5’Leader defective HIV-1 proviruses from PWH with non-suppressible viremia produce soluble gp120

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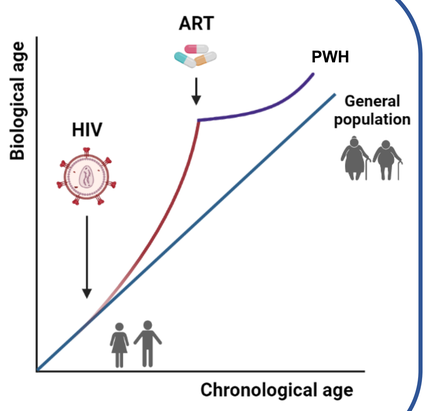
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BACKGROUND

Despite antiretroviral therapy, people with HIV (PWH) show signs of chronic immune activation and dysfunction.

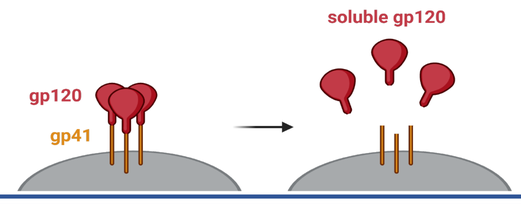
PWH have higher incidence of :

- Cardiovascular events
- Kidney impairments
- Cognitive disorders
- Cancer
- Persistent chronic inflammation

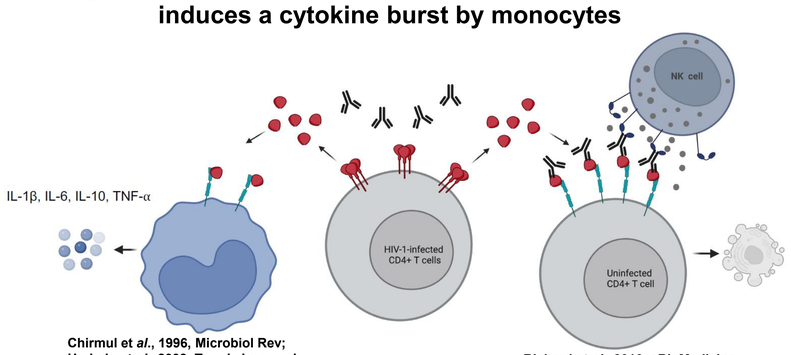


Modified from Rodés et al., 2022, eBioMedicine

gp120 shedding



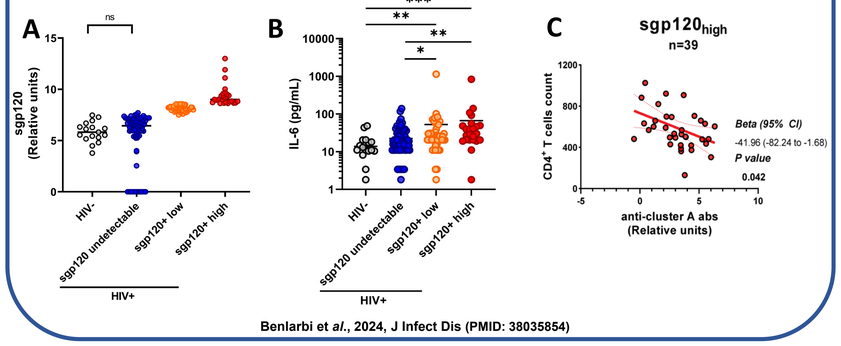
Shed gp120 sensitizes uninfected bystander cells to ADCC and induces a cytokine burst by monocytes



Chirmul et *al.*, 1996, Microbiol Rev;
Herbein et *al.*, 2008, Trends Immunol;
Rychert et *al.*, 2010, AIDS Res Hum Retroviruses;
Levast et *al.*, 2017, PLoS One;
Richard et *al.*, 2023, Cell Chem Biol;
Benlarbi et *al.*, 2024, J Infect Dis

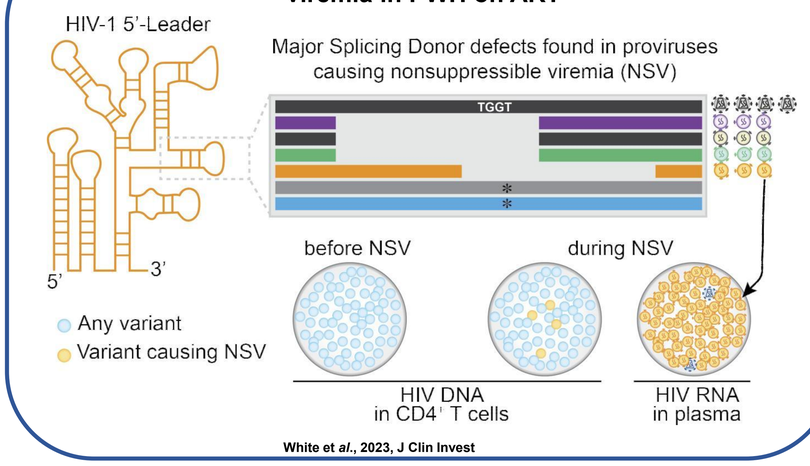
Richard et *al.*, 2016, eBioMedicine;
Richard et *al.*, 2018, mBio;
Richard et *al.*, 2023, Cell Chem Biol;
Benlarbi et *al.*, 2024, J Infect Dis;
Benlarbi et *al.*, 2025 eBioMedicine

