Fixed Dosing vs. Body Weight-Based Dosing of HIV-1 Prophylactic Monoclonal Antibodies in Adults

Yunda Huang[1], Lily Zhang[1], Huub Gelderblom[1], Kelly E. Seaton[2], Nicole L. Yates[2], Carmen A. Paez[1], Julie E. Ledgerwood[3], Stephen R. Walsh[4], Magdalena E. Sobieszczyk[5], Srilatha Edupuganti[6], Colleen F. Kelley[6], Michael N. Pensiero[3], Peter B. Gilbert[1], Richard A. Koup[3], Georgia D. Tomaras[2]

[1]Fred Hutchinson Cancer Center, Seattle, WA. [2]Duke University, Durham, NC, [3]National Institutes of Health, Bethesda, MD, [4]Brigham and Women's Hospital, Boston, MA, [5]Columbia University Irving Medical Center, New York, NY, [6]Emory University, Atlanta, GA

Background

- Weight-based dosing regimens have been commonly used in monoclonal antibody (mAb) therapies based in part on an expected reduction of inter-individual variabilities in mAb concentrations, pharmacokinetics (PK), and protection
- Several studies comparing fixed dosing and weight-based dosing have shown mixed outcomes for different mAbs, suggesting each option should be explored in the context of optimizing PK and simplifying clinical implementation
- PK modeling and simulations have recently been used to facilitate label changes of multiple marked mAbs

Methods

- We generated population PK (popPK) models for three HIV-1 mAbs (**VRC07-523LS, PGT121.414.LS, PGDM1400LS**) using data collected across five phase 1 trials (**Fig 1**)
- For each mAb, we used a two-compartment model to describe the overall trend and inter-individual variabilities in serum concentrations over time post mAb administration
- We simulated serum concentrations over time under fixed and weight-based dosing strategies using data from participants who enrolled in the Antibody Mediated Protection (AMP) trials, comparing PK and predicted neutralization (PT80) as surrogate markers of prevention efficacy

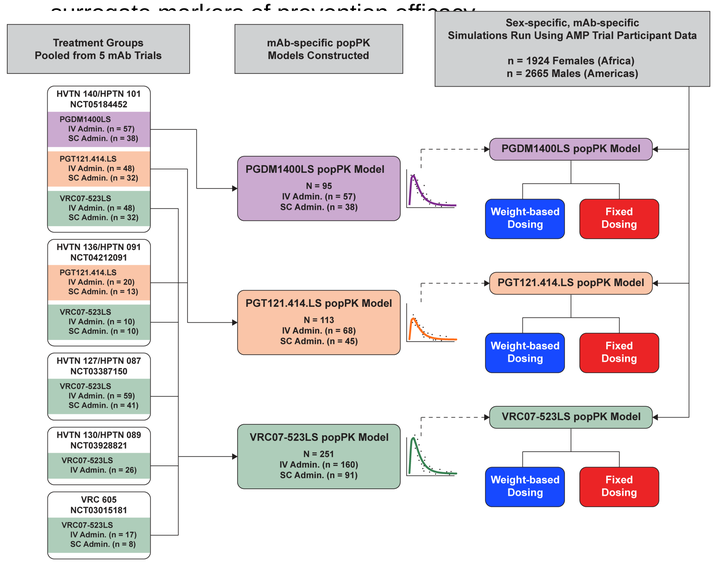


Fig 1. Study flow diagram showing trials that contributed mAb PK data (left column), mAb-specific models that were generated (center column), and simulations that were run (right column).

