Safety and Antiviral Effect of the Bispecific Monoclonal Antibody 10E8.4/ibalizumab to Inform Development for HIV Prophylaxis

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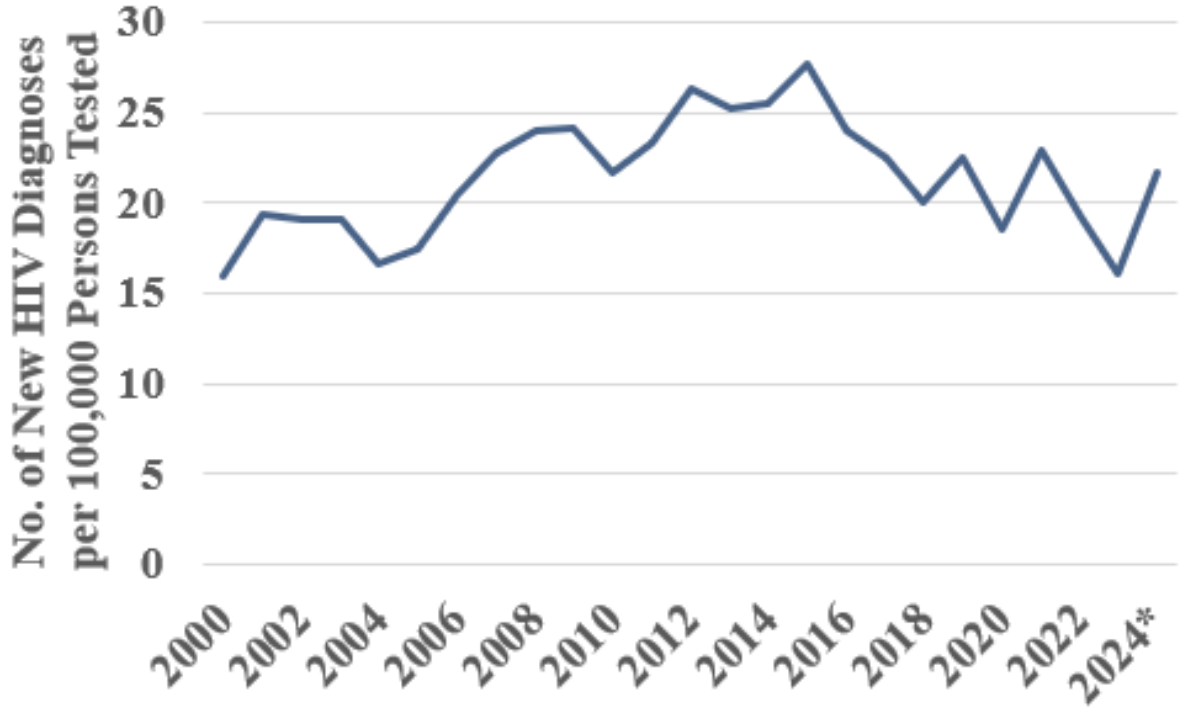
RESEARCH & DEVELOPMENT

Disclosure

- The authors have no conflicts of interest to report.
- The views expressed here reflect the results of research conducted by the author(s) and do not necessarily reflect the official policy or position of the Defense Health Agency, Department of War, U.S. Government or HJF.
- The study protocol was approved by the relevant Institutional Review Board(s) in compliance with all applicable Federal regulations governing the protection of human participants.

