IMAGING-BASED ANTI-HIV ANTIBODY EXPOSURE IN ANORECTAL TISSUE IS MORE CLOSELY LINKED TO PROTECTIVE EFFICACY DURING CLINICAL PREVENTION TRIALS

Danny (Hoi Tsun) Chu[1], Lance Kuo-Esser[1], Denis R Beckford-Vera[2], Robert R Flavell[2], Youngho Seo[2], Henry VanBrocklin[2], Timothy J Henrich[3], Amelia N Deitchman[1]

[1]Department of Clinical Pharmacy, UCSF School of Pharmacy. [2]Department of Radiology and Biomedical Imaging, UCSF School of Medicine. [3]Department of Experimental Medicine, UCSF School of Medicine.

UCSF University of California San Francisco

Abstract

Background: HIV remains a global public health burden with 1.3 million new cases in 2022 alone[1]. Broadly neutralizing antibodies (bNAbs) are a novel class of monoclonal antibodies that bind conserved protein domains on HIV and are of great interest for use as long-acting pre-exposure prophylaxis (PrEP), treatment and cure[2]. Recent PrEP clinical trials of the bnAb VRC01 (i.e., the AMP Trials[3, 4]) established a relationship between plasma exposure, viral susceptibility, and clinical prevention efficacy (PE) indicating that plasma VRC01 levels need to exceed IC80 by 200-fold to confer 90% clinical protection[5]; This discrepancy indicates a disconnect between plasma levels observed to prevent clinical HIV infection and expected inhibitory concentrations. Our group's positron emission topography (PET) study of VRC01 distribution provides a platform for predicting tissue exposure and corresponding PE. We hypothesize that VRC01 exposure in anorectal tissues, which is the common site of infection in men who have sex with men (MSM), will be more closely linked to PE compared to plasma[6].

Method: We have used data from our PET imaging study with 89Zr-VRC01 (NCT03729752) to predict expected anorectal tissue exposure during the AMP trials[3, 4]. Ratios of average VRC01 radiotracer uptake in blood and tissue were calculated from PET-based standardized uptake values (SUV) across 5 people without HIV. These tissue-to-blood ratios were then used to predict PE in an established logistic regression model from the AMP trials and compared to existing plasma-based PE[5, 7]. All analyses were performed in R (version 4.3.1).

Results: Anorectal tissue:blood VRC01 exposure ratios were 0.03 (range: 0.01 to 0.04) across participants as determined from tracer uptake (SUV). As shown in Figure 1, to achieve 90% PE, a VRC01 concentration in anorectal tissue to IC80 ratio of 7.18 (range across participants, n=5: 2.75 to 8.89) is required (Figure 1). This is 28.6-fold lower than the ratio needed in plasma, as predicted by the original clinical AMP trial PKPD models (205.85 VRC01 concentration/IC80).

Conclusion: Based on these studies, target site VRC01 levels in anorectal tissue are likely more closely linked to clinical PE than plasma concentrations observed during the AMP trials. These findings should be validated using rectal tissue biopsies following VRC01 administration. To our knowledge this is the first PET based PKPD analysis for bnAbs. This approach can be leveraged in future studies to predict PE of bnAbs in development and is the first step towards a whole body physiologically based pharmacokinetic (PBPK) analysis of PET data to inform dosing of bnAbs for prevention, treatment, and cure.

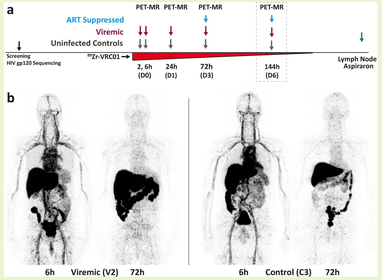


Figure 1. Study Design and PET Imaging of ^{89}Zr-VRC01 Distribution

(a) Timeline of PET-MR imaging sessions in ART-suppressed, viremic, and uninfected control participants following ^{89}Zr-VRC01 administration.

(b) PET images at 6h and 72h post-administration show ^{89}Zr-VRC01 distribution in a viremic participant (V2) and a control participant (C3).

Background

- VRC01 is one of the broadly neutralizing antibodies (bNAbs) proposed to prevent HIV, thought as a potential candidate for long-acting Pre-exposure Prophylaxis (PrEP) [3, 4]
- It works by blocking the CD4 binding site of the HIV envelope glycoprotein gp120
- Participants without HIV (n=5) underwent a PET imaging study (NCT03729752) following administration with a radiolabeled 1mg microdose of VRC01 (89Zr-VRC01) **(Figure 1).**
- Based on the population pharmacokinetics (popPK) model derived from the AMP trial data, a plasma concentration of VRC01 at 200 times the IC80 was required to achieve 90% prevention efficacy, highlighting a significant disparity between plasma levels and the desired prevention efficacy.
- Our study aims to explore the relationship between clinical prevention efficacy and anorectal concentration through the integration of PET data from the above-described study.

Results

- The initial findings of VRC01 concentration blood to anorectal ratio was 0.03 (range: 0.01 – 0.04).
- Based on this, a value of 6.81 (range: 2.61 – 8.43) of the ratio of average VRC01 level to IC80 was required to achieve 90% of prevention efficacy, which is 28.6-fold lower than plasma while simply calculated from the ratio **(Figure 5).**
- When using PBPK model, the value increased to 51.08, indicating a higher ratio of average VRC01 level to IC80 was needed for prevention at a tissue level. (**Figures 5 & 6)**

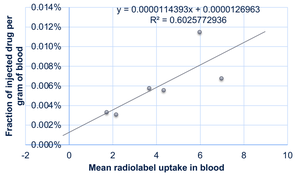


Figure 2. Correlation plot of mean radiolabel uptake recorded through PET and the percentage of injected drug per gram of blood measured

Physiological-Based PK (PBPK) Modeling

Figure 3 (above). PBPK model schematic.
The diagram of the minimal PBPK model implemented.