Pharmacokinetic modeling & simulation of fixed and weight-based mAb dosing regimens in adults produced comparable results, suggesting a fixed-dose approach can be considered for 3 HIV-1 mAbs in development for efficacy evaluation

Results

- For all three mAbs, we observed significant, but generally modest, effects of body weight on PK parameters (approximately 5% increase in each PK parameter per 10% increase in body weight)
- Magnitude and variability of time-specific concentrations and areas under the time-concentration curves (AUC) were comparable between the 2 dosing regimens for all mAbs and sex groups (**Fig 2**, **top row**)
- The relationship between body weight and stead state AUCs differed as expected between the two dosing regimens, with a positive correlation for weight-based dosing and a negative correlation for fixed dosing for all mAb and sex groups (**Fig 2**, **bottom row**)

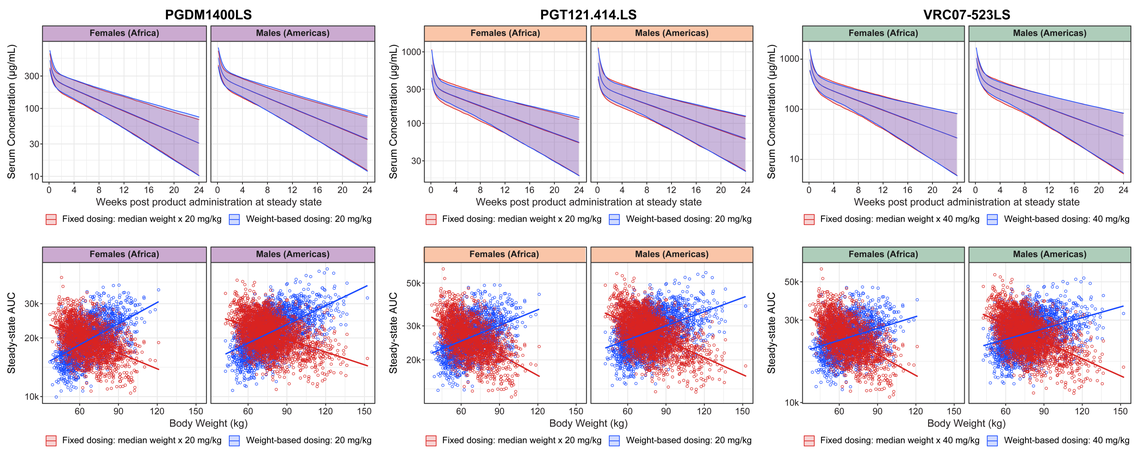


Fig 2. Simulated serum concentrations (top row, median with 95% confidence interval) and steady-state AUC (bottom row) of PGDM1400LS, PGT121.414.LS, and VRC07-523LS, for each sex group under the weight-based (blue) and fixed (red) dosing strategies.

Results (Cont.)

- Overall variations in median PT80 were comparable between the dosing strategies; PT80 levels were mostly above the potential efficacy threshold of 200 **(Fig 3)**

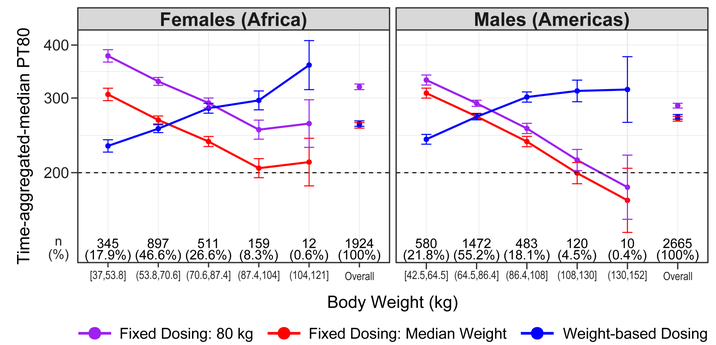


Fig 3. Predicted 80% inhibitory neutralization titers (PT80) of weight-based dosing (blue), fixed dosing based on median weight (red), and fixed dosing based on 80 kg (purple) for the combination mAb regimen. Error bars indicate 95% confidence intervals.

Conclusions

- Despite the commonality of weight-based dosing, fixed dosing performed similarly well in maintaining inter-individual consistency in mAb concentrations and overall predicted neutralization titers in PK simulations using relevant population data
- Fixed dosing is worthy of consideration for dosing of HIV-1 mAbs given associated advantages of reducing vial wastage and increasing operational efficiency without compromising overall mAb concentrations and PK
- Basing the fixed dose on a body weight slightly above the median or adopting weigh-based dosing for individuals above a certain weight threshold are pragmatic strategies to guard against potential underdosing of heavier individuals that may be considered

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