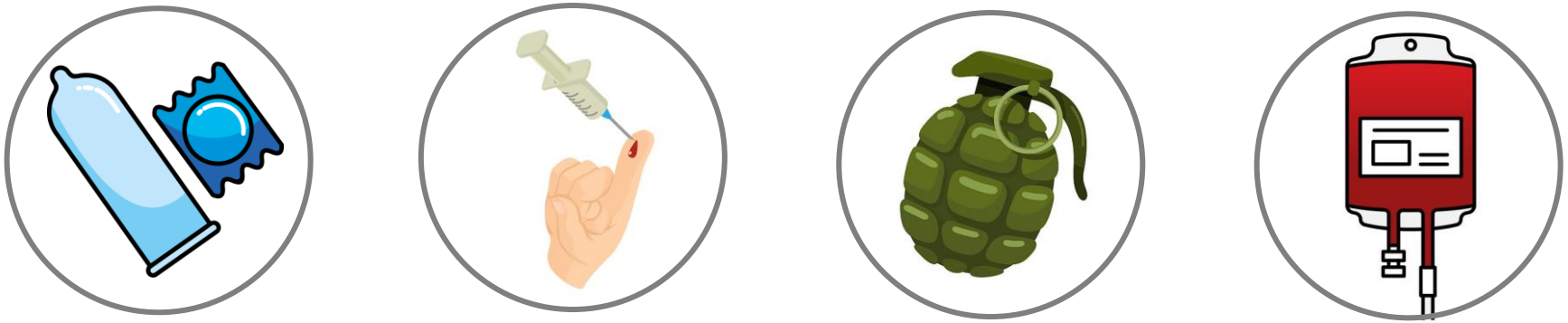
HIV Incidence in U.S. Military

- >300 new HIV diagnoses per year
- >$500,000 lifetime treatment cost per case



*through June 30, 2024; Data sources: Defense Medical Surveillance System (DMSS) 23JUL2024 & MSMR October 2024 Vol. 31 No. 10

Routes of HIV Exposure



Per-Exposure HIV Transmission Risk

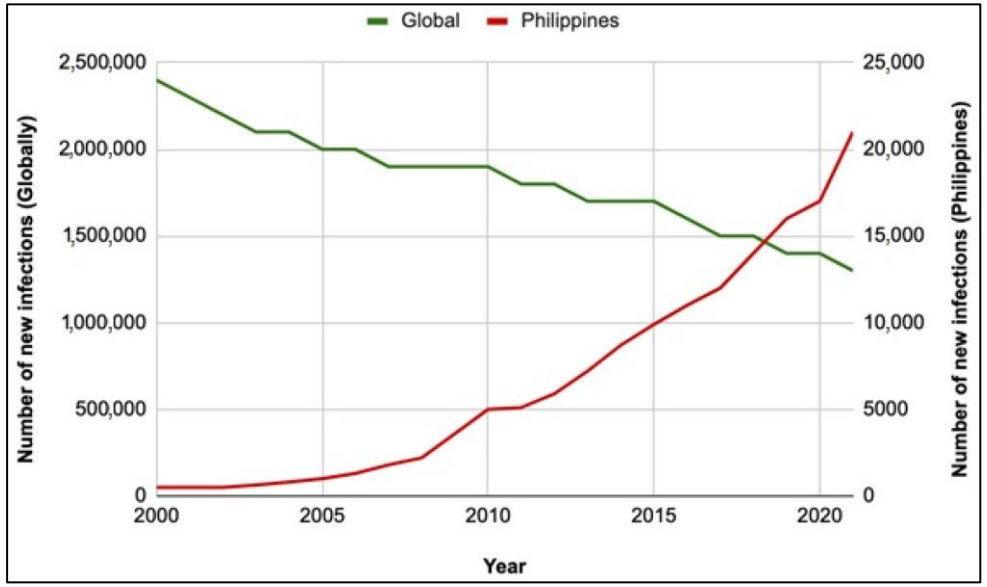
Unprotected Sex (0.04-1.4%)	Needlestick (0.2–0.5%)	Human Shrapnel (unknown)	Contaminated Blood Transfusion (93%)

