Anti-α4β7 antibody facilitates improved renal function during SIV infection in macaques

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BACKGROUND

Globally, approximately 38 million people are living with HIV (PLWH) and are at high risk of kidney injury, known as HIV-associated nephropathy (HIVAN). This progressive disease is characterized by collapsing focal segmental glomerulosclerosis (FSGS), segmental scarring of the glomeruli. Combination antiretroviral therapy (cART) significantly reduces HIVAN incidence, but chronic kidney disease remains elevated in PLWH. Prior research has suggested that one mechanism contributing to FSGS is loss of mature podocytes, which provide critical structural support for the glomeruli[1]. The differentiation of podocytes requires all-trans retinoic acid (atRA), which is significantly reduced in the plasma during HIV. More recent findings also suggest that Galectin-3, a pro-fibrotic signal, are closely associated with kidney dysfunction in people living with HIV[2].

Previously, we have characterized the ability of anti-α4β7 antibody administration to facilitate increased lamina propria macrophage differentiation in the gut of SIV-infected macaques[3]. Because we found increased abundance of these critical cells, which are lost during SIV progression, we tested whether their return was also associated improvements in retinoid signaling[4]. We hypothesized that the return of atRA may ameliorate lost podocyte differentiation during HIV. Here, we determine if these pathways are modulated by anti-α4β7 administration utilizing a non-human primate model. We aimed to contextualize these findings in the current landscape of HIVAN research, and we offer new avenues for therapeutic intervention efforts to improve the lives of PLWH.

METHODS

Nine rhesus macaques (*Macaca mulatta*) were CD8-depleted and inoculated with TCID50 1000 SIVmac251. Daily cART was begun at week two, along with antibody infusions (anti-α4β7 mAb: n=5; IgG controls: n=4) every three weeks until week 23. cART was discontinued (analytical treatment interruption) at week 14. Longitudinal plasma measurements were performed for retinoids utilizing high-performance liquid chromatography (HPLC)-UV, for serum chemistry (blood urea nitrogen and creatinine), and for Galectin-3 by Luminex. atRA metabolism and podocyte differentiation gene expression were determined by real-time polymerase chain reaction (qPCR) using kidney samples collected at necropsy and compared to uninfected (SIV negative) rhesus macaques (n=4).

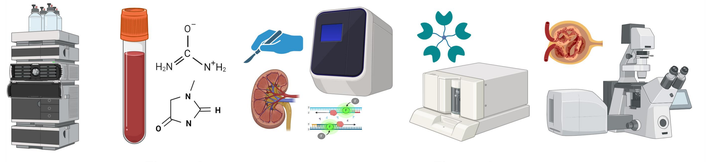


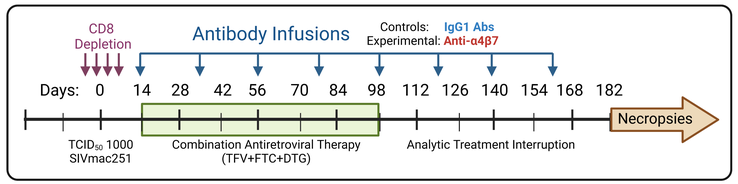
Figure 1: Retinoids **HPLC-UV**

Figure 2: BUN and Creatinine **Serum Chemistry**

Figure 3: Gene Expression **qPCR**

Figure 4: Plasma Galectin-3 **Luminex**

Future: Podocyte Differentaition **Microscopy**



1) Anti-$\alpha_4\beta_7$ mAb led to significant ***increases*** in plasma *all-trans* retinoic acid during SIV infection.
2) ***Increased*** retinoid signaling was associated with improved renal function, as measured by BUN:creatinine.
3) Anti-$\alpha_4\beta_7$ mAb facilitated ***increased*** ALDH1As and podocyte differentiation marker SYNPO without increases in markers of retinoid-induced toxicity.
4) Plasma Galectin-3 (HIVAN marker) was ***decreased*** and associated with other measures, including renal function.

RESULTS

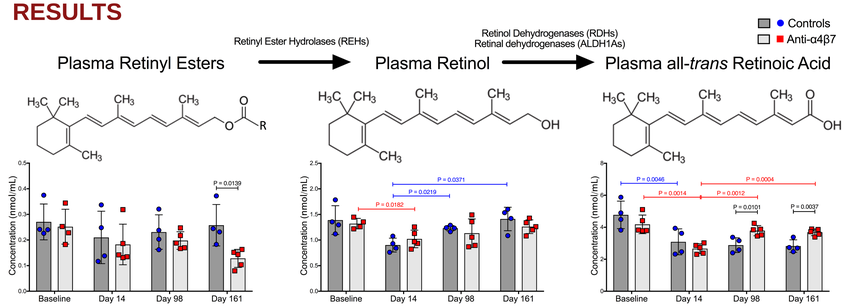


Fig. 1. Anti-α4β7 facilitates increased plasma all-trans retinoic acid levels: Plasma retinoid levels at baseline, acute infection (Day 14), viral suppression and therapy administration (Day 98), and analytical treatment (cART) interruption (Day 161).

