INFLTRATION OF VRC01 INTO THE CEREBROSPINAL FLUID IN HUMANS IN THE RV397 STUDY

Madhu Prabhakaran1, Sandeep Narpaia, Lucio Gama1, Donn J. Colby2,3, Phillip Chan2, Cario Sachdalan2, Khinthulee Benjapornpong2, Jintanat Ananworanich2,3, Nittaya Phanupak2, Suteiraporn Pinyakorn1, Trevor A. Crowe4, Serena Spudich4, Adrian B McDermott1 on behalf of the RV397 study team

1Vaccine Research Center, National Institutes of Health, USA; 2SEARCH - Thai Red Cross AIDS Research Centre, Thailand; 3US Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, USA; 4Yale University, USA

Background
- Persistence of HIV infection in the neurological compartments may continue despite the use of suppressive antiretroviral therapy (ART), creating a barrier to HIV eradication.
- Novel strategies to reduce the latent HIV reservoir may need to cross the blood brain barrier (BBB) into the cerebrospinal fluid (CSF).
- Targeting the CD4 binding site, VRC01 is a broadly neutralizing antibody (bNab) capable of potentially neutralizing over 90% of HIV-1 strains.
- We wanted to measure the infiltration of VRC01 into the CSF following passive immunization.

Methods

Study:
The RV397 SEARCH Thai VRC01 efficacy study was a randomized, double-blind, placebo-controlled trial of participants who initiated during acute HIV infection followed by at least 24 months of sustained ART. Participants were randomized to receive VRC01 40 mg/kg (n=13) or placebo (n=5) intravenously every 3 weeks during analytic interruption (ATI) of ART. CSF collection was an optional procedure for study participants.

Participants:
CSF samples were collected at two time points from 3 participants who received VRC01: pre-ATI/pre-VRC01 infusion and 2-4 days after first detectable plasma viral load during ATI.

Method:
VRC01 levels were quantified using a standardized sensitive Singleplex single molecule counting technology with a lower limit of quantitation (LLQ) of 50pg/ml for VRC01. CSF VRC01 concentration was compared to concurrently plasma level for each participant. Total IgG levels in plasma and CSF samples were measured using ELISA.

Summary of Findings
- We were able to successfully quantify VRC01 levels in CSF in 3 people living with HIV who received VRC01 infusion following ATI, thus reporting for the first time the detection of a HIV bNab in this compartment.
- VRC01 levels detected in CSF were on average 1000-fold lower compared to concurrent plasma levels.
- This difference in VRC01 levels can be attributed to the 1000-fold difference in IgG levels between the CSF and plasma compartments.
- On average, 6% of all IgG in the CSF compartment comprised of VRC01, while in the plasma, 2% of all IgG comprised of VRC01.

Results

Conclusions
- One of the strategies to accomplishing eradication of HIV latent reservoirs in the central nervous system (CNS) is to achieve delivery of vaccine candidates past the BBB into the CSF.
- We report here the successful quantification of the bNab VRC01 in CSF from 3 people living with HIV from the RV397 trial who received VRC01 during ATI.
- This detection of VRC01 in CSF is a significant milestone in fighting HIV that illustrates the infiltration and bioavailability of this relevant bNab in the CNS.
- These results thus serve to inform the design of immunotherapies to target HIV infection in the CNS.

Future Directions
- Measurement of VRC01 class bNabs in the CSF compartment are being planned for additional studies (samples from Thai RV398 study, ACTG studies, etc.).
- PK modelling of relationship between blood and CSF penetration of VRC01 is being evaluated.
- Potential insight obtained from the AMP trials regarding therapeutic levels of VRC01 needed to neutralize HIV in plasma may be used to model levels of bNab required in the CSF to neutralize virus.

References

Acknowledgements
We would like to thank the study participants who committed so much of their time for this study. The participants were from the RV397 study, which is supported by cooperative agreements (W81XWH-18-2-0040) between the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. and the U.S. Department of Defense (DOD) and by an intramural grant from the Thai Red Cross AIDS Research Centre. This research was funded, in part, by the U.S. National Institutes of Health: NIAID- NINDS (R01NS089691), and NIH/NIMH support of the International NeuroHIV Cure Consortium. Antiretroviral therapy was supported by the Thai Government Pharmaceutical Organization, Gilead, Merck, and VIV Healthcare.

Disclaimers
The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above, the U.S. Department of the Army or the U.S. Department of Defense, the Henry M. Jackson Foundation for the Advancement of Military Medicine, the National Institutes of Health, the Department of Health and Human Services, or the United States government, nor does mention of trade names, commercial products, or organizations imply endorsement by the Thai Red Cross AIDS Research Centre. The investigators have adhered to the policies for protection of human participants as prescribed in 38 CFR 70-25.

Figure 1: Schematic of the Singulex VRC01 quantitation assay
VRC01 is captured by SCx-coated magnetic beads and detected using A647-conjugated anti-human IgG. Fluorescence is read by the Singulex xPro instrument.