Adapted from Shelly Karuna

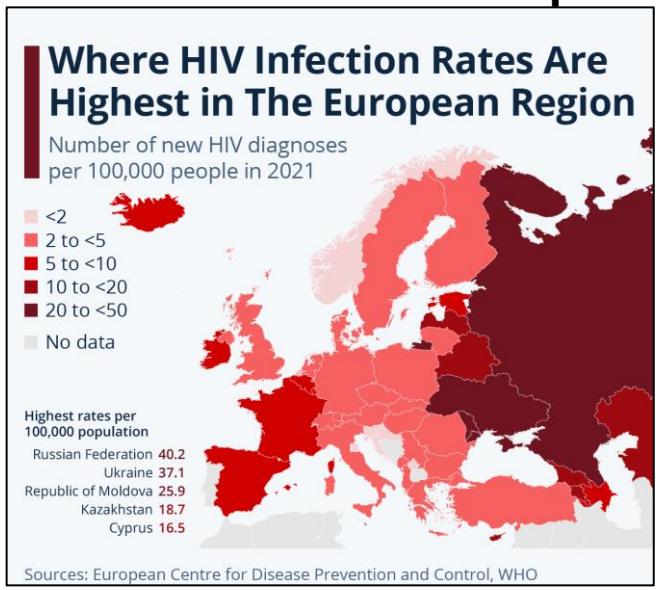
Regions Most Affected by HIV

- Regions at risk for future large-scale combat operations (LSCO) are also regions with expanding HIV epidemics
  - HIV transmission risk from under-screened blood supply (e.g. fresh whole blood transfusion from “walking blood bank” of allied forces and local populations)

HIV incidence in the Philippines increased 543% from 2010 to 2023



Russia and Ukraine have highest HIV incidence in Europe

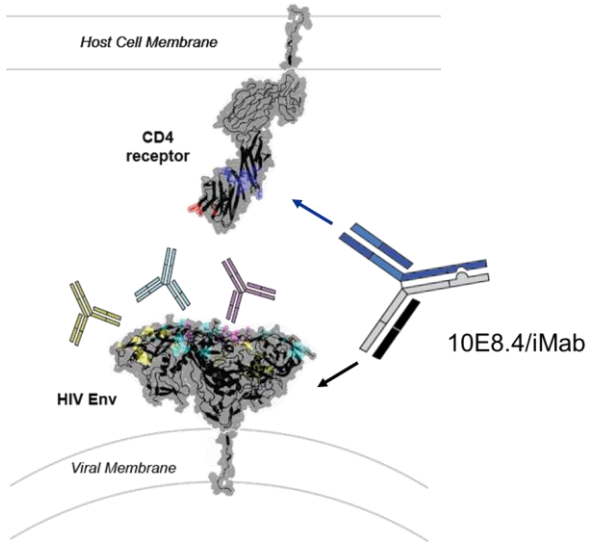


Gangcuangco, *Trop Med Infect Dis 2023;* Statista.com

10E8.4/iMab

- 10E8.4/iMab is an engineered antibody with two arms:
  - Ibalizumab targets CD4 cells and is licensed for salvage therapy
  - 10E8.4 targets HIV-1 envelope membrane proximal external region (MPER)
- This combination of targets places 10E8.4 near the primary entry receptor utilized by HIV, facilitating binding and neutralization of incoming viral particles