Soluble gp120 is immunomodulatory in PWH on ART with undetectable viral load



Benlarbi et *al.*, 2024, J Infect Dis (PMID: 38035854)

5’Leader defective proviruses contribute to non-suppressible viremia in PWH on ART



White et *al.*, 2023, J Clin Invest

RESULTS

Insertion of 5’Leader mutations within infectious molecular clones reduces cell-surface Env expression

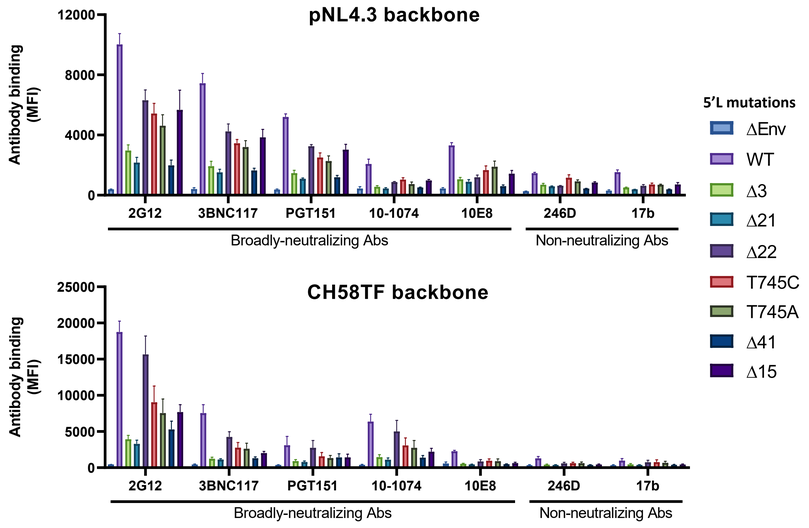


Figure 1. Cell-surface Env expression of 5’Leader defective proviruses. HEK293T cells were transfected with different constructs and Env expression was measured using a panel of monoclonal antibodies.

5’Leader defective proviruses produce detectable levels of soluble gp120

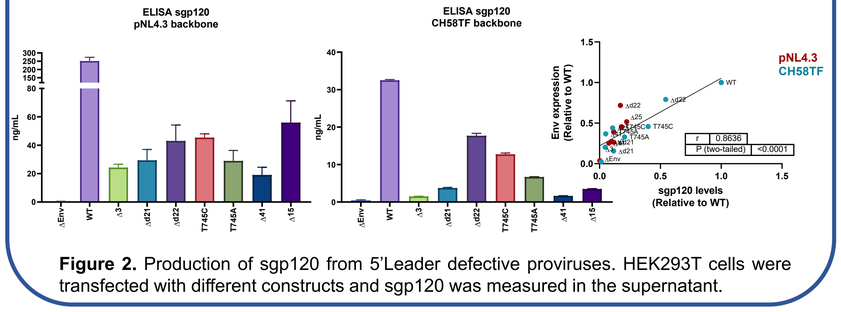


Figure 2. Production of sgp120 from 5’Leader defective proviruses. HEK293T cells were transfected with different constructs and sgp120 was measured in the supernatant.

Shed sgp120 from 5’Leader defective proviruses sensitize uninfected bystander CD4 T cells to ADCC-mediated killing

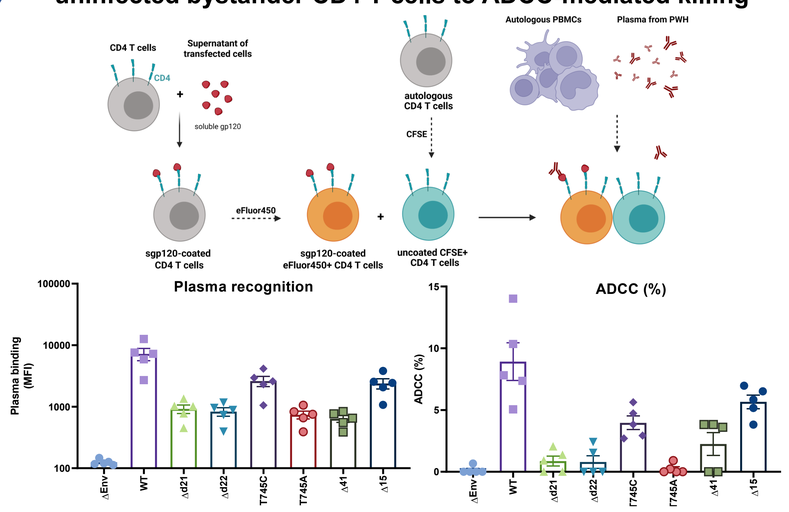
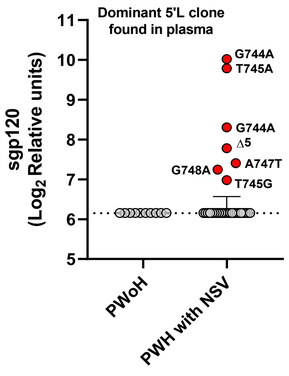
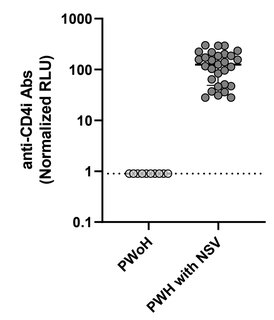


