

Weight-band based simplification of allometric miltefosine dosing in pediatric patients with visceral leishmaniasis in Eastern Africa

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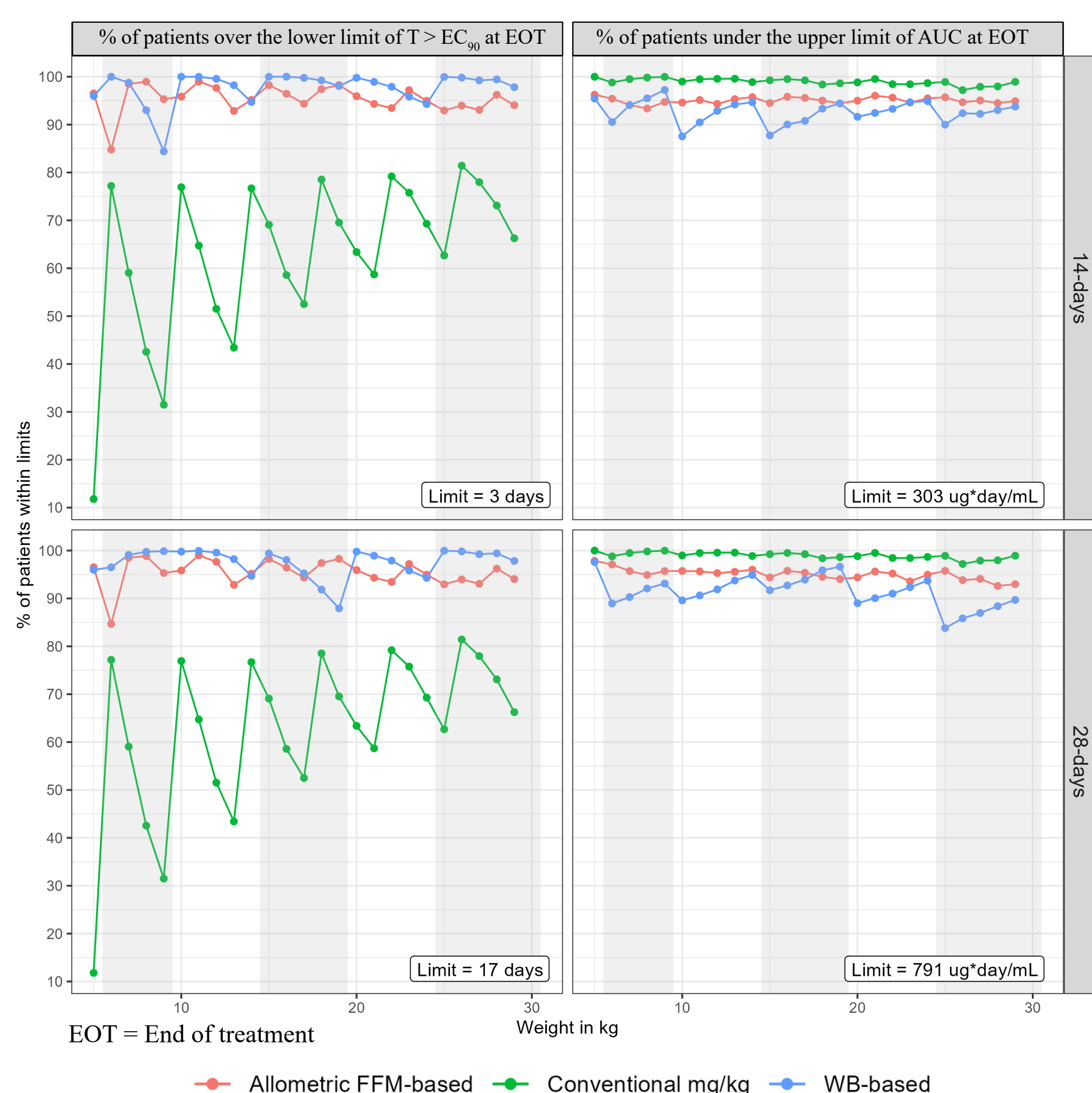
1. Introduction

- Visceral Leishmaniasis (VL) is a neglected tropical disease caused by the *Leishmania* parasite, that is fatal if left untreated. Eastern Africa alone represents 45% of the global occurrence of cases, where over 50% of patients are children.¹
- Conventional mg/kg dosing of miltefosine (2.5 mg/kg/day) for children under 30kg with VL has led to large treatment failure due to under-exposure.²
- An allometric fat-free mass (FFM)-based dosing improved outcomes but doses differently based on sex, height and weight.³
- 14- and 28-days treatment with allometric miltefosine FFM-based have been evaluated, e.g. in combination therapy, with positive results.⁴
- An adequate exposure over the course of the treatment duration ($T > EC_{90}$) is strongly associated with efficacy and less relapses.^{2,5}
- A simplified **Weight Band (WB)-based** dosing that maintains effective and safe exposure levels would be a useful tool to implement in areas where VL is most prevalent.
- This work is targeted for children from Eastern African suffering from VL, who are typically malnourished and differ from reference growth curves, such as from the WHO.⁶