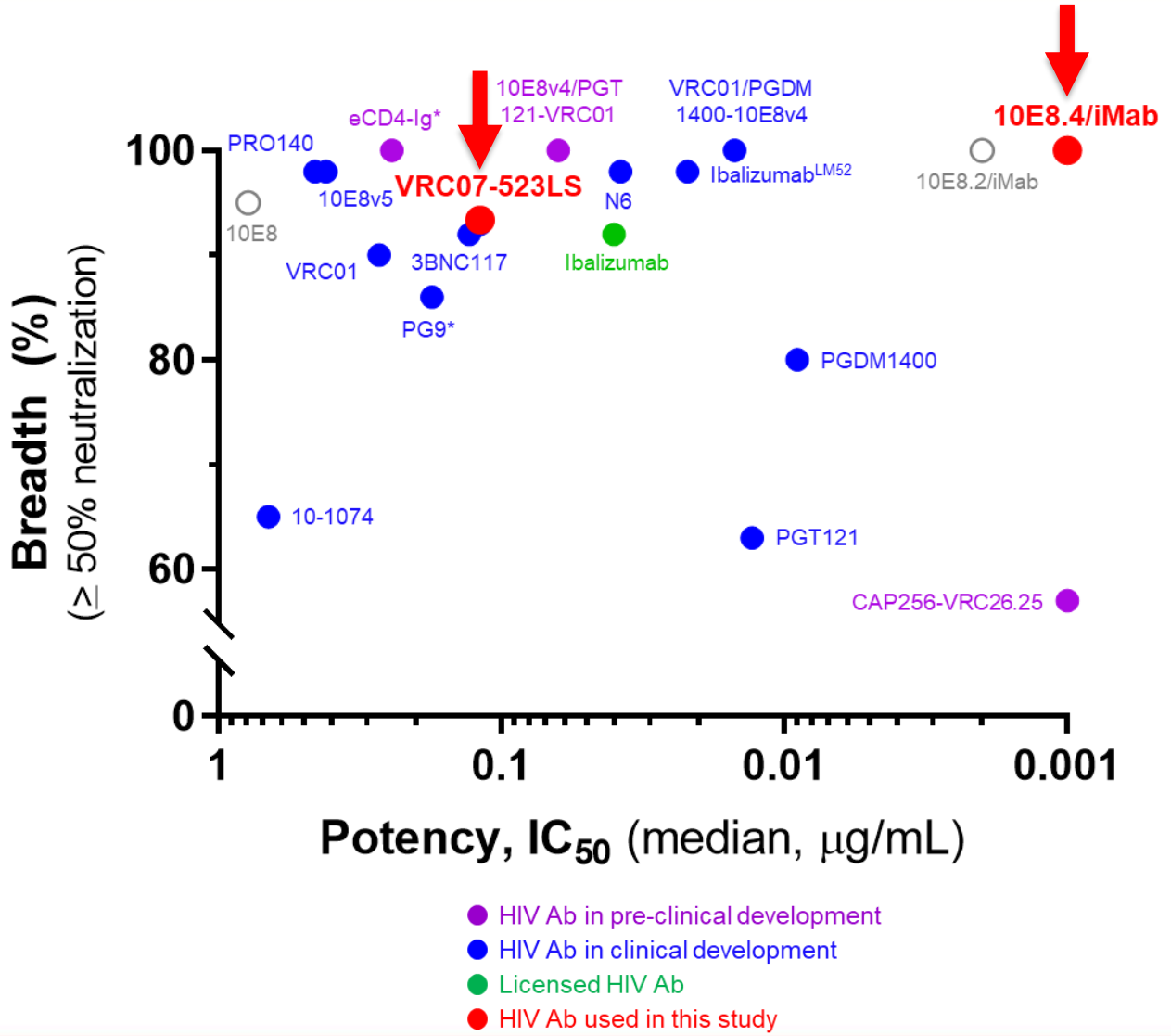
Aaron Diamond AIDS Research Center, Columbia University



Schematic of bispecific antibody binding to cell and virus

Breadth and Potency

- Combination of 10E8.4/iMab and **VRC07-523LS** offers exceptional breadth and potency
  - Engineered variant of VRC01 with prolonged half-life
  - Targets the CD4 binding site of the HIV-1 envelope
  - Has been administered safely in multiple clinical trials



