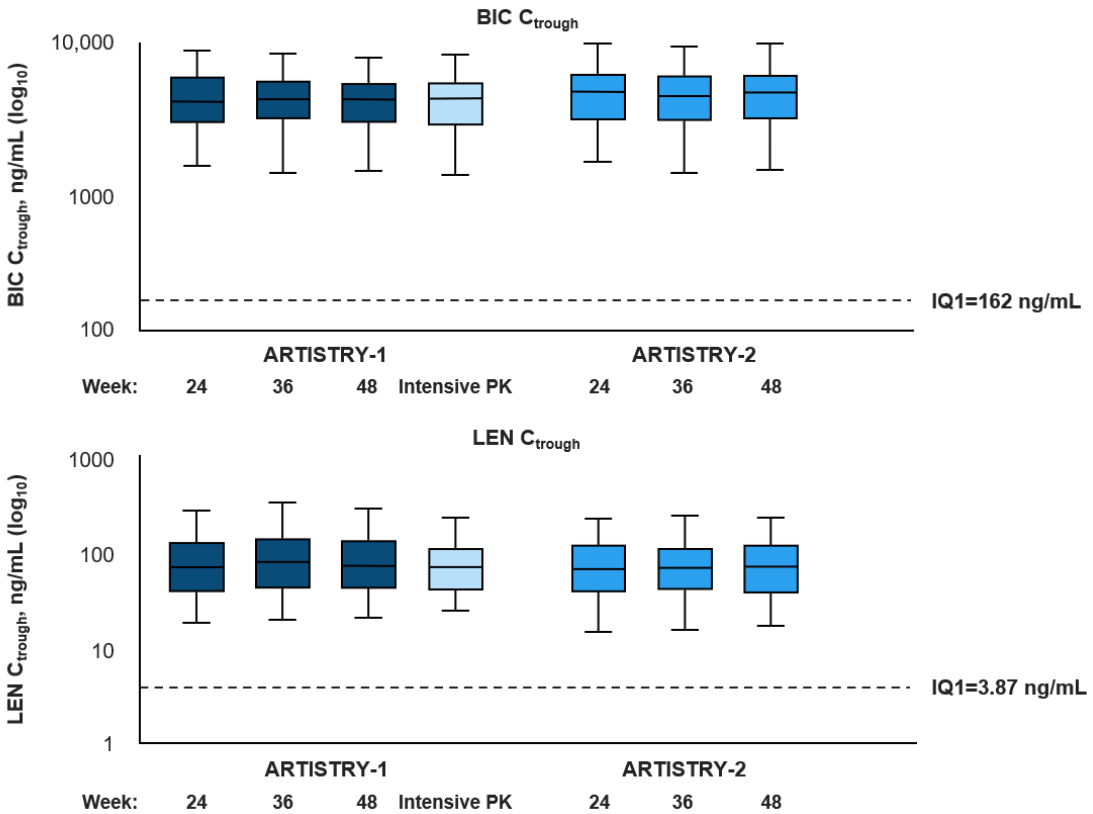
Table 4. ARTISTRY-1 and ARTISTRY-2: Steady-State PK Data for BIC and LEN[2]

Parameter				C_{trough}, Mean (%CV), ng/mL	C_{max}, Mean (%CV), ng/mL	AUC_T, Mean (%CV), h·ng/mL
BIC	ARTISTRY-1	Intensive PK		4190 (52.6), n=89	8670 (35), n=97	140,000 (40.6), n=89
		Sparse PK	Wk 24	4480 (55.4), n=264	-	-
			Wk 36	4400 (53.4), n=292	-	-
			Wk 48	4290 (49.6), n=211	-	-
	ARTISTRY-2	Sparse PK	Wk 24	4880 (53.7), n=314	-	-
			Wk 36	4630 (53.4), n=305	-	-
			Wk 48	4760 (50.4), n=191	-	-
LEN	ARTISTRY-1	Intensive PK		81.5 (70.8), n=51	107 (76.2), n=97	2130 (69.2), n=51
		Sparse PK	Wk 24	103 (104), n=267	-	-
			Wk 36	113 (109), n=293	-	-
			Wk 48	106 (100), n=213	-	-
	ARTISTRY-2	Sparse PK	Wk 24	94.8 (109), n=313	-	-
			Wk 36	89.2 (86.5), n=305	-	-
			Wk 48	94.8 (106), n=225	-	-

Note: PK data snapshots were taken on September 19, 2025 for ARTISTRY-1 and October 17, 2025 for ARTISTRY-2. BIC/LEN was administered with an oral loading dose of LEN 600 mg on Days 1 and 2. Intensive PK data were analyzed using standard non-compartmental analysis.

