Switching From Standard-of-Care Antiretroviral Therapy (SoC ART) to Dual-Therapy Lotivibart (LVB) Plus Cabotegravir (CAB) Is Associated With a Modest Reduction in Chronic Innate Immune Activation in Virologically Suppressed Adults With HIV

P045

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Key Takeaways

- Broadly neutralizing antibodies may offer immunologic benefits beyond direct antiretroviral activity
- In this exploratory analysis of the phase 2b EMBRACE study, we investigated the impact of switching from standard-of-care antiretroviral therapy to lotivibart (LVB; N6LS) + cabotegravir (CAB) on serum proteomics in virologically suppressed adults with HIV-1
- Suppressed switch from standard-of-care antiretroviral therapy to a regimen of LVB + CAB was associated with a proteomic signature consistent with modestly reduced chronic innate immune activation

Plain Language Summary

- In this study, 125 adults with HIV-1 whose virus was suppressed on daily pills either stayed on their daily pills or switched to a long-acting dual-therapy of lotivibart, an antibody-based HIV medicine in development, plus cabotegravir
- Levels of immune system-related proteins were measured from blood samples over 12 months to examine changes in inflammation and immune system activation
- People who switched to the long-acting lotivibart-based regimen showed a protein profile consistent with a reduction in immune activation; people who stayed on their daily pills did not show a reduction

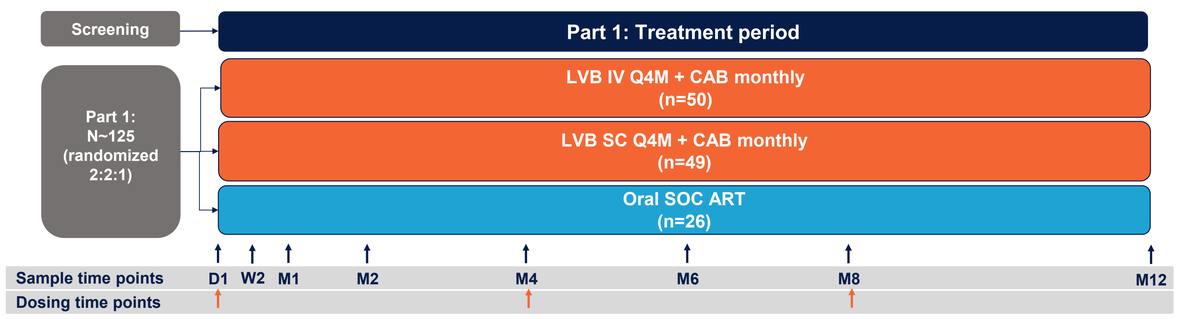
Introduction

- HIV-1–specific broadly neutralizing antibodies (bNAbs) are being investigated for their antiviral activities through neutralization of the HIV-1 Env protein, preventing interaction with cellular receptors and infection of new cells
- Moreover, bNAbs mediate important immunologic effects and may affect immune activation beyond direct antiviral activity
- Lotivibart (LVB; N6LS) is a bNAb in phase 2b clinical trials for maintenance of HIV-1 suppression
- In people with HIV and virologic suppression, plasma proteomics often reflects a mixture of residual myeloid activation, gut barrier and lymphoid perturbation, and intracellular leakage or release from activated or stressed cells rather than the classic cytokine storm associated with untreated people[1-4]
- In this exploratory analysis among adults with virologic suppression from the phase 2b EMBRACE study (NCT05996471), we used serum proteomics to assess the impact of switching from standard-of-care (SOC) triple-agent antiretroviral therapy (ART) to LVB plus cabotegravir (CAB)

Methods

- EMBRACE (Figure 1) is a phase 2b multicenter, randomized, open-label study in which participants with virologic suppression (N=125; median [range] baseline CD4+ cell count, 383 [179-850] cells/mm^3) continued their SOC ART (n=26) or switched to LVB, administered intravenously (IV; n=50) or subcutaneously (SC) with recombinant human hyaluronidase (rHuPH20) (n=49) every 4 months, in combination with CAB intramuscular injection every month
- Serum samples were drawn at Day 1 (pre-dose); Week 2; and Months 1, 2, 4, 6, 8, and 12
- Key inclusion criteria in EMBRACE were inclusion of people with plasma HIV-1 RNA <50 c/mL and CD4+ T-cell count ≥350 cells/mm^3; key exclusion criteria included noninfectious liver disease, pancreatitis, cardiovascular disease, and malignancies

