Beating the Clock: Timing 10E8.4/iMab Administration to Block SHIV Infection

Matthew S Parsons[1,2,3], Decha Silsorn[3], Jumpol Sopanaporn[3], Panupat Nadee[3], Dutsadee Inthawong[3], Rawiwan Imerbsin[3], Caroline Subra[1,2], Alexandra Schuetz[1,2,3], Jian Yu[4], Yaoxing Huang[4], David D Ho[4], Eric Garges[3], Sandhya Vasan[1,2], Julie A Ake[1], and Diane L Bolton[1,2]

[1]U.S. Military HIV Research Program, CIDR, Walter Reed Army Institute of Research, Silver Spring, MD; [2]Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD; [3]Department of Retrovirology, Walter Reed Army Institute of Research-AFRIMS, Bangkok, Thailand; [4]Aaron Diamond AIDS Research Center, Columbia University, New York, NY

0295

BACKGROUND

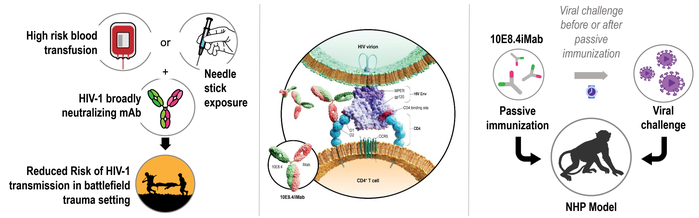


Figure 1. Bottom Line Up Front. To support the development of a rapid-acting single-use HIV prevention tool for battlefield settings, we evaluated the bispecific bNAb 10E8.4/iMab as an immunoprophylaxis candidate. We assessed its pre- and post-exposure efficacy in a nonhuman primate high-dose intravenous SHIV challenge model.

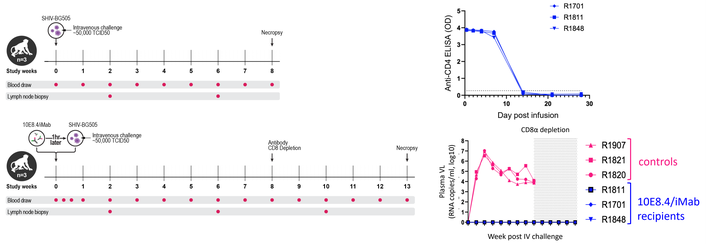


Figure 2. Pilot Study Design and Outcomes (CROI 2024). A pilot study (CROI 2024 - Poster #412) tested the prophylactic efficacy of 10E8.4/iMab in rhesus macaques challenged with high-dose SHIV-BG505 one hour after antibody infusion or without antibody (controls). Graphs depict plasma 10E8.4/iMab detection and longitudinal viremia measurements.

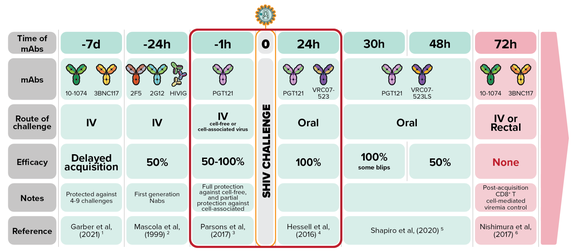


Figure 3. Window of Opportunity for Prophylaxis. The critical window for effective immunoprophylaxis after high-dose intravenous viral exposure is unknown; while prior studies suggest bNAbs offer a broad protection window, those findings stem from lower-dose challenges and varied exposure routes, leaving the timing requirements for high-dose intravenous exposures unresolved.

Pre- or simultaneous administration of the bispecific bNAb 10E8.4/iMab protected against high-dose intravenous SHIV challenge, whereas delayed dosing showed markedly reduced efficacy.

METHODS

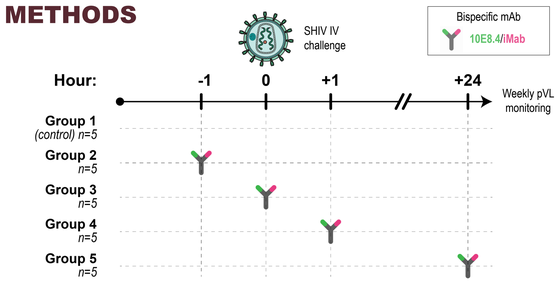


Figure 4. Study schema to assess the window of opportunity for prophylaxis (WOOP).

