BICTEGRAVIR DISTRIBUTION AND BICTEGRAVIR/FTC/TAF ACTIVITY IN GENITAL TRACT AND RECTUM (PreEC/RIS 58)

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BACKGROUND

Antiretroviral (ARV) distribution in the genital tract (GT) and rectum is required to suppress HIV replication within these compartments.

In addition, understanding HIV decay kinetics in these sites may assist in predicting risk of sexual transmission after initiating an ARV regimen.

The new second generation integrase strand transfer inhibitor bictegravir (BIC), in combination with emtricitabine and tenofovir alafenamide (BIC/FTC/TAF), has shown high efficacy in large phase III randomized clinical trials.

However, pharmacokinetics of BIC as well as HIV decay in the GT and rectum with BIC/FTF/TAF have not yet been described.

OBJECTIVES

The objectives of this study were:

To evaluate HIV-1 RNA decay kinetics in seminal plasma (SP), cervicovaginal fluid (CVF) and rectal fluid (RF) in ARV-naive male and female individuals living with HIV initiating a first ARV regimen with BIC/FTC/TAF.

To determine BIC concentrations in genital fluids and rectal tissue in male and female individuals living with HIV and receiving BIC/FTC/TAF as their first ARV regimen.

METHODS

Design and population:

Prospective study of HIV-1–infected, ARV–naive male (n=15) and female (n=8) adults (>18 years) initiating BIC/F/TAF 50/200/25 mg, as fixed dose combination, once daily.

Procedures:

HIV-1 RNA was measured in blood plasma (BP) SP and RF in men, and CVF in women, at baseline (BL), days 3, 7, 14 and 28, and weeks 12 and 24. HIV-1 RNA was determined by real time PCR (Abbott RealTime HIV-1; quantification limit 40 copies/mL).

Total and protein-unbound BIC concentrations were quantified at 24 hours post dose (C_{24h}) on day 28 and week 12 in BP, SP and rectal tissue (RT) in men, and in BP and CVF in women. BIC concentrations were measured using a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) method. Protein-unbound BIC concentrations were analyzed using a rapid equilibrium dialysis (Thermo Scientific) and LC/MS/MS analysis (Dynamic range of assay: 20-20,000 ng/mL for BP samples; 1-1000 ng/mL for SP and CVF samples; and 0.100 -100 ng/g for RT samples).

Statistical methods:

For the HIV-1 RNA analyses, measurements below the quantification threshold (40 copies/mL) were set to 1/2 of the threshold (20 copies/mL).

Wilcoxon signed rank tests were used for comparisons between compartments and associations between variables were assessed using Spearman correlation coefficient.

Mean survival time was computed as the area under the Kaplan-Meier estimate of the survival curve. Comparisons between compartments were assessed by restricted mean survival time.

Longitudinal dynamics in log_{10} HIV-1 RNA were analyzed with nonparametric methods. Smoothing-splines mixed-effects models were fitted in each compartment and a numerical approximation of their gradient was computed at initial time as an estimation of the first phase decrease slope.

RESULTS

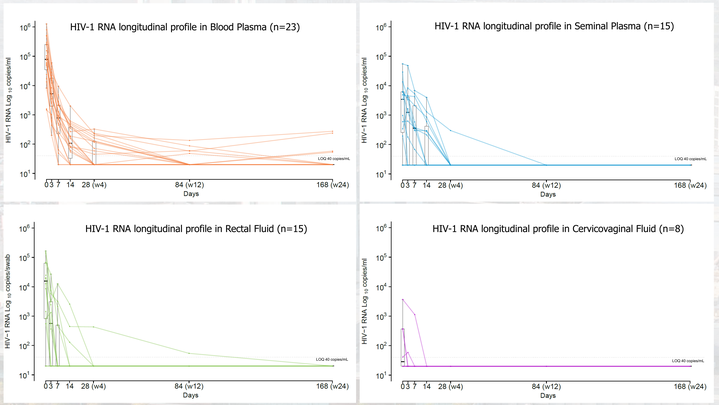
1. Baseline characteristics

Characteristic	n=23
Age (years), median (range)	30 (20-57)
CD4 count, cells/µL, median (range)	419 (9-1165)
HIV B subtype*, n (%)	11/16 (69%)*
Blood plasma HIV-1 RNA, log_{10} copies/mL, median (range)	4.89 (3.17-6.10)
Male (n=15)	4.94 (3.20-6.10)
Female (n=8)	4.88 (3.17-5.71)

*5/16 Non-B subtype: recombinant BC, recombinant BG, A, G, CRF02_AG. HIV-1 subtype not available in 7 individuals.