Figure 1. Study Design



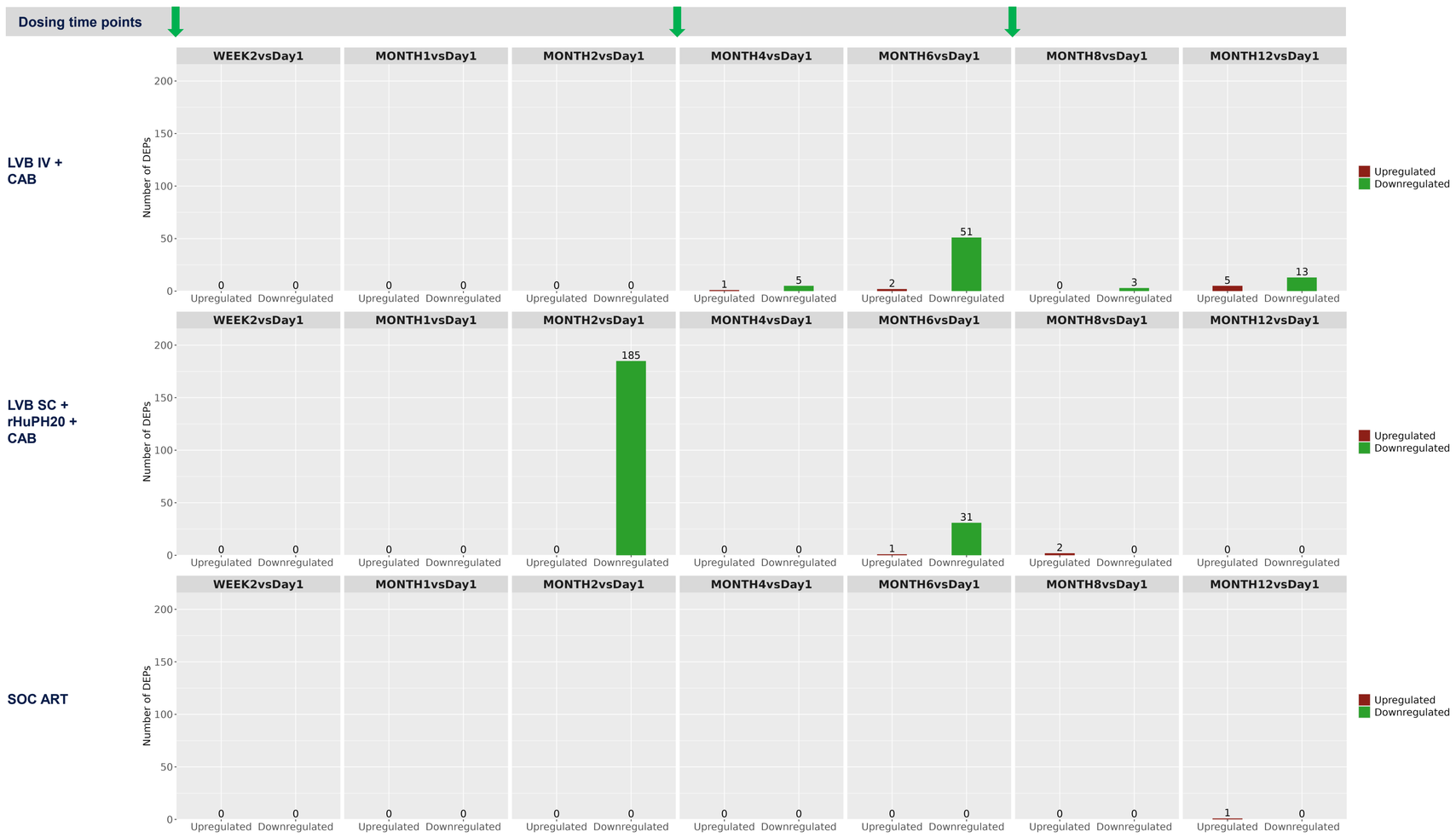
D, Day; M, Month; Q4M, every 4 months; W, Week.

