Safety and Antiviral Activity of CD4 mimetic treatment in SHIV-infected Rhesus macaques

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BACKGROUND

Antiretroviral therapy (ART) suppresses HIV-1 replication in people living with HIV (PWH) but does not eliminate replication-competent HIV-1-infected CD4 T cells. Multiple strategies aimed at targeting the viral reservoir to achieve an ART-free remission have been explored, including strategies that increase antibody-dependent cellular cytotoxicity (ADCC). PWH naturally develop CD4-induced (CD4i) Abs targeting Env that mediate ADCC. However, HIV-1 Vpu-mediated CD4 downregulation at the cell membrane keeps Env in a closed conformation, thereby hiding CD4i epitopes. We developed a CD4-mimetic compound, CJF-III-288, together with anti-Co receptor-binding site (Co-RBS) and anti-cluster A Abs, to fully open the Env and induce ADCC in infected CD4 T cells. Here, we evaluated the safety and antiviral efficacy of CJF-III-288 in SHIV-AD8-EO–infected RMs when administered with anti-cluster A and anti-CoRBS abs.

METHODS

Twelve Indian-origin rhesus macaques (RMs) were intravenously (i.v.) infected with 1,000 TCID50 of SHIV-AD8-EO. All RMs received a single i.v. infusion of 17b and A32 non-neutralizing antibodies (nnAbs; 20 mg/kg each) at day 35 p.i. (**Fig. 1**). They also received either the vehicle (15% Kleptose solution; n=6) or CJF-III-288 (36 mg/kg in 15% Kleptose; n=6) subcutaneously (s.c.) every 3-4 days. All 12 RMs initiated ART at day 43 p.i. and underwent analytical treatment interruption (ATI) at day 209 p.i. On day 7 post-ATI, animals received an additional i.v. dose of nnAbs, with vehicle or CJF-III-288 administered every 3–4 days for six doses. Plasma viral load and intact proviral DNA were quantified.

Fig 1. Study design

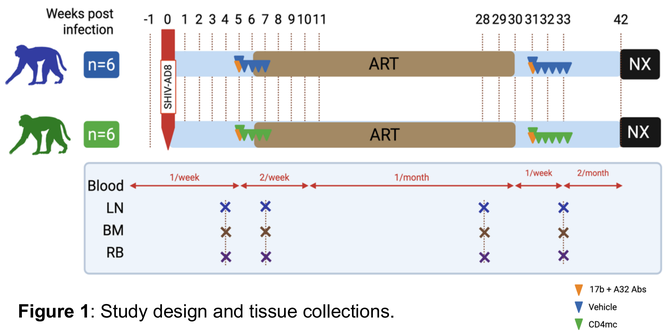


Figure 1: Study design and tissue collections.

CJF-III-288 in SHIV-infected RMs is safe and slightly reduces SHIV-AD8 plasma viral load and SHIV-DNA-harboring CD4 T cells in LN

RESULTS

Fig 2. Transient elevation of ALT and AST

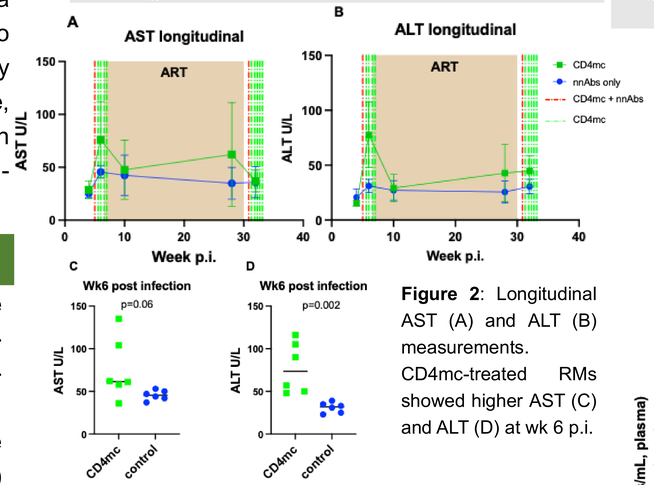


Figure 2: Longitudinal AST (A) and ALT (B) measurements. CD4mc-treated RMs showed higher AST (C) and ALT (D) at wk 6 p.i.

CJF-III-288 treatment is well tolerated with no major side effects. Compared with controls, treated RMs showed a transient increase in serum levels of Aspartate aminotransferase (AST, p=0.06) and Alanine transaminase (ALT, p=0.002) during treatment (d43 p.i.), which rapidly normalized thereafter (**Fig. 2A-D**). CD4mc treatment did not impact on the timing to or extent of viral rebound after ATI (**Fig. 3A**). Despite comparable levels before CJF-III-288 treatment (**Fig 3B,** wk5 p.i.), we observed a slightly lower PVL at wk6 p.i. in treated RMs compared to control (**Fig. 3C;** Median 5.0 x 10^4, IQR 1.4 x 10^4 vs Median 2.4 x 10^5, IQR 1.2 x 10^5). As a result, the fold change (FC) in PVL between wk6 and wk5 p.i. is lower (i.e., higher reduction) in treated RMs (0.50 ± 0.25) as compared to controls (1.00 ± 0.40) (**Fig. 3D**).