2. Aim

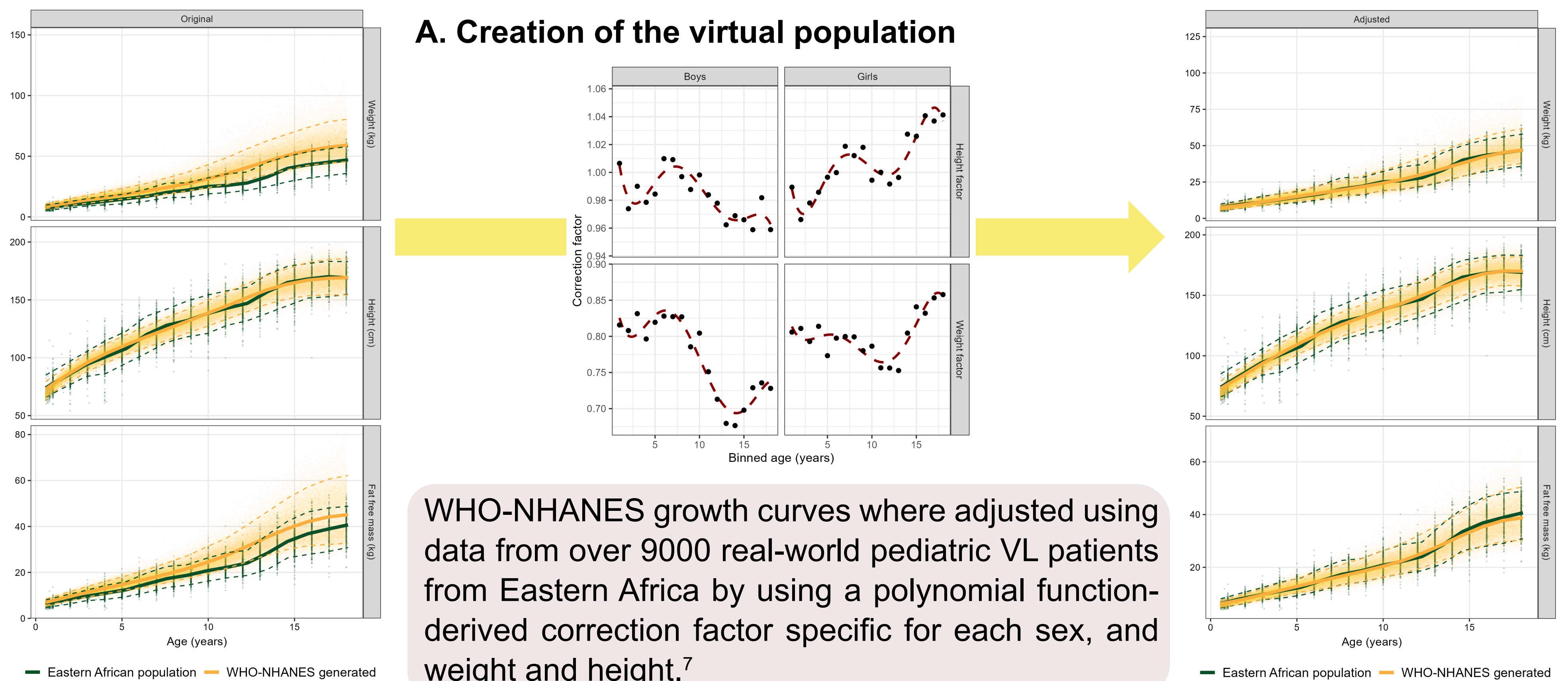
Simplify the current allometric FFM-based dosing regimen with a WB-based that ensures equivalent miltefosine exposure by using pharmacokinetic (PK) targets: AUC_{0-EOT} and $T > EC_{90}$ through population PK simulations with a representative Eastern African pediatric population.