Vaccine Research Center,
U.S. National Institutes of Health

Adapted from Padte, Retrovirology 2018

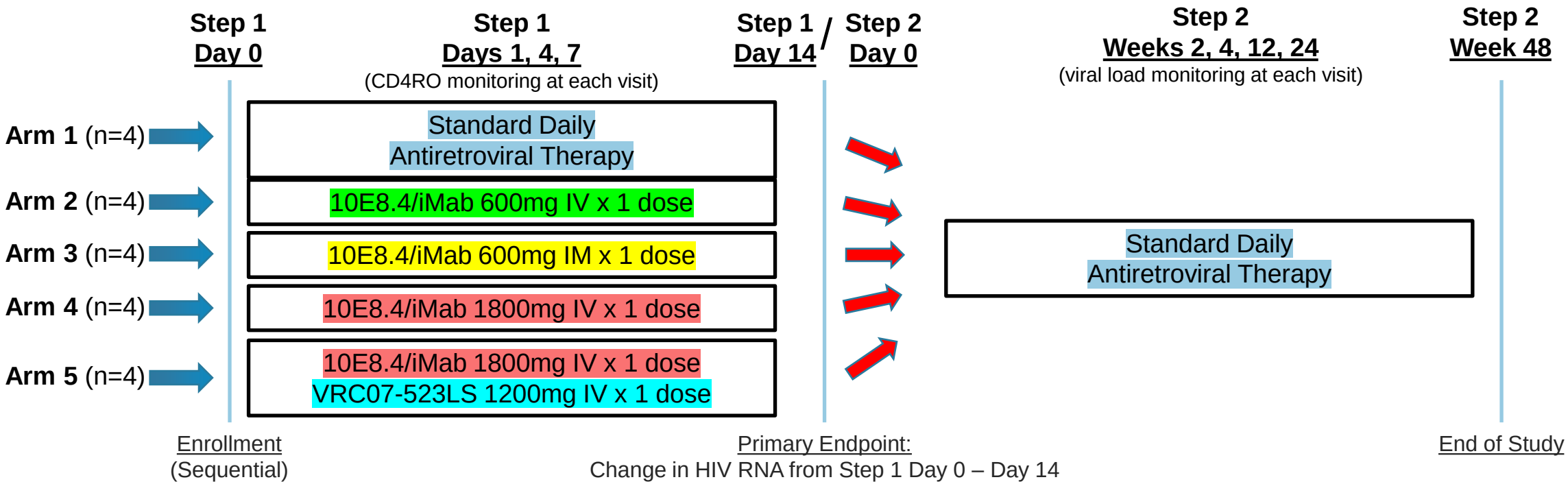
Objectives

1. Evaluate **safety and tolerability** of 10E8.4/iMab, alone and in combination with VRC07-523LS, at various doses and routes (IV and IM)
   - » Endpoint:
     - » Grade 3 or higher antibody-related reactogenicity and adverse events
2. Determine and compare the **antiviral effects** of 10E8.4/iMab, alone and in combination with VRC07-523LS, at various doses and routes, against standard daily oral ART in viremic PLWH for 14 days after administration
   - » Endpoints:
     - » Change in plasma HIV RNA from day 0 to day 14
     - » Proportion of participants with HIV RNA <50 copies/mL at day 14

Study Schema

v1.0 Inclusion Criteria: (1) Age 18-50 years; (2) ART-naïve or no ART for ≥24 weeks; (3) HIV RNA 1,000-100,000 copies/mL; CD4 ≥ 500 cells/mm^3

Amended Inclusion Criteria*: (1) Age 18-50 years; (2) ART-naïve or no ART for ≥24 weeks; (3) HIV RNA ≥ 1,000 copies/mL; CD4 ≥ 300 cells/mm^3



Enrolled participants:
- Median age 28 years (range 20-45)
- Median weight 65.3 kg (range 52.0-80.2)

*Protocol amended to facilitate accrual after enrollment of Arm 3, Participant 1

Mbeya Medical Research Center

- The study was conducted at Mbeya Medical Research Center (MMRC), part of the National Institute for Medical Research (NIMR) in Mbeya, Tanzania
  - Prior experience conducting bNAb studies
  - Linked to multiple PEPFAR-supported clinics

