Sialidase Inhibition Prevents HIV-mediated Inflammation and Immune Activation *in vivo*

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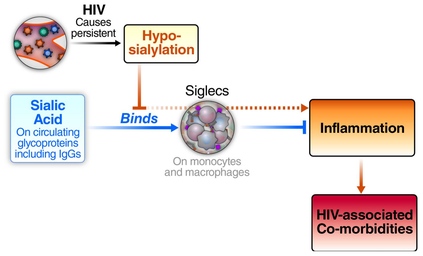
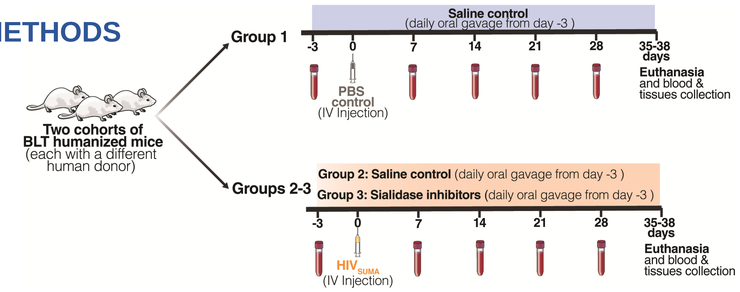
BACKGROUND

- Proteins containing a glycan sialic acid (sialylated) are reduced during HIV infection (both viremic and antiretroviral-therapy (ART)-suppressed), and levels of sialidase (enzyme cleaving sialic acid) are elevated.
- Sialylated glycoproteins initiate anti-inflammatory immune responses by engaging the inhibitory sialic-acid binding proteins (Siglecs) expressed on several immune cells.



- We tested whether inhibiting sialidase via sialidase inhibitors commonly used clinically to treat influenza (oseltamivir and DANA), would attenuate HIV-mediated immune activation/inflammation *in vivo.*

METHODS



- Plasma markers of inflammation, T cell activation in blood and tissued, and levels of cell-associated HIV DNA were measured by qPCR.

RESULTS

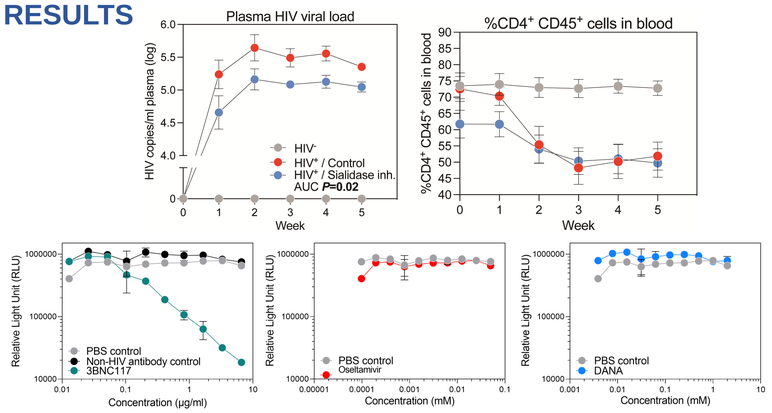


Figure 1. Sialidase Inhibitor treatment reduces viral load but does not have direct antiviral activity. Top: Plasma viral load and CD4+ T Cell count from weekly bleed. Bottom: TZMbl assay showing that despite lower viral load *in vivo*, sialidase inhibitor treatment does not directly impact viral infection and that the impact on viral load is likely indirect by modulating immune activation.

Normalizing glycosylation patterns - in particular **sialylation**- represents a novel approach to preventing the development of inflammation during HIV infection.

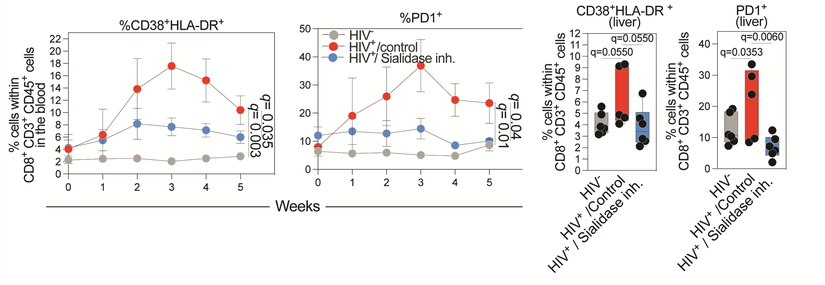


Figure 2. Sialidase inhibition significantly attenuated HIV-mediated induction of CD8+ T cell activation and exhaustion. Percentage of CD8+ T Cells CD38+HLA-DR + and PD1 + in the blood (A) over time and tissue (B) at the sacrifice.