- Participants who experienced confirmed virologic failure (CVF) were excluded from this analysis. These include: LVB IV, n=2; LVB SC, n=3; and SOC ART, n=1
- Serum proteins were measured using Olink Reveal, a high-throughput, next-generation sequencing proteomics workflow that employs Proximity Extension Assay technology to quantify 1034 human proteins. The assay is focused on markers of immune activation
- The analysis data set included $\log_2$-transformed normalized protein expression (NPX) values for each protein
- Differentially expressed protein (DEP) analysis was performed using limma on proteins with NPX values greater than the limit of detection in ≥50% of samples
- The differential expression cutoff was a fold change of 1.2, and a Benjamini-Hochberg (BH)-adjusted *P* value of ≤0.05 was used
- Findings were confirmed using per-protein pairwise *t* tests with a BH-adjusted *P* value set at 0.05. DEPs at each follow-up time point up to Month 12 were compared with Day 1 (pre-dose) within each group
- Pathway enrichment analysis was performed using R package clusterProfiler based on GO-BP, KEGG, and Reactome databases

Results

- The number of statistically significantly up- and downregulated DEPs are shown for each time point by study treatment in Figure 2

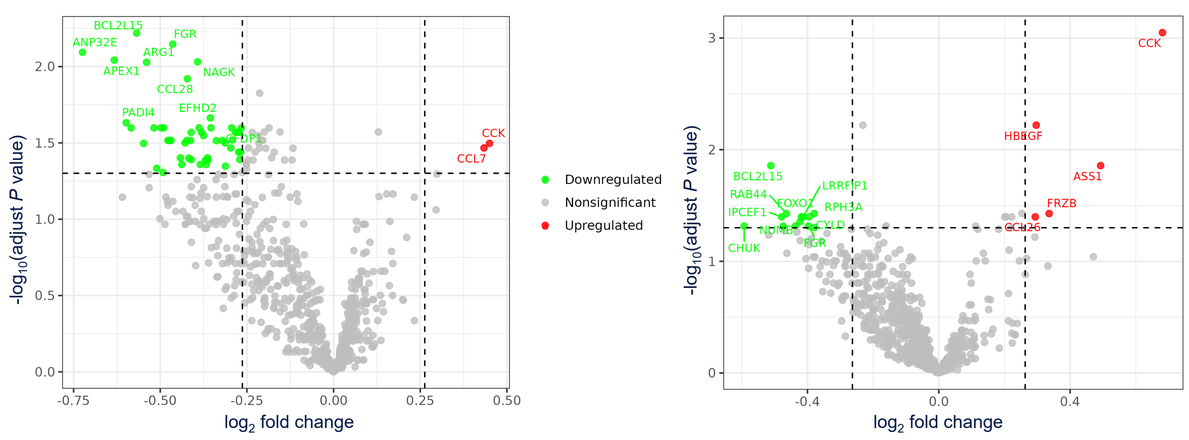
Figure 2. Number of Differentially Expressed Proteins at Each Time Point by Study Treatment



Bar plots of DEPs identified by limma between baseline (Day 1) and post-treatment time points. Filtered to keep proteins with NPX > limit of detection in at least 50% of samples and to exclude participants with CVF. DEPs defined as $|\log_2 FC| > \log_2(1.2)$ and BH-adjusted $P \leq 0.05$.

- The DEPs in the LVB IV + CAB arm at Months 6 and 12 are shown below (Figure 3A and 3B)

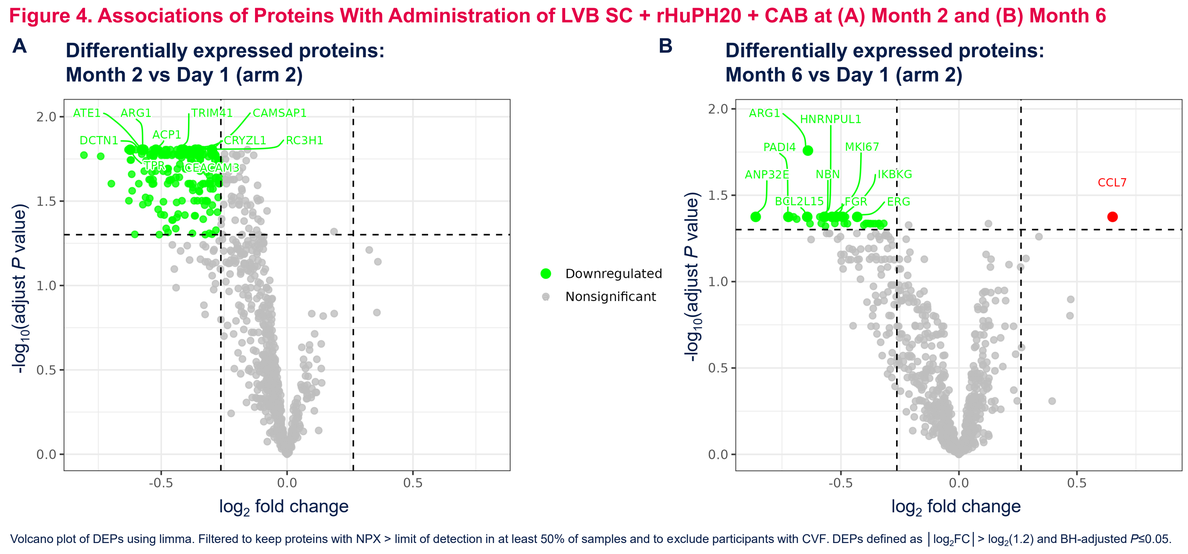
Figure 3. Associations of Proteins With Administration of LVB IV + CAB at (A) Month 6 and (B) Month 12