D. Final dose selection and dose harmonization



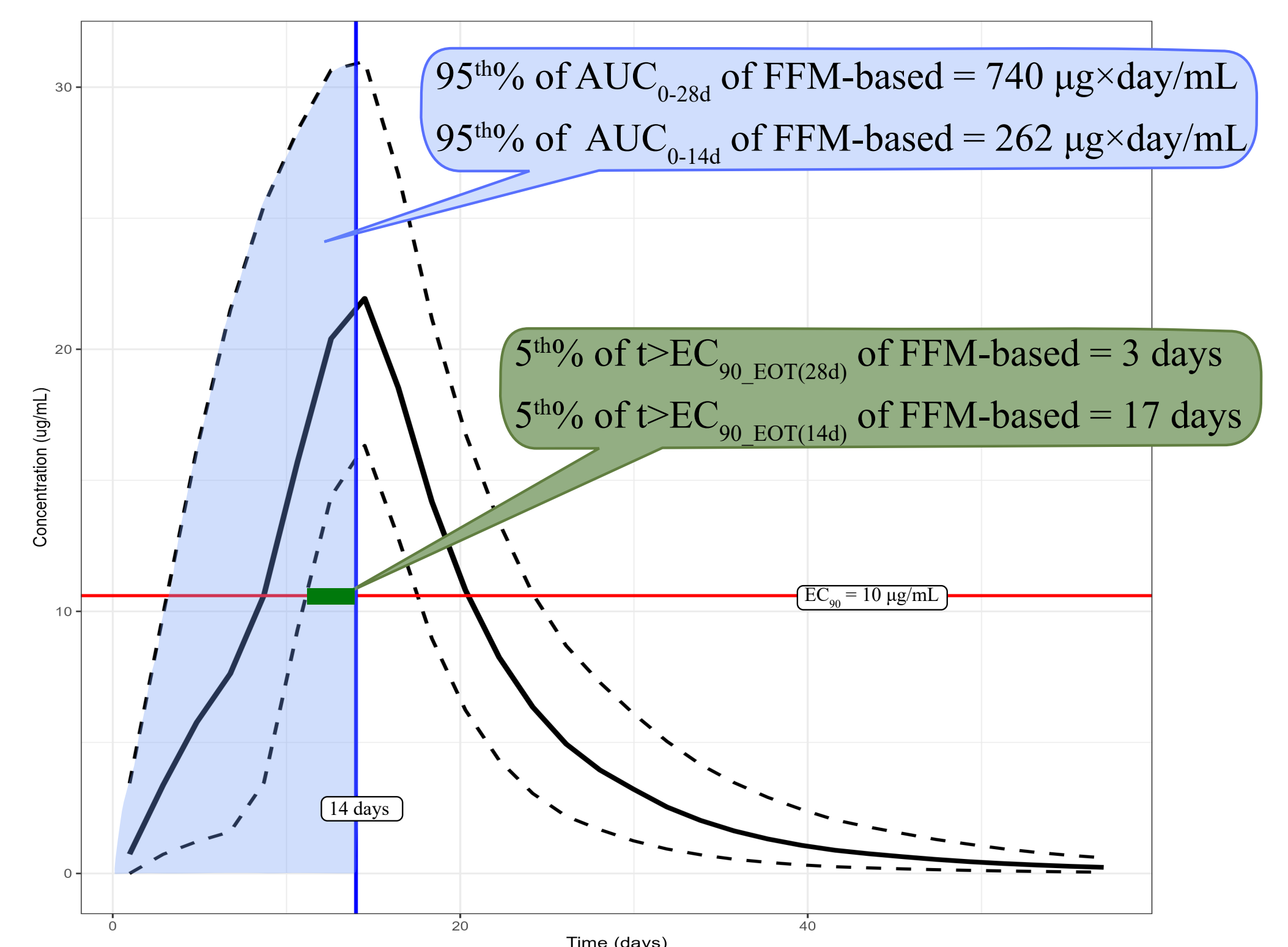
3. Methods & Results

A. Creation of the virtual population



WHO-NHANES growth curves were adjusted using data from over 9000 real-world pediatric VL patients from Eastern Africa by using a polynomial function-derived correction factor specific for each sex, and weight and height.⁷

B. Simulation of the allometric FFM-based dosing and target derivation



An upper (AUC_{0-EOT}) and lower limit ($T > EC_{90}$) target for the 28- and 14-day regimen were determined from simulated allometric FFM-based pediatric patients' PK profiles at the end of treatment. An existing population-PK model was used to generate the concentration-time individual profiles used for target establishment.⁸

C. Utility score-aided selection of the best dose per WB

$$Score_{WB} = \frac{\sum (n_{below} + n_{over})}{n_{total}}$$

The selection of the best dose was based on the number of patients outside either limit and selected the best dose based on the lowest score within each WB. The WB ranges used were the proposed harmonized bands by GAP-f.⁹

The selected WB-based doses for the 14- and 28-day regimen had similar exposures compared to their allometric FFM-based counterparts. On the $T > EC_{90}$ target achievement most weights reach over 90% of target attainment. In comparison, the conventional 2.5 mg/kg miltefosine has as little as 10% target achievement for the same target.

4. Findings & Future perspective

- We successfully **developed a simplified miltefosine dosing using comprehensible WB for pediatric patients under 30 kg** suffering from VL with a comparable exposure profile to the more specific allometric FFM-based dosing, which has also proven to be effective.
- An understanding of the demographics of the target population is key, as **most of these children have low weights for their height/age as a result of poverty and malnutrition, compared to WHO-NHANES curves**. Our virtual population is tailored to the region of interest and thus provides a realistic scenario to conduct simulations on.
- The proposed **utility score considers** both ends (**under- and over-exposure**) **with the same degree of importance**, in our case **two different parameters: AUC_{0-EOT} for the upper and $T > EC_{90}$ for the lower**, so that the selected dose would not be one-sided and thus recommend potentially unnecessarily high doses.
- By using the proposed WHO harmonized WBs, **the proposed dosing strategy will be easier to implement**, particularly in patients with other concomitant diseases such as TB and/or HIV.
- Currently, miltefosine exists only in 10 and 50 mg capsules which often means that children have to swallow multiple units to achieve the right dose. This works **opens the possibility to explore more optimized and child-friendly dosing forms** that minimize the number of units to swallow.

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