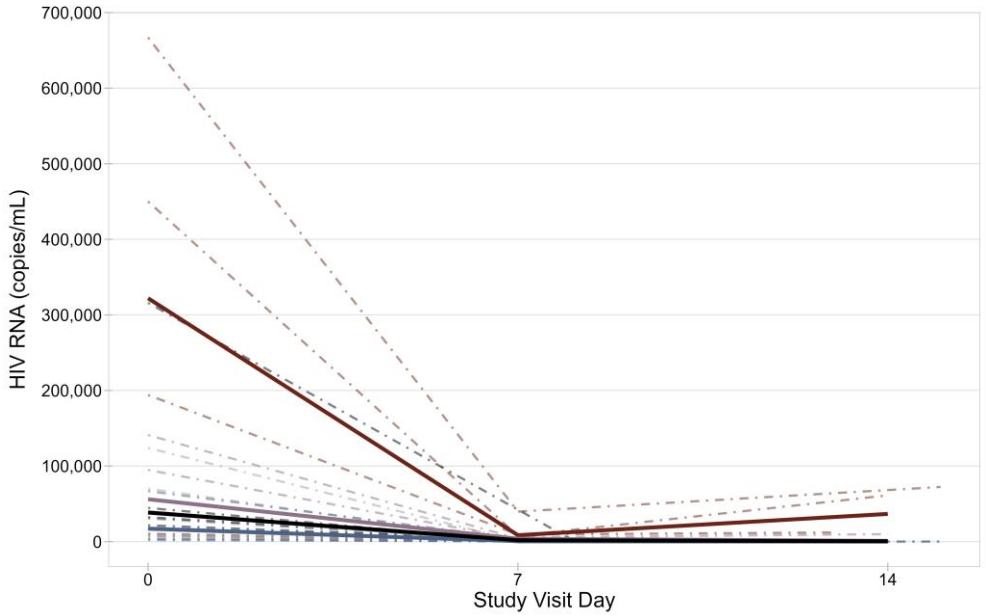
Safety

- 13 participants (65%) reported ≥1 systemic solicited reactogenicity event
- Most AEs were mild or moderate (Grade 1 & 2)
  - Most AEs were attributed to study procedures (e.g., IV infusion) rather than investigational product
- No ≥ Grade 3 AEs deemed related to IP
  - Two grade 3 AEs deemed not related to IP
    - Headache & malaise reported by a participant after 10E8.4/iMab 600mg IM
- No SAEs deemed related to IP
  - Two SAEs deemed not related to IP (proximate to ART initiation)
    - Elevated ALT and elevated AST reported in a participant after 10E8.4/iMab 600mg IM
- Two pregnancies occurred (ART-only & 10E8.4/iMab 600mg IM arms) without adverse outcome

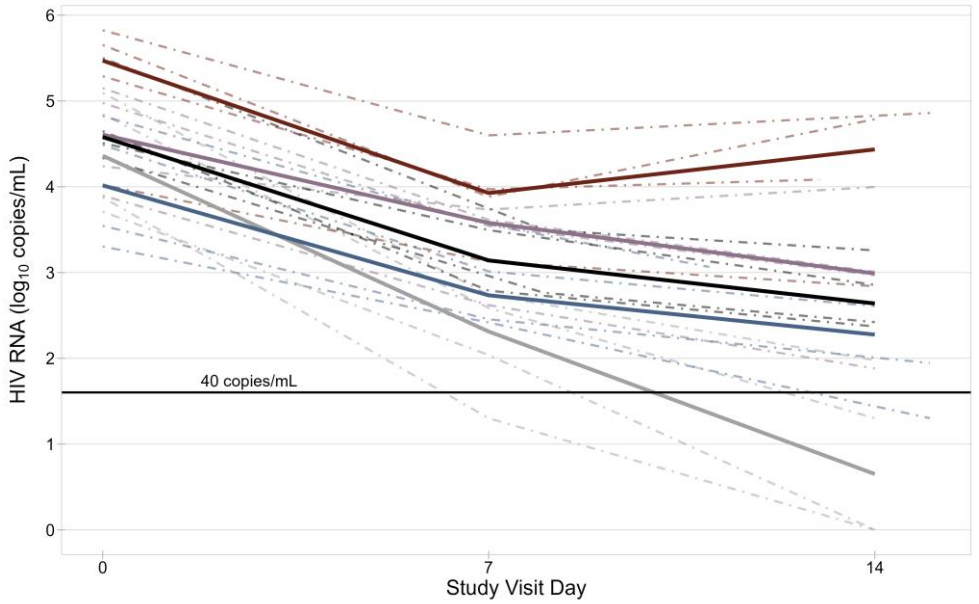
Antiviral Effect

- Similar antiviral effect was observed with all doses and routes (p=0.205)
  - 10E8.4/iMab 600mg IM had the steepest slope of HIV RNA decline (from highest baseline)