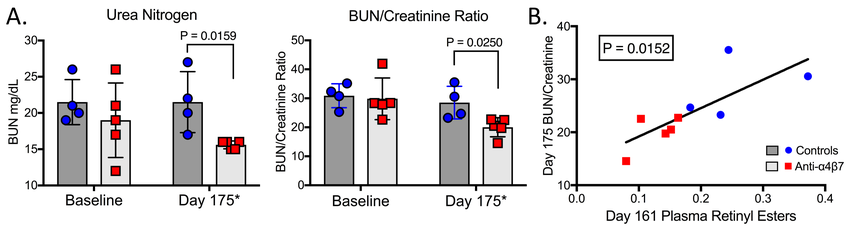


Fig. 2. Improved retinoid signaling is associated with renal function: A) Serum chemistry measures of blood urea nitrogen (BUN) and creatinine. B) Association between BUN:creatinine ratio and un-utilized atRA precursors (retinyl esters).

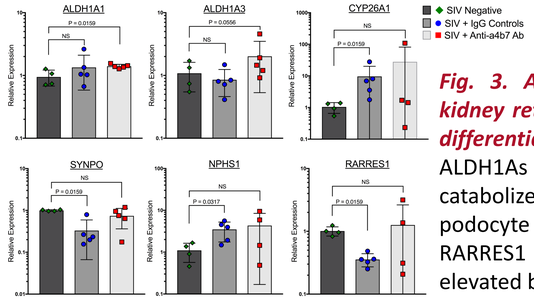


Fig. 3. Anti-α4β7 is associated with kidney retinoid signaling and podocyte differentiation gene expression: ALDH1As synthesize atRA, CYP26A1 catabolizes atRA, SYNPO and NPHS1 are podocyte differentiation markers, and RARRES1 indicates retinoid toxicity (not elevated by anti-α4β7 administration).

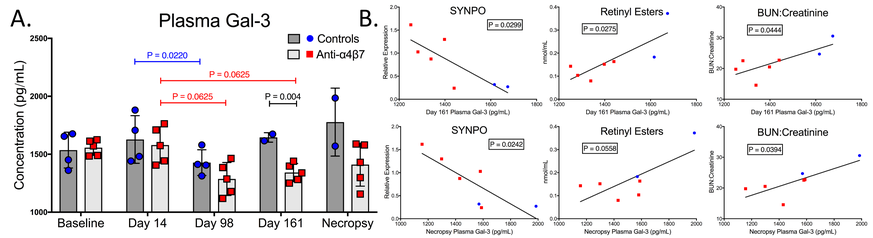
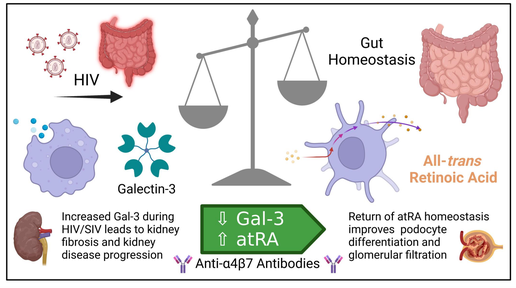


Fig. 4. Anti-α4β7 is associated with reductions in plasma HIVAN marker Galectin-3: A) Pro-fibrotic Galectin-3 levels at baseline, acute infection (Day 14), viral suppression and therapy administration (Day 98), analytical treatment (cART) interruption (Day 161), and necropsy. B) Associations of Galectin-3 with podocyte differentiation marker (SYNPO), atRA precursors (retinyl esters), and renal function (BUN:creatinine).

CONCLUSIONS

- We found that anti-α4β7 administration was associated with increased *all-trans* retinoic acid synthesis, and this improved retinoid signaling was associated with improved renal function.
- Additionally, anti-α4β7 was associated with lower levels of Galectin-3, a recently described marker of HIVAN progression in people living with HIV.
- The data described here suggest that anti-α4β7, which has already been approved as a therapy for inflammatory bowel diseases (vedolizumab), may also facilitate improved renal function in people living with HIV. New studies are thus warranted.



Summary Figure. Anti-α4β7 facilitates a shift from pro-fibrotic Galectin-3 to pro-podocyte differentiation *all-trans* Retinoic Acid in the plasma. These changes are associated with improved renal function, including BUN:creatinine Ratio.

FUTURE DIRECTIONS

- Future studies will use microscopy to confirm increased SYNPO gene expression is associated with podocyte differentiation in the glumeruli following anti-α4β7.
- Kidney fibrosis markers will also be characterized to test whether tubulointerstitial fibrosis associates with plasma Galectin-3 levels.
- Additionally, an analysis utilizing samples from a clinical trial (HAVARTI) will be performed to validate these findings in people living with HIV.

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