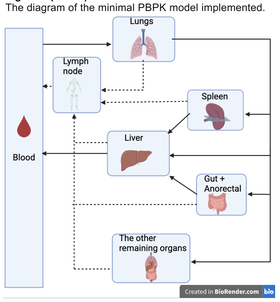


Figure 4 Visual Predictive Check. The plot of simulation (shaded) versus raw data (points and lines)

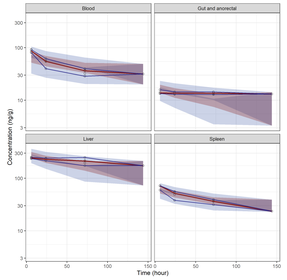


Table 1. PBPK Parameter estimates with bootstrap confidence intervals.

Parameter	Value (90% confidence interval)
Liver-blood partition coefficient*	8.06 (5.61 – 8.13)
Gut-blood partition coefficient*	1.31 (0.90 – 1.34)
Spleen-blood partition coefficient*	1.71 (1.02 – 1.79)
Total clearance (ml/h)	27.7 (0.28 – 49.82)
Fraction of lymphatic drainage contributing to blood concentration	0.837 (0.73 – 0.96)

* Partition coefficient between the interstitial space of the organ and blood

Figure 5. Predicted Prevention Efficacy vs. Average VRC01 level divided by IC80

The plot denoted the relationship between anorectal level with plasma level, divided by IC80

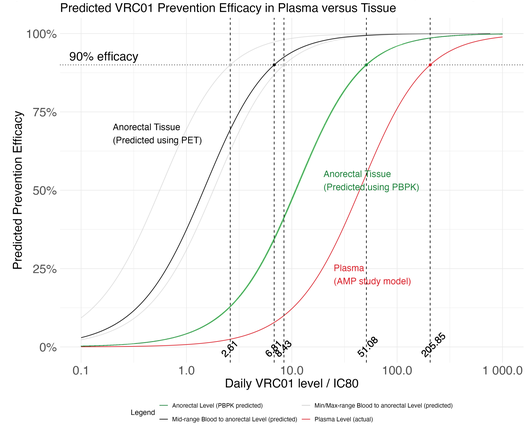
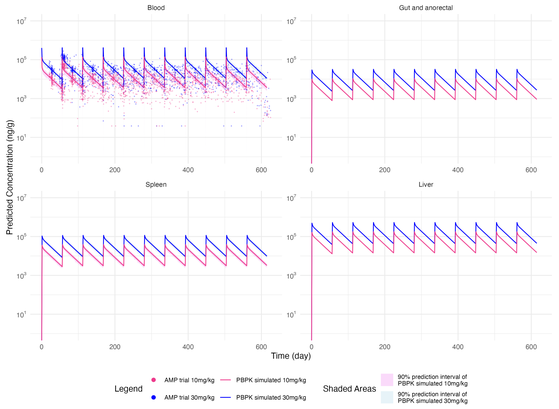


Figure 6. PBPK model simulated VRC01 vs AMP trial data

PBPK model simulating 30mg/kg and 10mg/kg compared with the respective dose and PK of AMP trial



Method

- Initial analysis was performed by calculating the ratio of tracer uptake between blood and anorectal tissue at each time point to estimate VRC01 tissue exposure
- Blood VRC01 concentration during the PET study was predicted from tracer uptake values and their relation to the percent of drug per gram of blood (**Figure 2**)
- A minimal PBPK model was built using NONMEM (version 7.5) incorporating physiological parameter values from previously published antibody PBPK models [8, 9, 10, 11, 12]

Discussion

- Using the PBPK model, we can estimate the concentration of VRC01 accumulated in the GI tract and anorectal tissue.
- Using the plasma concentration and corresponding anorectal tissue concentration after scaling to a therapeutic dose could provide a better understanding of the relationship, as modelled by the PBPK approach, compared to the simple ratio estimation based on PET imaging signals, which may result in an overestimation of prevention efficacy
- This allows us to observe the differences between the prevention efficacy curves derived from the PBPK model and the observed PET imaging signal ratios.
- The model was not precise in estimating clearance, resulting in a wide 90% confidence interval
- Further studies need to be performed to model prevention efficacy directly to the VRC01 concentration in anorectal tissue with PET imaging technique, on a therapeutic dose, to confirm the result

References

[1] https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/strategic-information/hiv-data-and-statistics Accessed: Apr 07, 2024
[2] C. G. Rivera et al., *Drugs*, 2023
[3] P. B. Gilbert et al., *Nature Medicine*, 2022
[4] M. J. McElrath et al, *Journal of Acquired Immune Deficiency Syndromes*, 2013
[5] L.Corey et al., *New England Journal of Medicine*, 2021
[6] D. R. Beckford-Vera et al., *Nature Communication*, 2022
[7] A. Pegu et al., *Cell Host & Microbe*, 2019
[8] D. Bae et al., *Journal of Pharmaceutical Sciences*, 2019
[9] M. J. Eigenmann et al., *mAbs*, 2017
[10] J.P. Davda et al., *International Immunopharmacology*, 2008
[11] D. Davies et al., *Pharmaceutical Research*, 1993
[12] D.K. Shah et al., *Journal of Pharmacokinetics and Pharmacodynamics*, 2012

Acknowledgements: We'd like to thank the study participants who participated in the PET and AMP trials.

Funding: This work was funded in part by NIH R01AI52932 (TH, HV), K23AI162249 (AD), and P30AI027763 (AD).