# Plasma Correlates of Rebound After Discontinuation of Antiretroviral therapy in Persons Living With HIV-1 (PLWH)

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## BACKGROUND

The discovery of biomarkers that predict viral rebound after antiretroviral therapy (ART) discontinuation (ATI) would significantly contribute to the HIV cure field. Further, the discovery of biomarkers predicting viral rebound after ART discontinuation will inform and guide ATI studies to understand who is more likely to experience a viral rebound and could help select participants for ART interruption studies to make ART discontinuation safer and more effective.

## METHODS

### a. Study Design

We initiated a multi-center, open-label trial of three monthly intravenous (IV) administration of 20 mg/kg each of PGT121, PGDM1400, and VRC07-523LS (n=12) in persons living with HIV-1 (PLWH) following discontinuation of antiretroviral therapy (ART).

Participants were eligible if they were 18-65 years of age, had CD4 ≥ 400 cells/µl, no history of AIDS-defining illness within the previous 5 years, and if they were on antiretroviral therapy for a minimum of 24 months, with plasma HIV-1 RNA levels of < 50 copies/ml for at least 12 months. ART was interrupted 2 days after the first broadly neutralizing monoclonal antibodies (bNAb) infusion (**Fig.1**).

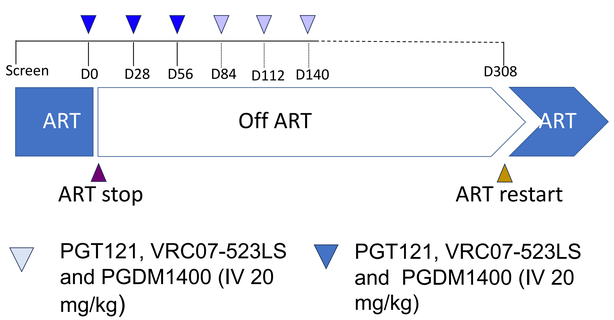


**Fig. 1**. Study Design

### b. Plasma Proteomics Profiling

We collected plasma from all participants at three key times: two days before stopping antiretroviral therapy (ART), at multiple points during the time they were off ART, and following their viral rebound (VL> 200 cp/ml). To assess changes in plasma biomarkers that occurred after the interruption of ART and before a detectable viral rebound (VL < 200 cp/ml), as well as after the viral rebound (VL > 200 cp/ml), we used the high-plex, high-throughput proteomics technology by SomaLogic known as the SomaScan 7k platform.

## RESULTS

### a. Viral Rebound

7 of 12 participants experienced rebound after 28 weeks, and 5 of 12 participants showed no viral rebound (controllers) for the duration of the follow-up (**Fig. 2**). We conducted proteomics profiling before ATI (D0) and prior to detectable rebound (VL< 200 copies/ml) in 7 rebounders. Sampling time points are indicated in colored vertical arrows (**Fig. 2**).

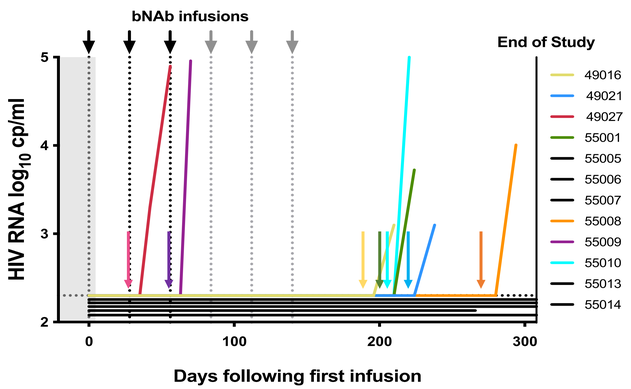


**Fig. 2**. Plasma HIV-1 RNA levels (Log10 RNA copies/ml) over the course of the study are shown for each of the twelve participants (color-coded). The horizontal dotted line indicates the lower limit of quantification for HIV-1 RNA levels (viral load (VL)<40 copies/ml). Controllers are shown in horizontal black lines.

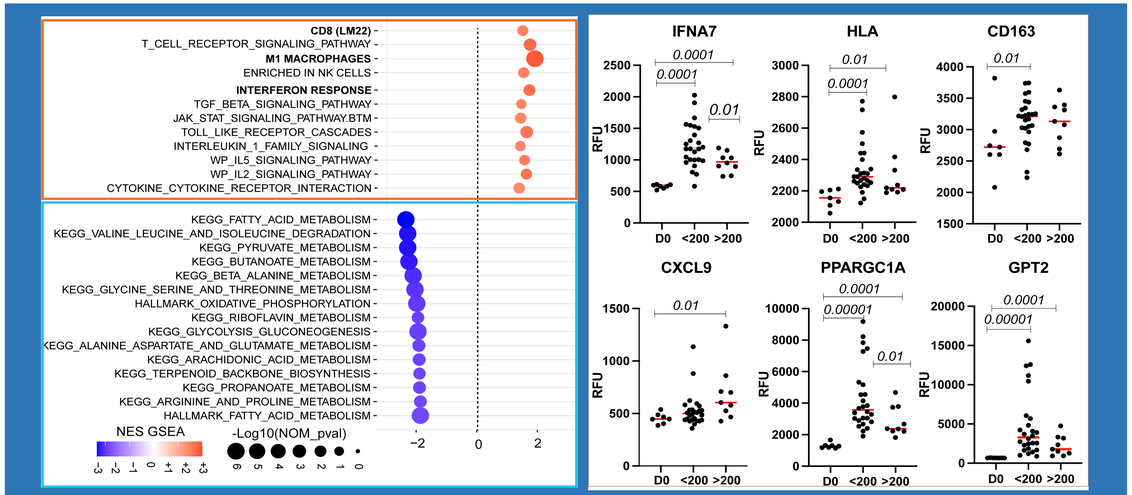


**Fig.3**. Left panel: Pathways increased (in red) or decreased (in blue) before detectable rebound (VL<200 cp/ml) compared with D0 (before ATI). Circle size depicts pathway enrichment score.
Right panel: Plasma level of IFNA7, HLA, CD163, CXCL9, PPARGC1A and GPT2 increased before (VL<200 cp/ml) and after detectable rebound (VL>200 cp/ml) compared with pre ATI (D0)

### b. Plasma biomarkers predicting viral rebound after ATI

We observed a significant increase (pathway enrichment analysis, adjusted p-value < 0.05) of T cell receptor signaling, CD8 T cell, and proinflammatory signatures preceding detectable rebound (VL<200 cp/ml) that were augmented after rebound (**Fig. 3: left panel**). Signatures of activated proinflammatory macrophages M1, response to interferon-alpha and gamma as well as proinflammatory markers (CD163, IFNA7, CXCL9, TNFRSF1B, HLA, CD14, CSF1) were elevated before detectable rebound compared with pre-ATI (**Fig. 3: right panel**). Metabolic pathways such as fatty acid metabolism and oxidative phosphorylation show dysregulation or a decrease after ATI and before detectable rebound, indicating metabolic alterations in the rebounders preceding rebound (**Fig 3**).

## CONCLUSIONS

Our preliminary observations highlight the role of proinflammatory signatures and macrophages activation and metabolic pathways as potential plasma biomarkers to predict imminent rebound following ART discontinuation in PLWH.

## ADDITIONAL KEY INFORMATION

### Acknowledgements

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