Dolutegravir vs Efavirenz: Comparison and factors associated with viral blips in an acute HIV infection cohort study

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Background

•Viral blips may occur for a variety of reasons:

- Benign causes such as random biological fluctuations, statistical variations, and artefacts of HIV RNA assay variability
- Early indicator of non-adherence or incomplete adherence to antiretroviral therapy (ART).
- May represent bursts of viral replication and activation of viral reservoirs or immune activation with expansion and contraction

- Detection of viral blips often prompts additional patient monitoring but, because of the multiple potential reasons for blips, their clinical management is not straightforward.
- We compared blip incidence while on first-line dolutegravir vs efavirenz-based ART started during acute HIV infection (AHI) and evaluated associated factors.

Methods

RV254/SEARCH010 enrolls participants who are diagnosed and initiated treatment during acute HIV infection and follows participants for up to 20 years. The rate and magnitude of blips were observed after the first recorded suppressed HIV VL (<20 copies/ml). The length of follow-up Median (IQR) was 1.84 (0.93 - 3.03) years.

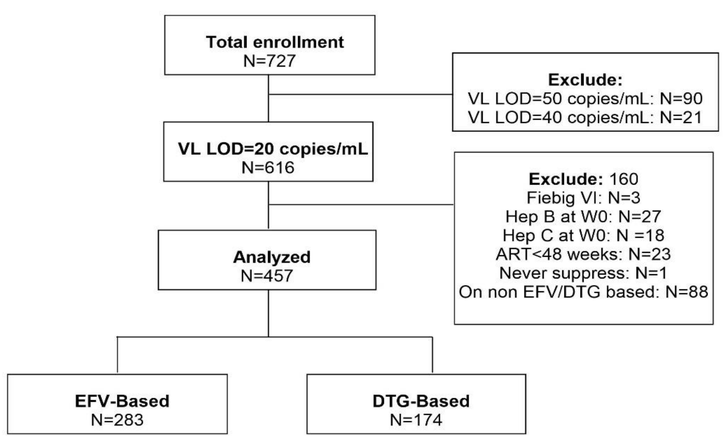
Inclusion Criteria:

- RV254/SEARCH010 participants started on efavirenz (EFV) or dolutegravir (DTG) with two nucleoside reverse transcriptase inhibitors and remained on the initial ART for at least 48 weeks.

Exclusion Criteria:

- Participants not starting ART at week 0
- Any participant not reaching viral control.
- Participants with HIV viral load (VL) testing with level of detection (LOD) >20 copies/mL
- Participants with Hepatitis B or Hepatitis C at baseline

Figure 1 shows the number and reasons for participant exclusion in the analysis.



Statistical analysis

- Comparisons between EFV and DTG groups were done using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables.
- Blip density rate was calculated by the number of blips divided by the total of observation time.
- Factors potentially associated with VL blips were assessed using negative binomial regression. Exposure time was calculated from ART initiation until last follow up visit, censored upon persistent low-level viremia, first viral failure, change in ART regimen, diagnosis with hepatitis B or C, study withdrawal, enrollment into ATI study, death, or loss to follow-up.

Results

- 457 participants were analyzed, 283 starting efavirenz and 174 starting dolutegravir, predominantly MSM (93.9%) with a median age of 26 (IQR 23-32). The groups did not differ by gender, HIV risk, CD4, or HIV RNA at ART initiation (all p>0.05). See **Table 1**.

Table 1. Baseline characteristics during acute HIV infection and VL blips summary. The significant p-values are in bold.

	Efavirenz (N=283)	Dolutegravir (N=174)	Total (N=457)	p-value
Age, (years, IQR)	25 (22 - 31)	27 (23 - 33)	26 (23 - 32)	**0.013**
Sex				
F	2 (0.7%)	3 (1.7%)	5 (1.1%)	0.374
M	281 (99.3%)	171 (98.3%)	452 (98.9%)	
Fiebig stage				
I-II	102 (36.0%)	62 (35.4%)	164 (35.9%)	1.000
III-V	181 (64.0%)	112 (64.6%)	293 (64.1%)	
Risk				
Heterosexual female	2 (0.7%)	3 (1.7%)	5 (1.1%)	0.359
Heterosexual male	12 (4.2%)	11 (6.3%)	23 (5.0%)	
MSM	269 (95.1%)	160 (92.0%)	429 (93.9%)	
CD4 T cells (cells/mm^3, IQR)	364 (265 - 501)	337 (259 - 467)	350 (262 - 495)	0.224
HIV-RNA (log_{10}copies/mL,IQR)	6.02 (5.34 - 6.84)	6.14 (5.04 - 6.78)	6.07 (5.29 - 6.83)	0.637
Time to VL suppression (weeks, IQR)	23 (12 - 24)	8 (5 - 12)	12 (8 - 24)	**<0.001**
Observation time, (years, IQR)	1.45 (0.74 - 2.30)	3.19 (1.45 - 5.02)	1.84 (0.93 - 3.03)	**<0.001**
Participants with VL Blips				
No	257 (90.8%)	136 (78.2%)	393 (86.0%)	**<0.001**
Yes	26 (9.2%)	38 (21.8%)	64 (14.0%)	
Single blip	22 (84.6%)	28 (73.7%)	50 (78.1%)	0.367
Multiple blips	4 (15.4%)	10 (26.3%)	14 (21.9%)	
Magnitude of VL blips				
Median (copies/ml, IQR)	27.5 (22 – 33)	34.5 (24 – 66)	31 (23 – 48)	**0.020**
Range	20 – 119	20 - 517	20 – 517	
Total Events of VL blips	30	54	84	
Low (20-200 copies/ml)	30	53	83	
High (201-999 copies/ml)	-	1	1	
Time to first blip (Weeks, IQR)	38 (36 - 72)	65 (36 - 96)	60 (36 - 84)	**0.008**
Adherence:				0.818
No. of missed doses	0 (0 - 6)	0 (0 - 3)	0 (0 - 3)	