Raw Viral Load Trajectories by Study Arm



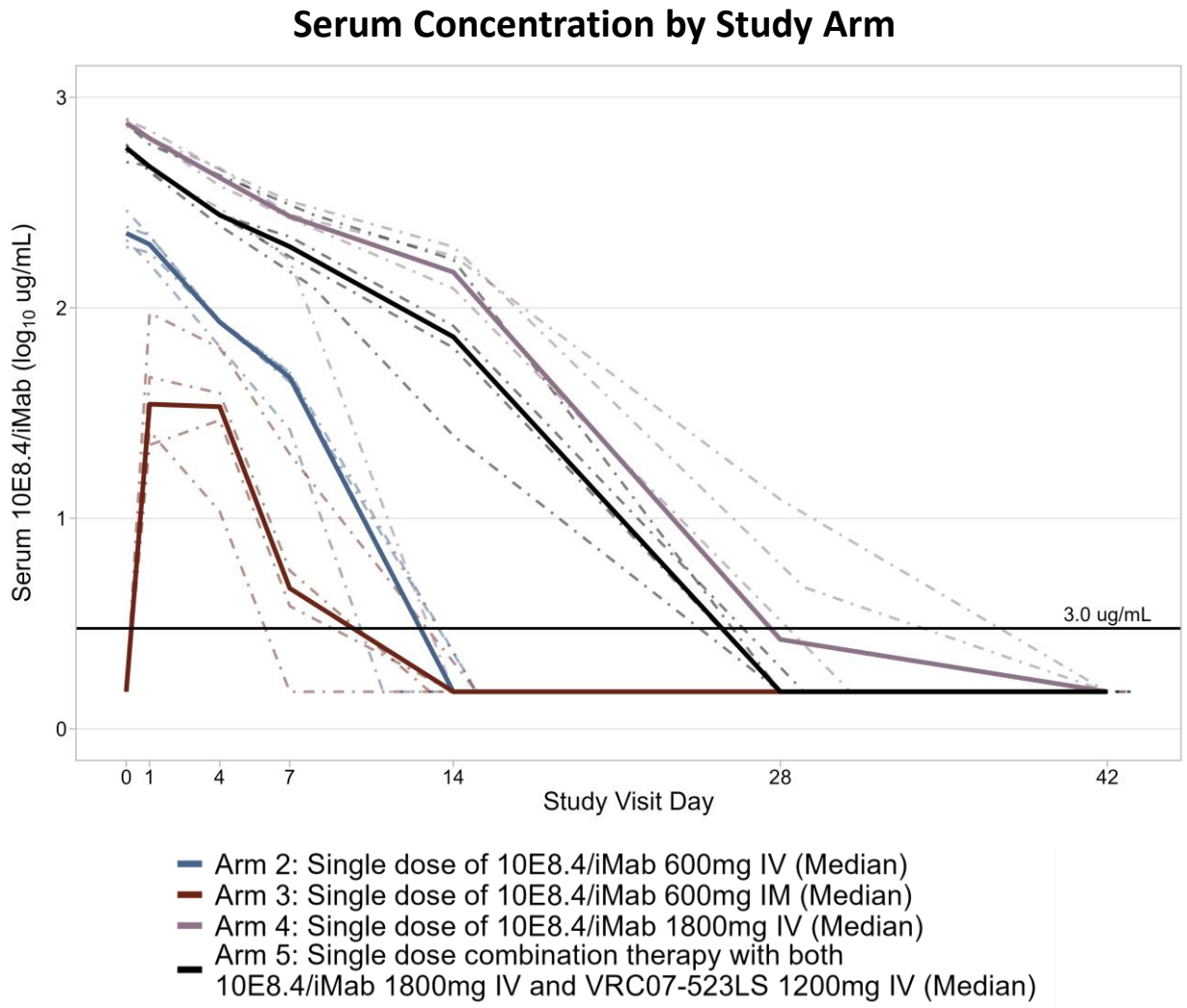
Log-Linear Viral Load Trajectories by Study Arm



Arm 1: Standard daily oral ART (Median)
Arm 2: Single dose of 10E8.4/iMab 600mg IV (Median)
Arm 3: Single dose of 10E8.4/iMab 600mg IM (Median)
Arm 4: Single dose of 10E8.4/iMab 1800mg IV (Median)
Arm 5: Single dose combination therapy with both 10E8.4/iMab 1800mg IV and VRC07-523LS 1200mg IV (Median)

