

bNAbs Detected in Tissue Up to 46 Weeks Post-Administration

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Objective

- To determine if VRC bNAbs persisted in tissue collected from UCSF-amfAR trial participants using a VRC-developed anti-HIV bNAb idiotype antibody (5C9, broadly binding to VRC bNAbs).

Introduction

- Developing functional HIV cure strategies remains a top research priority.
- Despite promising results from a recent combination immunotherapy trial (NCT04357821, the UCSF-amfAR trial), including boosted vaccine, TLR9 agonist, and two doses of dual broadly neutralizing antibodies (bNAbs, VRC07-523LS and 10-1074) prior to and at the time of antiretroviral treatment interruption.
- A lack of an established approach to evaluate bNAb levels in tissues has limited the understanding of their persistence at tissue sites.

Methods and Materials

- Formalin-fixed paraffin-embedded rectal biopsies were collected 26-51 weeks following VRC07-523LS administration from six participants (26.9, 29.0, 43.0, 46.1, 46.6, and 51.1 weeks post-bNAb, participants 1-6, respectively), and from control participant without HIV not receiving bNAbs.
- For immunohistochemistry (IHC) imaging, sections were subjected to antigen retrieval with pepsin, and incubated with 5C9 primary antibody of 2.5 µg/mL (Vaccine Research Center) overnight. Next day, sections were incubated with secondary antibody (Leica, pv6119), stained with DAB, counterstained with hematoxylin, and mounted.
- Staining intensity of anti-bNAb binding was manually evaluated by three blinded researchers with a scale of 0 (no stain) to 5 (strongest).

IHC staining demonstrated presence of bNAbs up to 46 weeks post-VRC07-523LS administration.

Results and Discussion

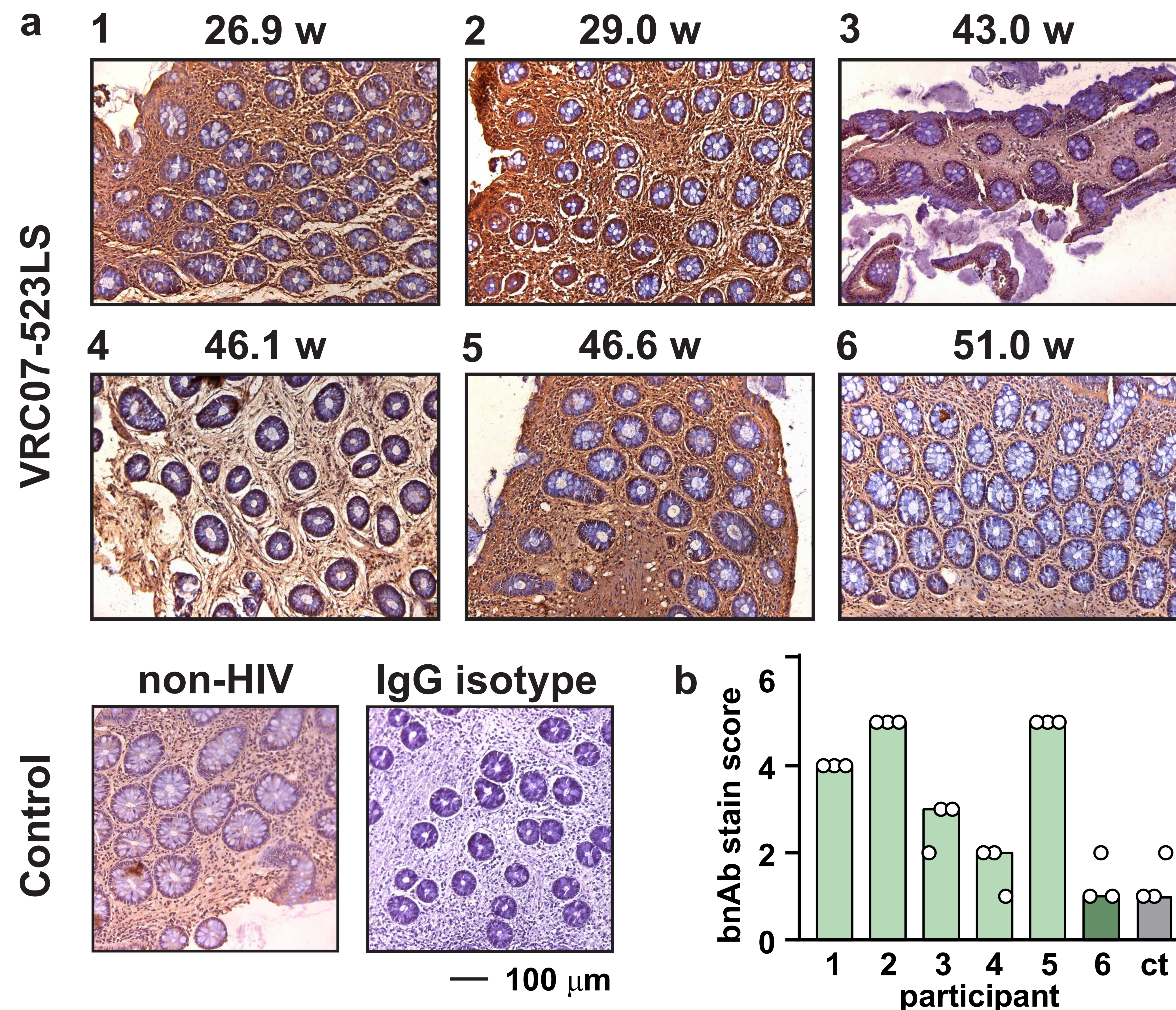


Figure.1 Localization of the VRC07-523LS in the rectal tissues. Panel a) IHC images of VRC07-523LS in the rectum of six participants (top: time in weeks after 2nd dose of VRC07-523LS for participant 1-5, and after 1st dose for participant 6), non-HIV healthy control, and IgG isotype control (participant 1), n ≥ 3 independent experiments of IHC. **b)** Manual scoring of VRC07-523LS staining based on the intensity of IHC images (min 0 and max score 5), medium score and three individual researchers scores (circle) were presented.

- IHC of rectal tissues revealed localized binding of 5C9 up to 46 weeks post VRC07-523LS infusion, indicating tissue penetration and retention of bNAbs in both parenchymal and perivascular regions (Fig 1a).
- Staining intensity scores were 4, 5, 3, 2, 5 for samples collected between 26.9-46.6 weeks post-bNAb (participants 1-5, respectively). Reduced staining was observed for a biopsy collected 51 weeks post infusion (participant 6, score 1) and for 3 control samples (scores 1-2) (Fig. 1b).
- Population pharmacokinetic (PK) model predicted plasma levels of VRC07-523LS were low and likely subtherapeutic: 8.5, 5.1, 0.7, 0.9, 2.2, and 0.6 µg/mL for participants 1-6, respectively. This suggests that even subtherapeutic systemic levels can support prolonged tissue retention of VRC07-523LS, though tissue staining does not scale linearly with plasma PK.

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Summary

- IHC staining demonstrated presence of bNAbs up to 46 weeks post-VRC07-523LS administration.
- Ongoing cross-validation of tissue quantitation using mass-spectrometry and ELISA-based approaches will determine an optimized strategy to successfully evaluate tissue levels of HIV bNAbs.
- This study underscores the importance of bNAb tissue PK in HIV cure trials to further understand underlying mechanisms of post intervention control.