Volcano plot of DEPs using limma. Filtered to keep proteins with NPX > limit of detection in at least 50% of samples and to exclude participants with CVF. DEPs defined as $|\log_2 FC| > \log_2(1.2)$ and BH-adjusted $P \leq 0.05$.

- The DEPs in the LVB SC + rHuPH20 + CAB arm at Months 2 and 6 are shown below (Figure 4A and 4B)

Figure 4. Associations of Proteins With Administration of LVB SC + rHuPH20 + CAB at (A) Month 2 and (B) Month 6



Volcano plot of DEPs using limma. Filtered to keep proteins with NPX > limit of detection in at least 50% of samples and to exclude participants with CVF. DEPs defined as $|\log_2 FC| > \log_2(1.2)$ and BH-adjusted $P \leq 0.05$.

- The top 10 DEPs by adjusted *P* value at each time point by study treatment are shown in the Table

Table. Top 10 DEPs by Adjusted *P* Value at Each Time Point by Study Treatment

	LVB IV + CAB				LVB SC + rHuPH20 + CAB			SOC ART
	M4vsD1	M6vsD1	M8vsD1	M12vsD1	M2vsD1	M6vsD1	M8vsD1	M12vsD1
Upregulated proteins	CA9	CCK CCL7	NA	CCK HBEGF ASS1 FRZB CCL26	NA	CCL7	ALPI CTRL	ACP1
Downregulated proteins	BCL2L15 RPH3A EFHD2 NAGK MAP2K1	BCL2L15 FGR ANP32E APEX1 NAGK ARG1 CCL28 EFHD2 PADI4 CFDP1	BCL2L15 RAB44 FGR	BCL2L15 RAB44 RPH3A CYLD LRRFIP1 FOXO1 IPCEF1 NUMB CHUK FGR	TRIM41 ATE1 CEACAM3 RC3H1 TPR ACP1 ARG1 CAMSAP1 CRYZL1 DCTN1	ARG1 ERG ANP32E BCL2L15 FGR MKI67 NBN PADI4 HNRNPUL1 IKBKG	NA	NA

D, Day; M, Month; NA, not applicable.

Interpretation

- The proteomic signature in the SOC group was stable across 12 months
- The DEPs in the LVB groups consist of a mix of circulating mediators, tissue secretory or epithelial surface signal proteins, shed membrane proteins, and intracellular markers, likely reflecting cell activation or turnover
- The main biological pattern observed in the 2 LVB groups was a modest fall in serum markers of chronic monocyte activation (FGR, ARG1), chronic neutrophil activation (ARG1,CEACAM3, PADI4, RAB44), NF-κB–related proteins (CHUK, IKBKG), and cellular stress markers (BCL2L15, NAGK, ANP32E, APEX1, CFDP1)
- Pathway enrichment analysis based on GO-BP, KEGG, and Reactome databases suggests that downregulated proteins are related to regulation of innate immune responses, response to virus, and negative regulation of lymphocyte activation
- Given the low signal strength observed, these data must be interpreted with caution

Conclusions

- Switching from SOC ART to a dual regimen of LVB + CAB resulted in almost no proinflammatory signal and was associated with a serum proteomic profile consistent with a modest reduction in chronic immune activation

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