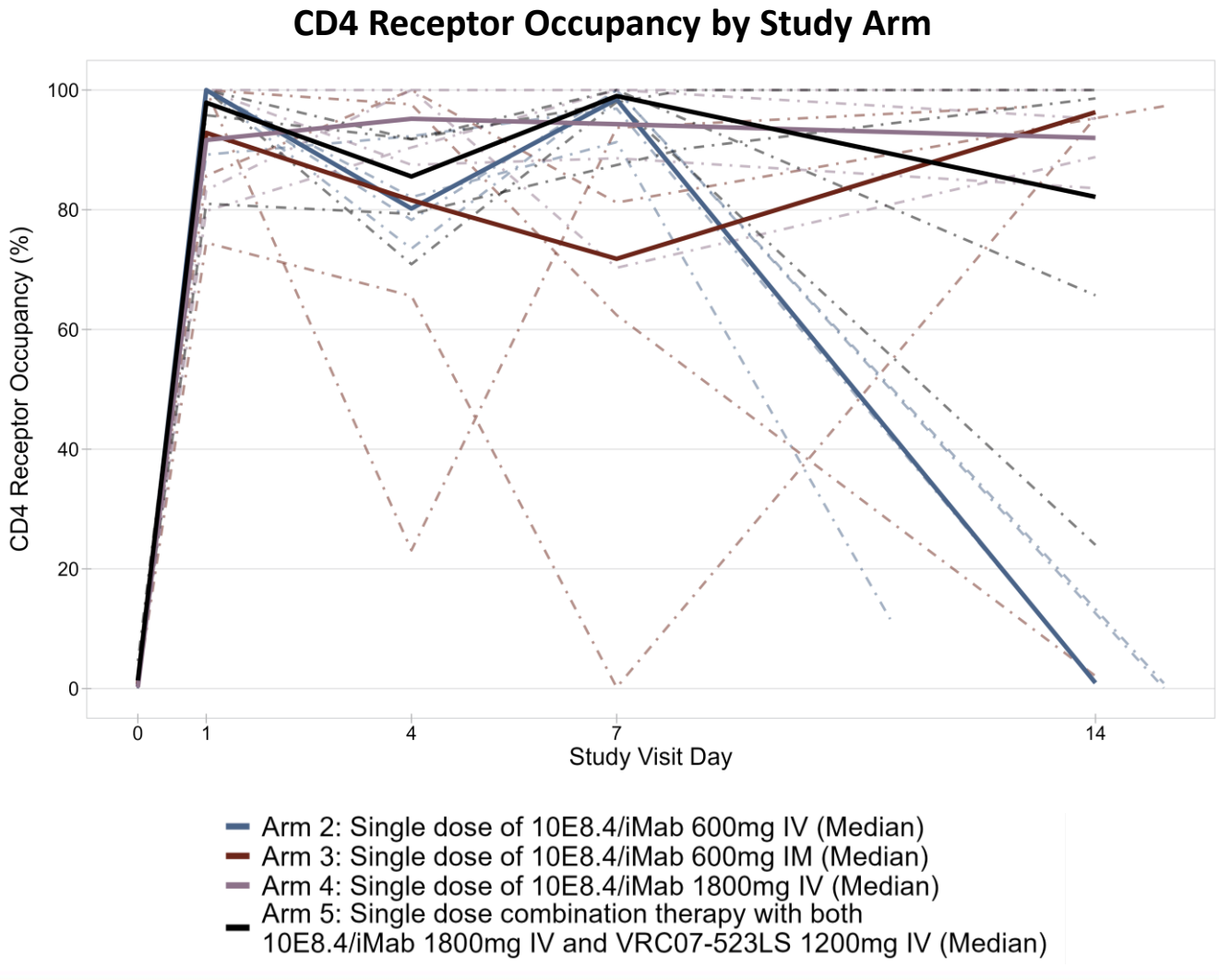
Serum Concentration of 10E8.4/iMab

- Higher 10E8.4/iMab serum concentration was observed with
  - Higher dose
  - IV route of administration (vs. IM)



CD4 Receptor Occupancy

- The CD4 receptor occupancy assay was run on fresh samples
  - Technology was transferred from ADARC to the MMRC lab in Mbeya
- >80% CD4 receptor occupancy was observed for 14 days after 10E8.4/iMab 1800 mg IV



Conclusions

- 10E8.4/iMab shows favorable safety and tolerability
  - Safety follow-up will continue for a total of 50 weeks after administration
- 10E8.4/iMab shows antiviral effect for all doses and routes of administration
- 10E8.4/iMab shows target CD4 receptor occupancy through day 14 when administered at 1800 mg IV
- Future clinical studies will expand the database of safety and pharmacokinetic data for 10E8.4/iMab in people without HIV to inform development for HIV peri-exposure prophylaxis

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