VIROLOGIC RESULTS

2. HIV-1 RNA decline through week 24



3. Comparison of HIV-1 RNA decline in BP, SP and RF at each timepoint

Time Point	HIV-1 RNA, Median (IQR) Log_{10} Copies/mL			HIV-1 RNA Decrease From Baseline, Median (IQR) Log_{10} Copies/mL			Wilcoxon signed rank test, p-value #		
	BP	SP	RF *	BP	SP	RF *	BP vs SP	BP vs RF	SP vs RF
Baseline	4.94 [4.54 - 5.4]	3.54 [2.41 - 3.79]	4.19 [2.98 - 4.7]						
Day 3	4.08 [3.37 - 4.35]	3.09 [1.3 - 3.61]	2.75 [1.3 - 3.49]	-1.11 [-1 to -1.29]	-0.23 [-0.02 to -0.72]	-1.42 [-1 to -1.5]	0.0522	0.4648	0.131
Day 7	2.95 [2.35 - 3.36]	2.55 [1.43 - 3.18]	1.3 [1.3 - 2.7]	-2.04 [-1.94 to -2.46]	-0.95 [-0.16 to -1.25]	-1.84 [-1.69 to -2.68]	0.0024	0.9697	0.019
Day 14	2.19 [1.52 - 2.65]	1.3 [1.3 - 2.63]	1.3 [1.3 - 1.3]	-2.8 [-2.55 to -3.06]	-1.23 [-0.89 to -1.53]	-2.61 [-1.8 to -3.11]	0.0049	0.3394	0.019
Week 4	1.3 [1.3 - 2.25]	1.3 [1.3 - 1.3]	1.3 [1.3 - 1.3]	-3.18 [-2.95 to -3.46]	-2.43 [-1.41 to -2.58]	-2.89 [-2.4 to -3.2]	0.0049	0.0269	0.206
Week 12	1.3 [1.3 - 1.3]	1.3 [1.3 - 1.3]	1.3 [1.3 - 1.3]	-3.64 [-3.24 to -3.93]	-2.43 [-1.64 to -2.58]	-2.99 [-2.44 to -3.49]	0.0024	0.0093	0.206
Week 24	1.3 [1.3 - 1.51]	1.3 [1.3 - 1.3]	1.3 [1.3 - 1.3]	-3.48 [-3.17 to -3.68]	-2.43 [-1.64 to -2.58]	-2.99 [-2.44 to -3.51]	0.0024	0.0425	0.206

Data from male participants (n=15); * Rectal Fluid: Log_{10} copies/swab; # Comparisons of HIV-1 RNA decrease from BL between compartments at each timepoint.

HIV-1 RNA decline from BL was significantly smaller in SP compared to BP at all timepoints, probably due to a lower BL HIV-1 RNA level in SP. HIV-1 RNA decline was comparable in BP and RF up to day 14 but significantly greater in BP thereafter. It could be probably explained by the lower BL HIV-RNA level in RF and the higher proportion of individuals with undetectable HIV-1 RNA after day 14 in this compartment. HIV-1 RNA decline was also significantly smaller in SP compared to RF up to day 14, without significant differences thereafter, probably due to a higher BL HIV-1 RNA in RF but a rapid HIV-1 suppression below the limit of detection in both compartments.

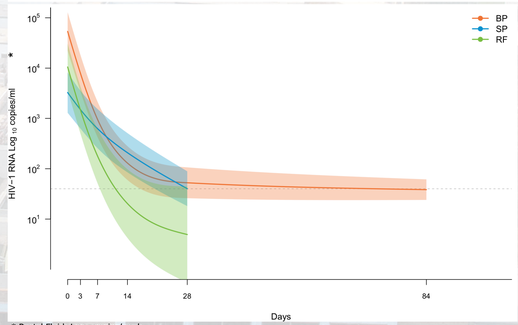
4. Time to achieve undetectable HIV-1 RNA

Time Point	Men (n=15)			Women (n=8)	
	BP	SP	RF	BP	CVF
Baseline	0 (0%)	3 (20%)	2 (13%)	0 (0%)	4 (50%)
Day 3	0 (0%)	5 (33%)	5 (33%)	0 (0%)	6 (75%)
Day 7	2 (13%)	5 (33%)	9 (60%)	0 (0%)	7 (87%)
Day 14	4 (27%)	8 (53%)	11 (73%)	2 (25%)	8 (100%)
Week 4	8 (53%)	14 (93%)	14 (93%)	4 (50%)	8 (100%)
Week 12	12 (80%)	15 (100%)	14 (93%)	6 (75%)	8 (100%)
Week 24	11 (73%)	15 (100%)	15 (100%)	8 (100%)	8 (100%)

Data presented as number (%) of individuals with HIV-1 RNA <40 copies/mL or swab at each timepoint.

