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

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## 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

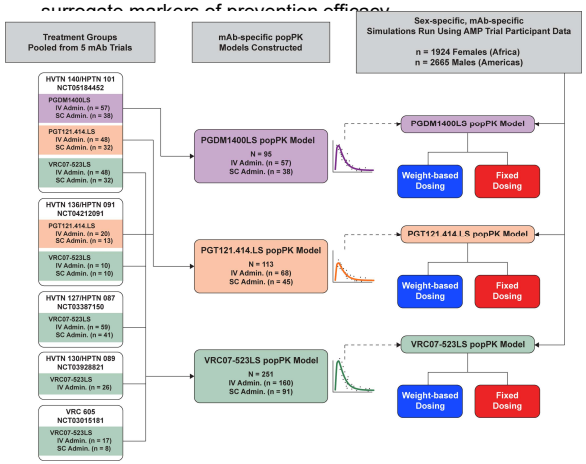


**Fig 1. Study flow diagram showing trials that contributed mAb PK data (left column), mAb-specific models that were generated (center column), and simulations that were run (right column).**

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**)

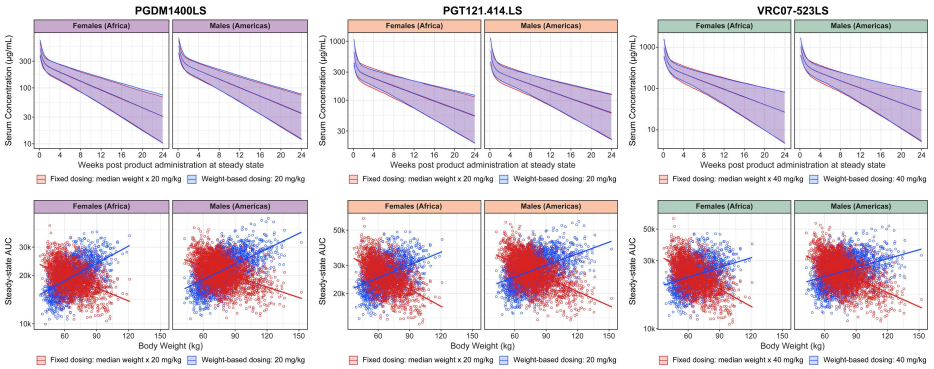


**Fig 2. Simulated serum concentrations (top row, median with 95% confidence interval) and steady-state AUC (bottom row) of PGDM1400LS, PGT121.414.LS, and VRC07-523LS, for each sex group under the weight-based (blue) and fixed (red) dosing strategies.**

## 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)**

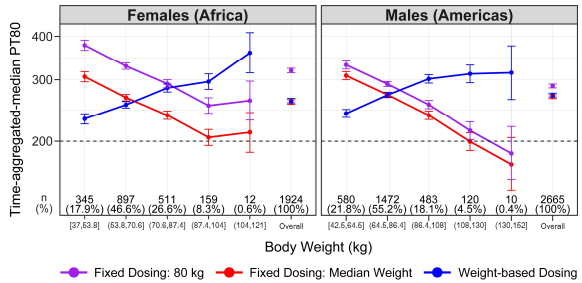


**Fig 3. Predicted 80% inhibitory neutralization titers (PT80) of weight-based dosing (blue), fixed dosing based on median weight (red), and fixed dosing based on 80 kg (purple) for the combination mAb regimen. Error bars indicate 95% confidence intervals.**

## 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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