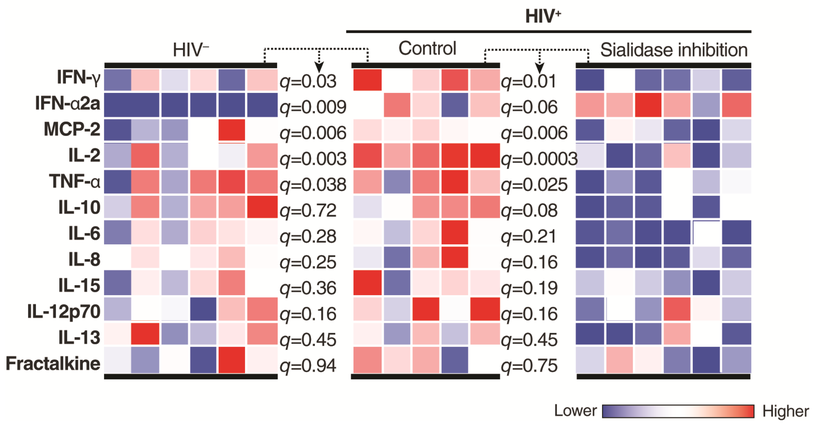


Figure 3. Sialidase inhibitor treatment significantly attenuated the HIV-mediated induction of several markers of inflammation. Markers of the pro-inflammatory type-II interferon, such as IFN-γ responses, are lower in mice receiving sialidase inhibitor treatment. In contrast, sialidase inhibition induced levels of the antiviral type-I interferon-α (q=0.06).

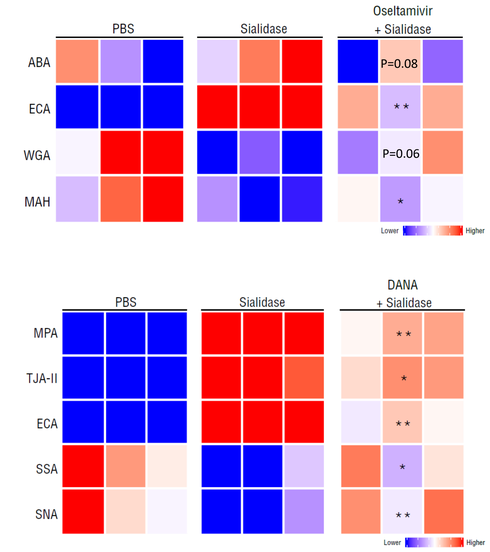


Figure 4. Sialidase inhibitors reverse the loss of sialic acid *in vitro.* Monocyte-derived macrophages were treated with sialidase in the presence or not of sialidase inhibitors. The inhibitors were able to reverse loss of Sialic acid, as well as reduce myeloid inflammation caused by sialidase (data not shown)

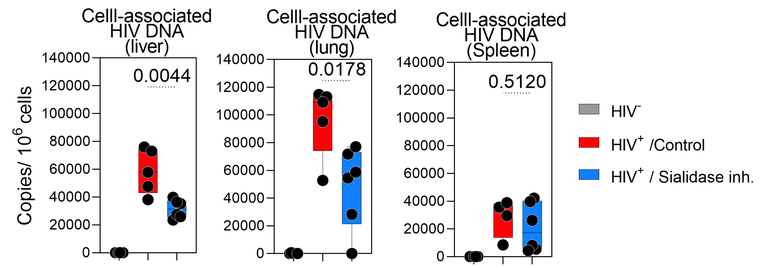


Figure 5. Sialidase inhibition significantly reduces cell-associated HIV- DNA in tissues. The reduction in HIV-mediated inflammation and immune activation was accompanied by a decrease in cell-associated HIV DNA in the liver and lungs.

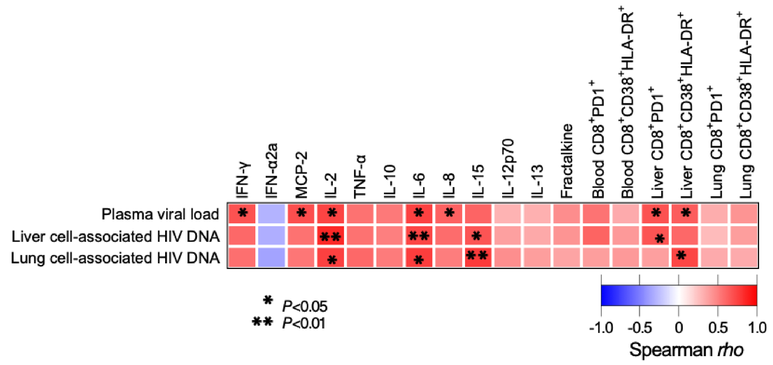


Figure 6. The degree of immune activation and inflammation significantly correlated with higher levels of HIV viral load in plasma and tissues.

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