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# *ABX464 Decreases the Total HIV Reservoir and HIV Transcription Initiation in vivo*

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## BACKGROUND

- Antiretroviral treatment (ART) intensification and disruption of latent HIV infection (reversal or silencing) have been suggested as strategies to eradicate HIV
- ABX464 (AbiVax) is a novel antiviral that binds to the cap binding complex, interfering with splicing and Rev-mediated export of newly transcribed HIV RNA
- ABX464 has been shown to inhibit HIV RNA biogenesis in vitro and delayed viral rebound in two humanized mouse models [1-5]

**AIMS: To investigate the effect of ABX464 on the HIV transcription profile and total and intact HIV DNA in circulating CD4+ T cells from ART-suppressed participants enrolled in the ABIVAX-005 clinical trial (NCT02990325)**

## METHODS

### Study design and sample processing

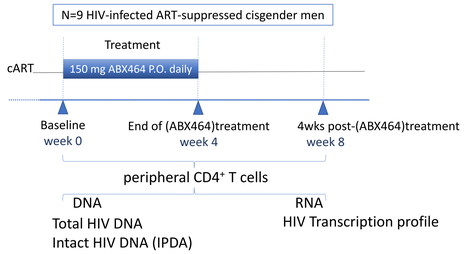



**Figure 1. Participants, collected samples and parameters studied.**
We analyzed peripheral CD4⁺ T cells purified from cryopreserved PBMC from 9 HIV-infected ART-suppressed men (cohort 1 ABIVAX-005, NTC02990325).
We quantified total and intact HIV DNA and the HIV transcription profile by ddPCR.

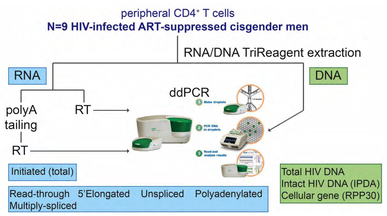



**Figure 2. Sample processing for HIV quantification.**
Nucleic acids from peripheral CD4⁺ T cells were extracted using TRI Reagent. Cell-associated HIV transcripts (read-through [U3-U5], initiated (total) [TAR], 5'elongated [R-U5-preGag], unspliced [Pol], polyadenylated [PolyA], and multiply-spliced [Tat-Rev]), total HIV DNA (LTR-Gag), intact HIV DNA (IPDA), and the cellular gene RPP30 were quantified using ddPCR [6,7,].

### HIV transcription profile

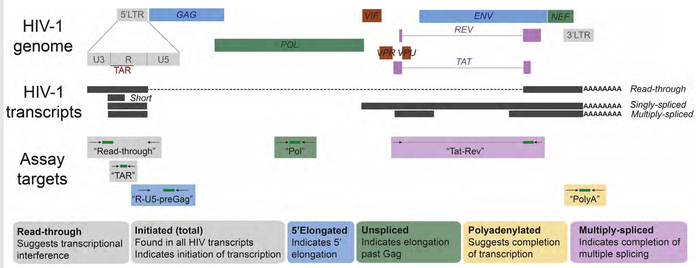



**Figure 3. Assays to investigate the HIV transcription profile.**
Diagram of the assays used to characterize the HIV transcription profile.

In this substudy, treatment with **ABX464 decreased total HIV DNA** (and possibly intact proviruses) **and decreased HIV transcription initiation**

## RESULTS

### 1. Characteristics of the study participants

| HIV-infected ART-suppressed cisgender men (N=9) | Median [IQR] |
|---|---|
| Age (years) | 48 [43-51] |
| Time from diagnosis to ART initiation (days) | 162 [64-405] |
| Time on ART (years) | 10.5 [6.2-23.0] |
| Nadir CD4+ T cells (cells/µl) | 501 [412-729] |
| Zenith viral load ($log_{10}$ copies HIV-1 RNA/ml plasma) | 4.4 [3.8-4.7] |
| Absolute CD4 count (cells/µl) | 906 [785-1,029] |
| Percentage CD4+ T cells | 36.6 [33.2-38.9] |
| Absolute CD8 count (cells/µl) | 807 [746-966] |
| Percentage CD8+ T cells | 32.3 [29.9-36.8] |
| Ratio CD4/CD8 | 1.1 [1.0-1.5] |

### 2. Effect of ABX464 on total and intact HIV DNA

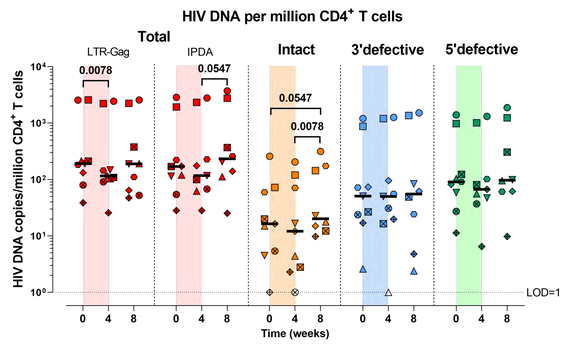



**Figure 4. Total, intact and defective HIV DNA.**
Colors represent different HIV DNA measurements and symbol shapes different participants. Individual values and median are shown. Shadowed areas represent treatment with ABX464. Results were analyzed using Wilcoxon signed rank test.

