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Measuring the impact of early 3BNC117 intervention at ART initiation on the productive reservoir in a cohort of diverse viral subtypes: results from the VIP-SPOT assay in the eCLEAR trial





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CONFLICTS OF INTEREST

A patent application on the VIP-SPOT assay has been filed (US patent 22/30875).

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Background: aiming a functional cure

Fine-tuning "shock-and-kill" therapeutic strategies



✓ Understanding the establishment of the viral reservoir is key to designing effective HIV cure strategies.



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The eCLEAR Trial: study design

Nowly	ART										rom initi ranc	
diagnosed	ART initiation							Option		a <mark>l ATI start</mark>		
individuals	Screening		Interve	terventional period				Follow-up			n=2	0
ART (n=15)												
ART + 3BNC117+ (n=15)			*									
ART + RMDI (n=13)			ł								*****	
ART + 3BNC1174 + RMDI	(n=16)		X								*****	
tudy visits (days)	-28	ò	710	17 21 24	30	60	90	180	270	365	400	484
linical safety	0	0	00	0 00	0	0	0	0	0	0	ന്നും റ	0
lasma HIV-1 RNA	0	0	00	တဝတ	0	0	0	0	0	0	00000000 0	0
HV-1 mRNA+ and/or p24+ cells (FISH-1	low)	0	Ø	0 0	0							
HIV-1-specific immunity (AIM)		0					0			0		
ntact HIV-1 proviruses (ddPCR)		0				********		0	**********	0		******
HIV-1 antigen production (VIP-SPOT)		0								0		
BNC117 sensitivity (pheno- or geno-t	ypic)	0	****************									

Shock&kill intervention at the time of ART initiation

nature medicine

Article

Early intervention with 3BNC117 and romidepsin at antiretroviral treatment initiation in people with HIV-1: a phase 1b/2a, randomized trial



Gunst. et al, Nat Med, Oct 2022. doi.org/10.1038/s41591-022-02023-7

MC Puertas, 16th Dic 2022

The eCLEAR Trial: main results

- 3BNC117 treatment (with or without RMD) enhanced plasma HIV-1 RNA decay rates.
 - 3BNC117 treatment accelerated clearance of active infected cells in the first 10 days of ART.
 - After 1 year, early 3BNC117+RMD was associated with enhanced HIV-1 Gag-specific CD8+ T cell immunity.
 - These effects of 3BNC117 were most pronounced in individuals whose pre-ART plasma HIV-1 envelope sequences were antibody sensitive



Gunst. et al, Nat Med, Oct 2022. doi.org/10.1038/s41591-022-02023-7

Measuring the impact on the viral reservoir

Which is our target population in a shock-and-kill intervention?



Measuring the impact on the viral reservoir

Which is our target population in a shock-and-kill intervention?



The novel VIP-SPOT assay

Quantify the frequency of peripheral CD4+ T cells able to reactivate and produce viral proteins (Gag).



Puertas MC, et al,. 2021. mBio 12:e00560-21.

Results 1: Frequency of HIV antigen producing cells at baseline

- ✓ Frequency of cells able to reactivate and produce viral protein is 1000-fold lower than total HIV DNA.
- ✓ Most proviruses (even intact) are not able to reactivate productively.
- ✓ Correlation between VIP-SPOT assay and other virological parameters at baseline.



Results 2: Performance of the VIP-SPOT assay with non-B subtypes

✓ Only half of the individuals (49%) had HIV-1 subtype B infection while the rest of the participants had a broad range of other HIV-1 subtypes and recombinant forms



VIP-SPOT results by subtype

 ✓ No differences in the frequency of detection of HIV-Ag producing cells were observed between B and non-B HIV-1 subtypes.

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VIP-SPOT results by subtype

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Results 3: Longitudinal changes throughout the study period

✓ After 1 year on treatment, the frequency of HIV antigen producing cells decreased significantly in all study groups.



Results 3: Longitudinal changes throughout the study period

- ✓ After 1 year on treatment, the frequency of HIV antigen producing cells decreased significantly in all study groups.
- ✓ A trend towards greater undetectability was observed in participants receiving 3BNC117, especially in individuals whose pre-ART plasma viruses were sensitive to the antibody.











COMMUNITY SUMMARY

KEY QUESTION:

How to evaluate the effectiveness of the shock-and kill interventions aimed at impacting the viral reservoir.

KEY FINDINGS:

- The novel VIP-SPOT assay is useful to evaluate the impact of shock-and-kill strategies on the productive * reservoir regardless of HIV-1 subtype.
- The results evidenced the clearance of CD4+ cells capable of producing HIV-1 protein upon ART ** initiation.

NEXT STEPS:

More work is needed to define the dynamics of this fraction of the reservoir to understand how it is established and whether it might be used as a biomarker of effectiveness of these kind of interventions.

EDITION HIV PERSIS TENCE DURING THERAPY Reservoirs & Eradication Strategies Workshop



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more...



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