Fig 3. A slight reduction in PVL is observed in the first cycle of CD4mc treatment

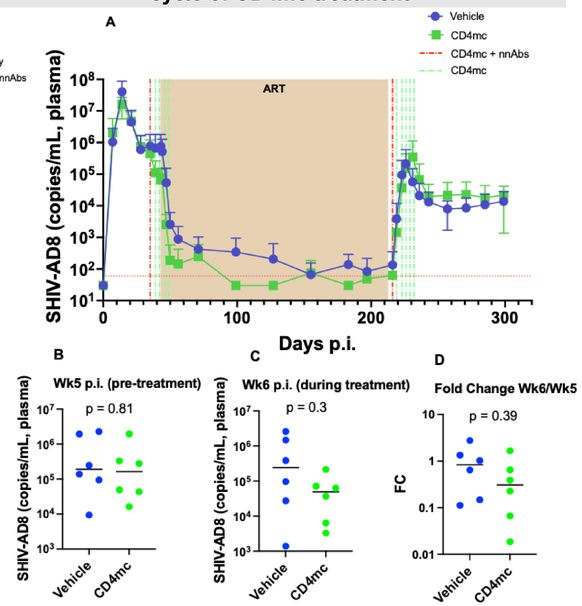


Figure 3: Longitudinal PVL measurements (A). PVL is slightly reduced in CD4mc treated RMs as compared to controls during treatment before starting ART (C), despite similar levels before starting treatment (B). The wk6 vs. wk5 FC is lower in CD4mc treated RMs (D)

Since we observed this higher reduction in PVL between ART initiation and after 3 doses of CJF-III-288, we then measured the levels of intact SHIV-DNA in CD4 T cells isolated from blood and LN with IPDA. In PBMC, we did not find significant differences between treated and control animals (**Fig. 4A**). In LN, we observed lower SHIV-DNA in treated RMs compared to control at wk6 p.i. (**Fig. 4B**); as a result, the FC calculated between wk6 and wk4 p.i. was 0.60 ± 0.09 in treated animals versus 1.07 ± 0.23 in controls (**Fig. 4D**).

Fig 4. Intact proviral DNA measures in blood and LN CD4+ T cells

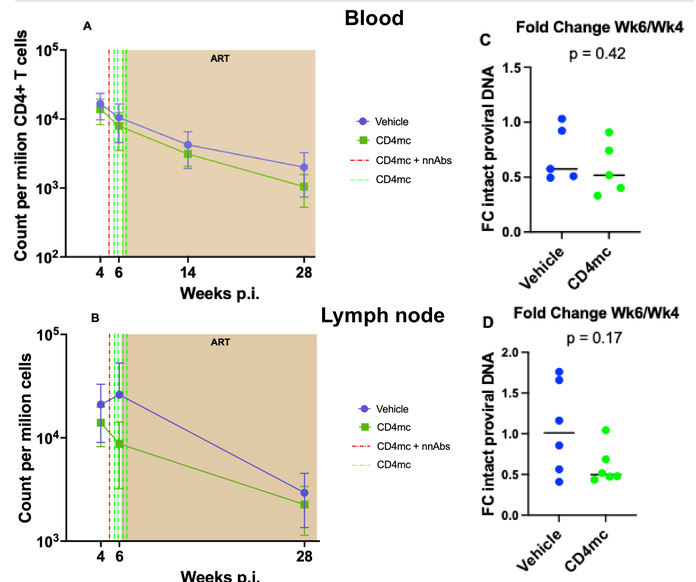


Figure 4: Longitudinal IPDA measurement in blood (A) and LN (B) purified CD4+ T cells. FC calculated between Wk6/Wk4 p.i. was similar in blood between CD4mc treated and control RMs (C). In LN CD4mc treated animals had slightly lower FC compared to controls (D).

CONCLUSIONS

Repeated treatment with CJF-III-288 was well tolerated in SIV-infected and ART treated RMs, with no major side effects. Our study suggests a biological impact of the CJF-III-288 in combination with nnAbs, resulting in a modest reduction in PVL and CD4+ T cells carrying SHIV-DNA in LN.

ACKNOWLEDGMENTS

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PLAIN LANGUANGE SUMMARY

This is the first proof of concept in the most clinically relevant animal model for HIV infection that treatment with CJF-III-288, a small CD4 mimetic compound paired with a cocktail of antibodies, is safe and has the potential to promote killing of SHIV-infected cells.