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Analytical treatment interruption (ATI) in patients with very small HIV reservoir

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1 Introduction

No single parameter reliably predicts post-treatment control (PTC) among HIV infected patients. However, both total HIV-1 DNA (tDNA) and cell-associated RNA (caRNA) have been individually associated to delayed viral rebound after ATI.
We evaluated the predictive value of the combination of low DNA and caRNA in the identification PTC.

2 Methods

The study is a two-step single arm multi-centric non-randomized prospective trial (NCT02590354). Major inclusion criteria in step 1 were: nadir CD4⁺ T-cell count >350cells/µl and plasma viral load (pVL) <50 cps/ml since ≥2 years. The size of the HIV reservoir was determined by droplet digital PCR measurement of tDNA and caRNA in peripheral blood mononuclear cells (PBMCs). In step 2, consenting participants with reservoir parameters below the detection limit (tDNA <66 cps/10^6 PBMCs and caRNA <10 cps/10^6 PBMCs) underwent a leucapheresis prior ATI.

cART was re-initiated whenever pVL, measured every other week, was >1,000 cps/ml at two consecutive measurements or at pVL > 10,000 cps/ml. tDNA and caRNA were measured at every visit during ATI as well as 4 and 12 weeks after cART re-initiation. Quantitative viral outgrowth assays (qVOA), viral release assays (VRA) and ultra-sensitive pVL were performed on pre-ATI samples. Associations between clinical, virological or immunological parameters and viral rebound dynamics were assessed with Kaplan-Meier estimates and Cox proportional hazard models.

3 Results

Of the 114 participants, 37 (32.5%) met the viral reservoir criteria for ATI. Of them, 16 (14.0%) consented and underwent ATI

Table 1: Participant accounting

	n (%)
Screen failure	17 (13.0)
Enrolled to step 1	114 (87.0)
Excluded from step 2	98 (86.0)
Active hepatitis B or C virus infection	1 (1)
Confirmed neutrophil count <1200/µL	1 (1)
Detectable level of tDNA or caRNA	75 (76.5)
Declined participation in step 2	20 (20.4)
Patient was lost to follow-up	1 (1)
Enrolled to step 2	16 (14.0)
Lost to follow-up	2 (12.5)
Completed the study	14 (87.5)

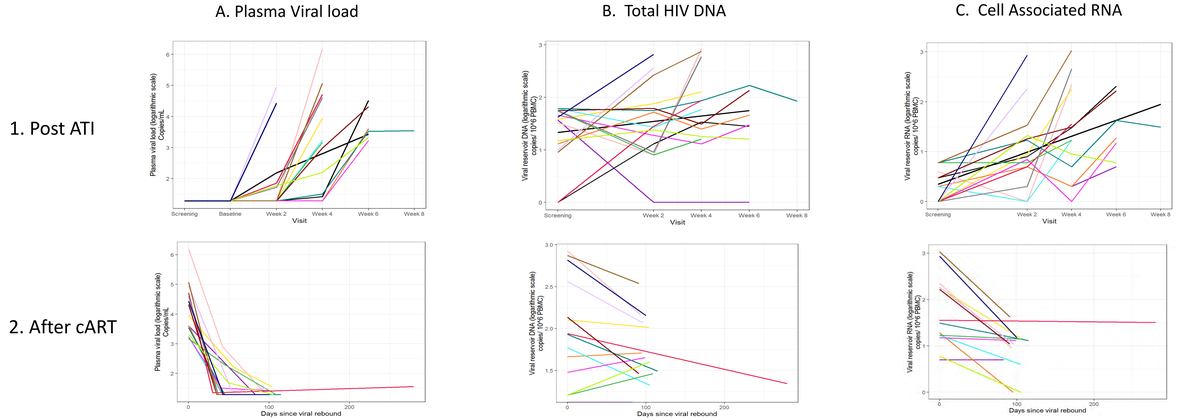
Table 2: baseline characteristics of participants in step2

	n(%)
N	16(100%)
Age: median (IQR)	43.5(38.0 - 54.0)
Gender Female	1(6.3%)
Gender Male	15(93.8%)
Ethnicity Caucasian	16(100%)
Risk group heterosexual contact	3(18.8%)
Risk group homo/bisexual	12(75.0%)
Risk group other: unknown	1(6.3%)
Time since HIV diagnosis (months): median (IQR)	47.2(33.1 - 75.3)
Duration of ART (months): median (IQR)	47.3(34.4 - 74.0)
Last used ART Int Inh + NRTI	11(68.8%)
Last used ART NNRTI + NRTI	4(25.0%)
Last used ART PI +NRTI	1(6.3%)
HIV subtype A	1(6.3%)
HIV subtype B	15(93.8%)
Nadir CD4 T-cell count: median (IQR) [/mm³]	440.5(342.0 - 500.5)
Baseline CD4 T-cell count: median (IQR)	758.0(679.0 - 845.0)
Ultra-sensitive plasma viral load: median (IQR) [copies/mm³]	0.3(0.0 - 2.5)

IQR: interquartile range; Int Inh: Integrase Inhibitor; (N)NRTI: (non) nucleoside reverse transcriptase inhibitor; PI: protease Inhibitor

Viral dynamics after treatment interruption and upon treatment resumption

All participants experienced rapid viral rebound two to eight weeks after ATI. All participants suppressed viremia to levels below the limit of detection within 14 weeks of cART re-initiation. tDNA and caRNA returned to baseline levels within the 12 weeks after cART re-initiation.



Safety analysis

Number of patients (%; 95% CI) with:	(N = 16)
Any adverse event	13 (81.3;57.0-93.4)
Any intervention-related adverse event	3 (18.8;6.59-43.0)
Any serious adverse event	0 (0.0;0.00-19.4)
Any intervention -related serious adverse event	0 (0.0;0.00-19.4)

No serious adverse events have been reported. The three episodes of adverse-events related to the intervention were one episode of fatigue, one influenza-like illness and one episode of oropharyngeal pain.

Predictor of viral rebound

No correlations were observed between viral rebound dynamics and any of the laboratory parameters studied at ATI: current or nadir CD4⁺ T-cell count, ultra-sensitive pVL, tDNA or caRNA, qVOA, VRA or any other clinical parameters.

4 Conclusions

- We report on the first prospective study evaluating ATI in participants selected on the basis of a very small and transcriptionally silent HIV reservoir. No PTC was identified.
- ATI was shown to be safe, despite rapid viral rebound.
- The impact of ATI on the reservoir size after cART re-initiation was limited and the viral load of all participants returned to undetectable level short after restarting cART.
- None of the measured baseline parameters were predictive for viral rebound dynamics.

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