SHIV-BG505[7] intravenous challenge

- Model blood transfusion risk from a donor with untreated HIV
  - ➢ Viral load ~10^4 copies/ml of blood
  - ➢ Eight unit trauma blood transfusion
- Target: 40 million copies of viral RNA
  - ➢ 50,000 $TCID_{50}$ (~50-500X typical IV dose)

10E8.4/iMab (IgG1)

- 10E8.4/iMab is a novel bispecific antibody that neutralizes HIV. It is an engineered antibody with two distinct antigen-binding arms (see Fig 1):
  - ➢Ibalizumab targets CD4
  - ➢10E8.4 targets the HIV-1 envelope membrane-proximal external region (MPER)
- 10E8.4/iMab has high potency against multiple HIV subtypes.
- 10E8.4/iMab has been manufactured for use in humans and has been safe to date.
- 30 mg/kg dose to maximize CD4 receptor occupancy
- Fc L234F, L235E and P331S triple mutation minimizes effector functions

RESULTS

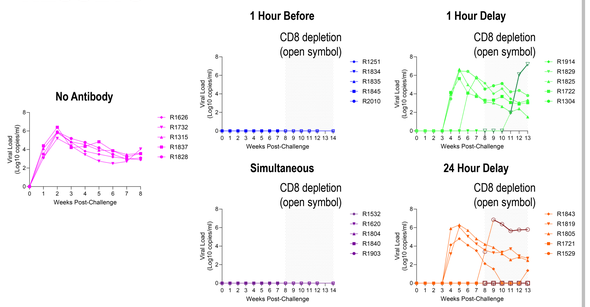


Figure 5. Viremia post-SHIV-BG505 challenge.

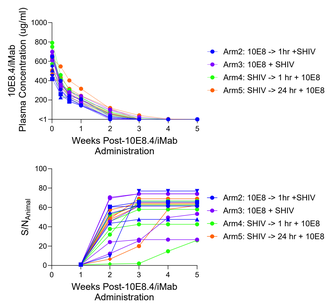


Figure 6. Plasma concentrations of 10E8.4/iMab were determined via ELISA.

Figure 7. Anti-drug antibody (ADA) responses were assessed via ELISA.

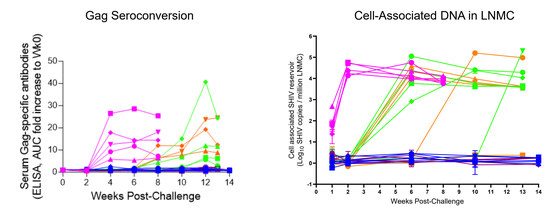


Figure 8. Assessments of seroconversion and viral DNA in lymph node mononuclear cells.

CONCLUSION

The 10E8.4/iMab bispecific antibody shows strong potential as an HIV-1 immunoprophylactic, with optimal protection achieved when administered at or before the time of viral exposure. The limited efficacy observed with post-exposure dosing suggests that at least a portion of the inoculum has completed viral entry within one hour of inoculation. Notably, the development of ADA and the rapid clearance of 10E8.4/iMab in macaques could result in an underestimation of the potential effectiveness of delayed administration in humans.

FUTURE DIRECTIONS

- Assess if 10E8.4/iMab confers protection from high-dose intravenous cell-associated viral challenge.
- Block ADA to extend the period of 10E8.4/iMab bioavailability and test the impact on the window of opportunity for prophylaxis.

REFERENCES

1.Garber et al. (2021). *AIDS*. 35:1567-1574; 2. Mascola et al. (1999). *J. Virol.* 73:4009-4018. 3. Parsons et al. (2017). *Sci. Transl. Med.* 9:eaaf1483. 4. Hessell et al. (2016). *Nat. Med.* 22: 362-368. 5. Shapiro et al. (2020). *Nat. Commun.* 11: 70. 6. Nishimura et al. (2017). *Nature.* 543: 559-563. 7. Li et al. (2017). *J. Virol.* 95: e00071-21.

ADDITIONAL INFORMATION

Acknowledgements: *This work was supported by the Assistant Secretary of Defense for Health Affairs endorsed by the Department of War, through the Walter Reed Army Institute of Research (WRAIR) under Award No. HT9425-24-3-0004. This work is supported by the DHA Military Infectious Diseases (DHA MID) under project #MI250186. Additional acknowledgement to Dr. George Shaw for provision of the SHIV-BG505 viral stock.*

Contact Information: *Matthew Parsons parsonsm@hiv-th.org*

PLAIN LANGUAGE SUMMARY

This study found that a specially engineered antibody, 10E8.4/iMab, can prevent HIV-like virus infection in monkeys when given at or before exposure. However, giving the antibody even one hour after exposure was far less effective, suggesting the virus enters cells very quickly after exposure.

Material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of War. Research was conducted under an IACUC-approved animal use protocol in an AAALAC International - accredited facility with a Public Health Services Animal Welfare Assurance and in compliance with the Animal Welfare Act and other federal statutes and regulations relating to laboratory animals.