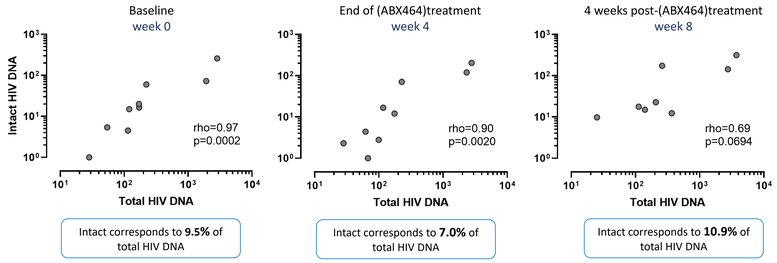


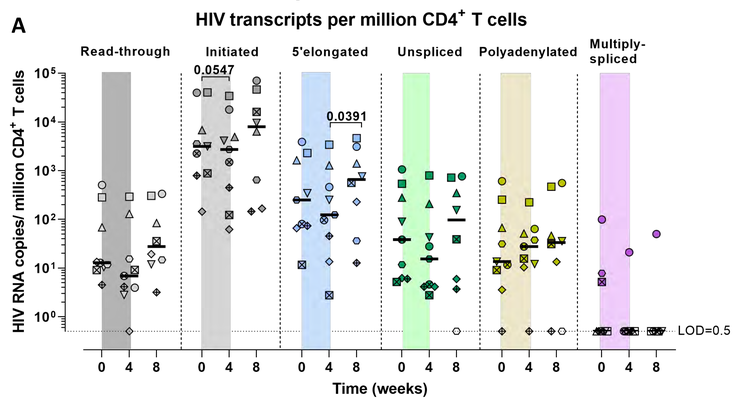

**Figure 5. Correlation between total and intact HIV DNA (IPDA).**
We observed a strong positive correlation between total and intact HIV DNA at weeks 0 and 4, but the correlation lost significance at week 8. Results were analyzed using Spearman.

## CONCLUSIONS

**After ABX464 treatment** we observed:

1. A **significant decrease in total HIV DNA** (median [wk4/wk0]=0.8), and a **similar trend for intact HIV DNA** (median [wk4/wk0]=0.8). However, intact HIV DNA increased significantly after stopping ABX464 (wk4 *vs* wk8).
2. A **significant decrease in initiated HIV transcripts** per million CD4⁺ T cells and per provirus (median [wk4/wk0]: 0.7, 0.5), and a **similar trend for 5'elongated and unspliced HIV transcripts** (median [wk4/wk0]: 0.6, 0.7; 0.5, 0.6). However, no significant change was observed in polyadenylated or multiply-spliced HIV transcripts.

### 3. Effect of ABX464 on HIV transcription



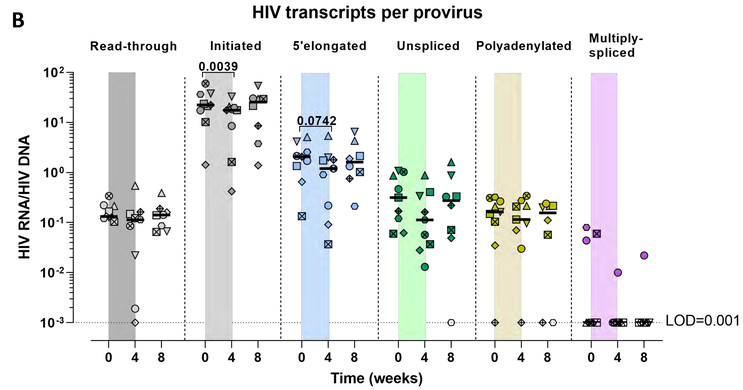




**Figure 5. HIV transcription profile. (A) HIV transcripts per million CD4⁺ T cells. (B) HIV transcripts per provirus.**
Colors represent different HIV transcripts and symbol shapes different participants. Individual values and median are shown. Shadowed areas represent treatment with ABX464. Results were analyzed using the Wilcoxon signed-rank test.

### Limitations

1. Low number of study participants - Low power to detect differences. Preliminary results that have to be confirmed in a larger cohort
2. Short-term treatment, effect reversed after treatment – Unclear if more pronounced or sustained results would be obtained with long-term treatment
3. These are preliminary results that should be confirmed by additional studies and/or experiments

**References**
1. Campos Retrovirology 2015; 2. Scherrer AAC 2017; 3. Steens AAC 2017; 4. Scherrer JAC 2017; 5. Rutsaert JVE 2019; 6. Yukl STM (2018); 7. Moron-Lopez PLoSOne 2017; 8. Bruner 2019 Nat

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