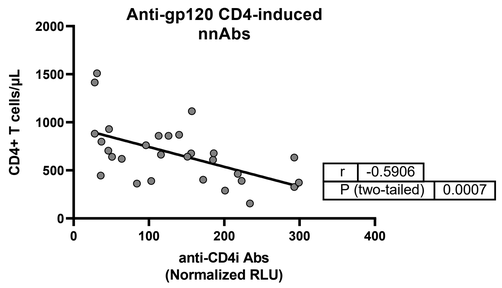
Figure 3. Shed sgp120 from pNL4.3 WT or 5’Leader defective constructs lead to recognition and elimination of uninfected bystander CD4 T cells by PWH plasma. Supernatant of transfected cells were used as a source of sgp120 and incubated with primary CD4 T cells. Recognition and ADCC-mediated killing was performed using 5 plasma from PWH and autologous PBMCs as effector cells.

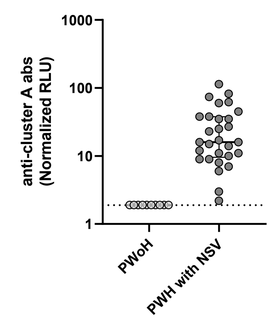
PWH on ART with NSV have detectable sgp120 in plasma and their CD4i Abs are negatively associated with CD4+ T cell count



	Sgp120 undetectable	Sgp120+
N	22	7
Sex, male (n, %)	20 (91%)	7 (100)
Nadir CD4 (mean, SD)	186.1 (122)	149.8 (59)
Min-Max	22-390	60-220
CD4 count (mean, SD)	690 (336)	611 (236)
Min-Max	155-1509	326-930
Years on ART (mean, SD)	17.33 (9.8)	16.47 (6.2)
HIV-1 RNA cp/mL, average during NSV (mean, SD)	227.5 (586)	200.1 (269)
Years of observed NSV (mean, SD)	4.86 (3.6)	5.6 (4.8)
NSV type (n, %)		
Short term ART	4 (18.1)	0 (0)
Intermittent	8 (36.4)	1 (14.3)
Continuous	10 (45.5)	6 (85.7)
number of 5’L variants found in plasma (mean, SD)	3.5 (2.5)	3.3 (3.0)
% intact 5’L RNA (mean, SD)	29 (37.7)	4.4 (8.6)







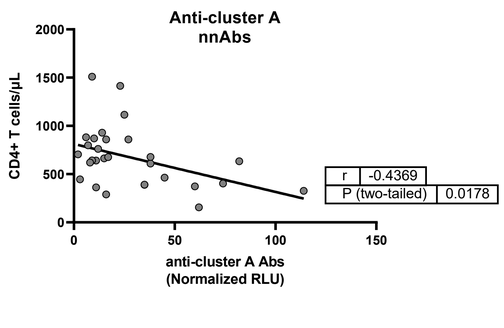


Figure 4. Detection of sgp120 and antibodies in the plasma of 29 PWH on ART with NSV. Sgp120 and CD4-induced antibodies in the plasma were measured using an ELISA assay as reported (PMID: 38035854, 40684476, 40990223). Association between CD4 counts and anti-gp120 non-neutralizing antibodies (nnAbs) was assessed using Spearman rank correlations.

CONCLUSION

- **5’Leader defective proviruses produce sgp120 and sensitize uninfected bystander CD4 T cells to ADCC responses**
- **Sgp120 is detected in PWH whose NSV are driven by dominant clones harboring 5’L defects**
- **Anti-gp120 nnAbs correlate negatively with CD4 counts**

Our results suggest that 5’L defective proviruses causing NSV may be a source of sgp120 in PWH on ART. Understanding the persistence of these clones is important to develop new strategies to decrease immune dysfunction in these individuals.

ACKNOWLEDGEMENTS

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Schematics prepared with BioRender (Biorender.com)