The average time to achieve HIV-1 RNA below the limit of detection (*mean survival time*) was 66.3 (95% CI 36.9-95.7) days in BP; 25 (95 %CI 13.6-36.4) days in SP; and 22.8 (95% CI 0-46) days in RF. The differences between SP vs. BP and RF vs. BP were statistically significant (p=0.018 and p=0.023, respectively). However, no significant differences were observed after adjusting by HIV-1 RNA at BL (SP vs BP p=0.683; RF vs BP p= 0.681). No significant differences were found between SP and RF (p=0.293).
*The average time to achieve HIV-1 RNA <40 copies/mL in CVF can not be estimated because of the small number of female participants and high proportion of undetectable HIV-1 RNA in CVF at BL.

5. HIV-1 RNA decay dynamics model



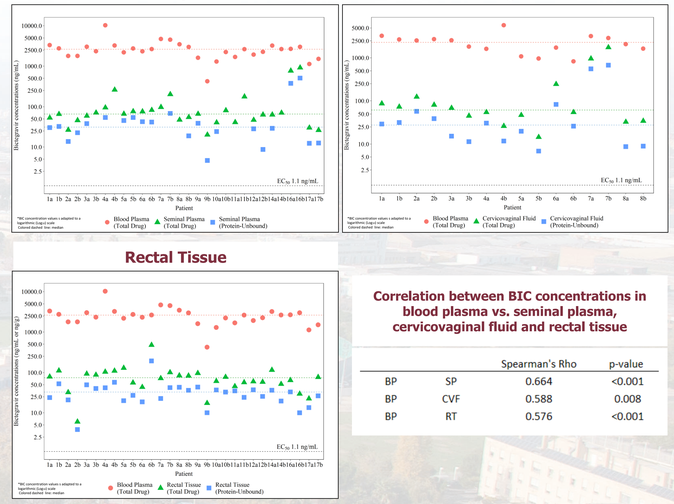
* Rectal Fluid: Log_{10} copies/swab.

The estimated HIV-1 RNA initial decay slopes in BP, SP and RF were -0.284, -0.117 and -0.295, respectively.
The decay slope was significantly lower in SP in comparison to both BP (p=0.0005) and RF (p=0.001) while no differences were found between BP and RF (p=0.42).

Limitations: The model can only estimate HIV-1 RNA decay slopes in BP and RF up to day 28 because of the high proportion of individuals with HIV-1 RNA <40 copies/mL after day 28 in these compartments. A decay slope can not be estimated in CVF because of the small number of female participants and high proportion of undetectable HIV-1 RNA in CVF at BL.

PHARMACOLOGIC RESULTS

6. Total and protein-unbound bictegravir concentrations (C_{24h}) in genital fluids and rectum



Correlation between BIC concentrations in blood plasma vs. seminal plasma, cervicovaginal fluid and rectal tissue

		Spearman's Rho	p-value
BP	SP	0.664	<0.001
BP	CVF	0.588	0.008
BP	RT	0.576	<0.001

7. Summary of BIC distribution, Total concentration and protein-unbound concentration in Seminal Plasma, Rectal Tissue and Cervicovaginal Fluid

	Total drug (ng/mL or ng/g)	Fluid or tissue/BP (%)	Protein-unbound fraction (%)	Protein-unbound concentration
Male				
BP	2640 (424-10300)		0.2 (0.1-4.2)	5.2 (1.1-91.4)
SP	65.55 (20.1-923)	2.72 (0.9-30.6)	51.1 (13.8-70.6)	31.3 (4.6-508.6)
RT	74.05 (6.01-478.50)	2.6 (0.3-18.1)	44.6 (15.5-76.8)	32.8 (3.9-192.7)
Female				
BP	2320 (834-5770)		0.2 (0.1-0.3)	5.5 (1.9-8.1)
CVF	61.6 (14.4-1760.2)	2.8 (0.5-60.7)	42.6 (22.1-58.0)	27.5 (6.8-679.4)

Values expressed as median (range); BIC concentrations in BP, SP and CVF were determined as ng/mL; BIC concentrations in RT were determined as ng/g; RT/BP ratio was estimated assuming tissue density of 1 g/ml.

A low BIC distribution was found in SP, CVF and RT. However, a high protein-unbound fraction of BIC was observed in these compartments resulting in median unbound BIC C_{24h} 28-fold, 25-fold and 30-fold above the EC_{50} for wild type HIV-1 (1.1 ng/mL) in SP, CVF and RT, respectively.

CONCLUSIONS

- BIC/F/TAF showed good activity in male and female genital tract and rectum, achieving undetectable HIV-1 RNA within the first 4 weeks in most individuals.
- HIV-1 RNA suppression was achieved earlier in SP, CVF and RF compared to BP, which can be explained by the lower baseline HIV-1 RNA levels in these compartments.
- Rapid viral suppression was observed in SP despite a slower HIV-1 RNA decay dynamics in this compartment compared to BP and RF.
- A low BIC distribution was found in male and female genital fluids and rectum. However, due to the high protein-unbound fraction of BIC in SP, CVF and RT the median unbound BIC C_{24h} highly exceeded the EC_{50} for wild-type HIV-1.

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