Plasma C_{trough} BIC and LEN concentrations from ARTISTRY-1 and ARTISTRY-2 were above each respective IQ1 at all assessed time points (Figure 3).

Figure 3. ARTISTRY-1 and ARTISTRY-2: Plasma BIC and LEN C_{trough} Concentrations[2]



Note: Box plots depict median (horizontal line), IQR (box), and 5th through 95th percentiles (whiskers).

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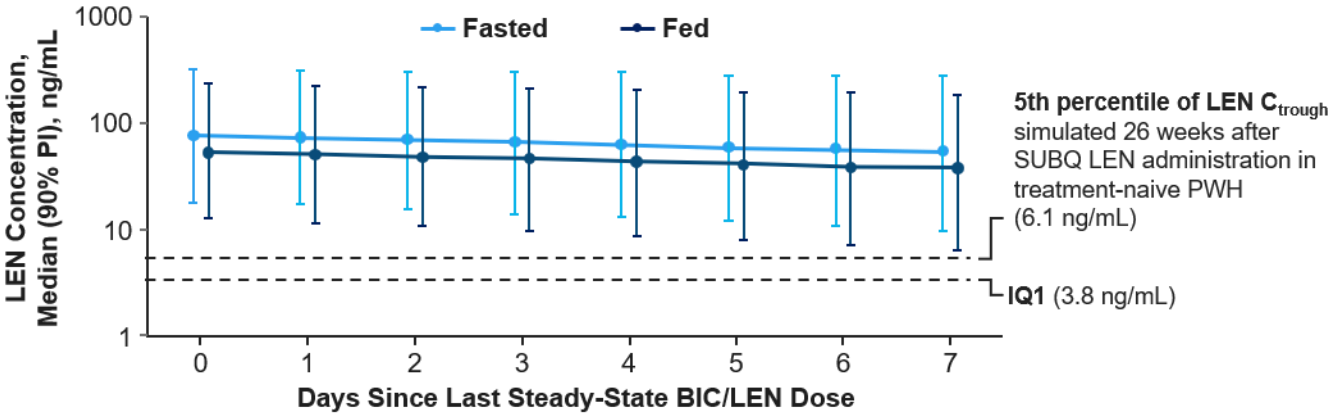
PK Model of LEN Reloading After Missed Doses[3]

PK and clinical data supporting reloading recommendations

A popPK analysis used data from 11 studies (N=1295), including ARTISTRY-1 and ARTISTRY-2, to assess LEN exposure following ≤7 days of missed BIC/LEN maintenance doses in 10,000 virtual individuals. A full fixed-effect covariate model estimated the effects of various covariates (ie, sex, Japanese ethnicity, body weight, kidney function, and food effect) on LEN PK. The study also evaluated LEN reloading after >7 days of missed BIC/LEN maintenance doses in ARTISTRY-1 and ARTISTRY-2 and virologic outcomes at Week 48 in participants who required LEN reloading.

After 7 days of consecutively missed BIC/LEN maintenance doses, simulations showed LEN C_{trough} medians (90% prediction interval) of 55.1 (9.86, 273) ng/mL under fasted conditions and 38.9 (6.49, 183) ng/mL under fed conditions, both of which exceed the IQ1 for LEN (3.8 ng/mL; Figure 4).

Figure 4. Projected Median LEN Concentrations Up to 7 Missed BIC/LEN Maintenance Doses (Arora et al)[3]



At 7 days after the last steady-state BIC/LEN maintenance dose, 99.3% and 98% of virtual participants on BIC/LEN under fasted and fed conditions, respectively, were projected to have LEN plasma concentrations >IQ1.