- The median time to viral suppression was 8 weeks on dolutegravir (IQR 5-12) and 23 weeks on efavirenz (IQR 12-24; p<0.001).
- The median blip magnitude was higher with dolutegravir (34.5 copies/ml [IQR:24–66]) than with efavirenz (27.5 copies/ml [IQR:22–33], p=0.02). See **Figure 2**.

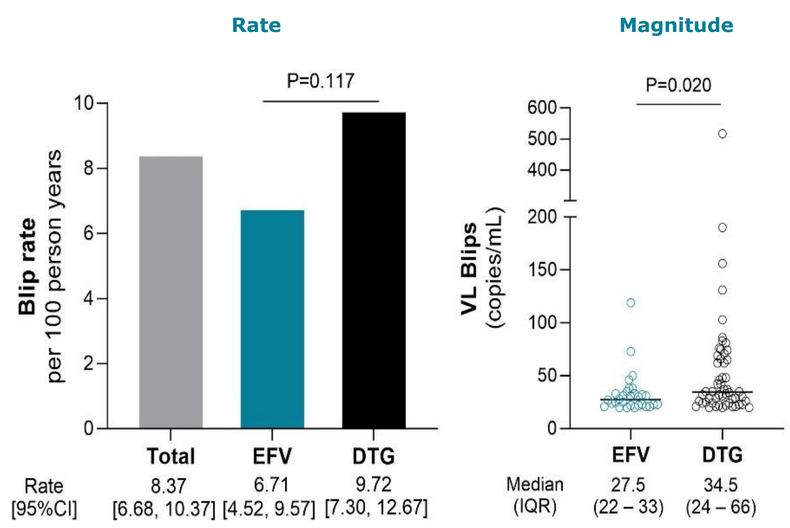


Figure 2. Comparison of rate and magnitude of blips between EFV and DTG

- 84 blips were observed with an incidence of 8.37 (95%CI: 6.68–10.37) per 100 person-years. Most blips were low (<200 copies/ml), except for one in the dolutegravir group (517 copies/mL).
- The median time from antiretroviral initiation to the first blip was 65 and 38 weeks on dolutegravir and efavirenz, respectively (p=0.008).
- In the multivariate model, factors associated with a higher incidence rate of blips were longer time to suppression, baseline HIV RNA >6 log copies/mL, and age. Fiebig stage at ART initiation, CD4 count, and antiretroviral (EFV or DTG) were not associated with blip incidence. See **Table 2**.

Table 2. Factors associated with VL blips. The significant p-values are in bold.

	Univariate			Multivariate		
	IRR	95%(CI)	P-value	aIRR	95%(CI)	P-value
Group						
Efavirenz	Ref.			Ref.		
Dolutegravir	1.52	[0.90, 2.56]	0.117	1.64	[0.97, 2.76]	0.065
Time to suppression (weeks)	1.03	[1.01, 1.05]	**0.001**	1.02	[1.002, 1.04]	**0.029**
Age (years)	1.03	[1.00, 1.06]	0.068	1.03	[1.003, 1.07]	**0.031**
Fiebig stage						
I-II	Ref.			Ref.		
III-V	2.26	[1.22, 4.18]	**0.010**	1.47	[0.79, 2.74]	0.227
CD4 T cells (cells/mm^3)						
>350	Ref.			Ref.		
≤350	1.72	[1.02, 2.91]	**0.041**	1.13	[0.67, 1.91]	0.653
Baseline HIV RNA (log_{10}copies/ml)						
≤6 log	Ref.			Ref.		
> 6 log	3.81	[2.12, 6.85]	**<0.001**	2.90	[1.52, 5.52]	**0.001**

Conclusions

- Early ART in AHI does not prevent viral blips in a highly adherent cohort.
- Dolutegravir was faster than efavirenz in suppressing HIV viral load and had a longer time to observe the first blip.
- Blips are not uncommon. However, it is reassuring that most blips were less than the viral load threshold used by U=U-supporting studies.
- Earlier viral suppression was associated with fewer viral blips, further reinforcing early treatment and adherence.

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