In ARTISTRY-1 and ARTISTRY-2, 7 participants missed >7 consecutive doses and reinitiated BIC/LEN for LEN reloading per the study protocols. All 7 participants maintained virologic suppression at Week 48, the last available measure, or after LEN reloading (Table 5).

Table 5. ARTISTRY Studies: Clinical Outcomes of Participants Who Underwent LEN Reloading After Missing >7 Consecutive Maintenance Doses (Arora et al)[3]

Participant	Study	Study Days of LEN Reloading	HIV-1 RNA at LEN Reloading	HIV-1 RNA at Week 48	Study Drug Discontinued
1	ARTISTRY-1	153 and 154	Not assessed	Undetectable	No
2	ARTISTRY-1	176 and 177	Not assessed	Undetectable	No
3	ARTISTRY-1	258 and 259 439 and 440[a]	Undetectable Undetectable	<20 c/mL	No
4	ARTISTRY-2	43 and 44	Undetectable	Undetectable	Yes[b]

Participant	Study	Study Days of LEN Reloading	HIV-1 RNA at LEN Reloading	HIV-1 RNA at Week 48	Study Drug Discontinued
5	ARTISTRY-2	54 and 55	Not assessed	Undetectable	No
6	ARTISTRY-2	111 and 112	Undetectable	No data[c]	Yes[c]
7	ARTISTRY-2	343 and 344[d]	Not assessed	<20 c/mL	No

[a]Occurred after Week 48; HIV-1 RNA was undetectable at Week 72 (Study Day 502).
[b]Participant decided to discontinue study drug.
[c]HIV-1 RNA was undetectable at the last available viral load assessment at Week 24 (Study Day 174). The participant discontinued study drug per investigator's decision before Week 48.
[d]Occurred after Week 48; HIV-1 RNA was <20 c/mL at Week 60 (Study Day 427).

References

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3. Arora P, Saqr A, Sklar P, Marathe DD, Johnston C. Pharmacokinetic and Clinical Data Supporting the LEN Reloading Strategy for BIC/LEN Single-Tablet Regimen Dosing in the ARTISTRY Studies [Poster P-1019]. Paper presented at: IDWeek; October 21-24, 2026; Washington, DC.
4. Mounzer K, Slim J, Ramgopal M, et al. Efficacy and Safety of Bictegravir Plus Lenacapavir: 48-Week Outcomes in People With HIV-1 Who Are Virologically Suppressed on Complex Antiretroviral Regimens at Baseline. *Open Forum Infectious Diseases.* 2025;12(11):ofaf615.
5. Mounzer K, Slim J, Ramgopal M, et al. Efficacy and Safety of Switching to Daily Bictegravir Plus Lenacapavir From a Complex HIV Treatment Regimen: A Randomized, Open-Label, Multicenter Phase 2 Study (ARTISTRY-1). *Clin Infect Dis.* 2025;80(4):881-888.
6. Meissner EG, Ramgopal M, Ruane PJ, et al. Safety and efficacy of switching to bictegravir-lenacapavir versus continuing bictegravir-emtricitabine-tenofovir alafenamide in virologically suppressed people with HIV-1 (ARTISTRY-2): a double-blind, multicentre, randomised, controlled, phase 3, non-inferiority trial. *Lancet HIV.* 2026;13(8):e538-e547.

Abbreviations

ART=antiretroviral therapy
ARV=antiretroviral
AUC_T=area under the concentration-time curve over the dosing interval
BIC=bictegravir
c/mL=copies per mL
C_{max}=maximum observed concentration
C_{trough}=lowest observed drug concentration
CV=coefficient of variation
FTC=emtricitabine
IQ1=inhibitory quotient 1
LEN=lenacapavir
PK=pharmacokinetic(s)
popPK=population pharmacokinetics
PWH=people with HIV-1
STR=single-tablet regimen
TAF=tenofovir alafenamide
VS=virologically suppressed

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Bixlenvo and Sunlenca US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/BIXLENVO/BIXLENVO_pi; www.gilead.com/-/media/files/pdfs/medicines/hiv/SUNLENCA/SUNLENCA_pi.

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