

Population pharmacokinetic modelling as a screening tool to expedite evidence for understudied/hard-to-study populations: a case study of atazanavir/ritonavir in people with HIV

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Background and Objectives

- Access to antiretroviral therapy (ART) is often delayed in **pregnant women, obese and underweight individuals, children, and adolescents**, as these groups are **often excluded from clinical trials**,^{1,2} rendering them **understudied**.
- When studied, they are often enrolled in **separate, delayed trials**—with different protocols, assays, and formulations—**slowing evidence generation** and making it harder to interpret differences in exposure.
- While **ritonavir-boosted atazanavir (ATV/r)** pharmacokinetics is well described in standard populations with HIV, data remains sparse in these **understudied groups**.
- ATV/r is a protease inhibitor widely used in combination ART in low-income settings, and both drugs are primarily metabolised by **CYP3A4/5** enzymes.³
- We **aimed** to use a population pharmacokinetic (**PopPK**) model developed in adults from the same **unified protocol** as the **understudied** groups as a **screening tool** to predict ATV/r exposures in these understudied groups, based on **sparse/opportunistic** sampling—allowing us to assess whether current dosing is appropriate, or if dose adjustments may be needed.

Methods

- Data on the **understudied populations with HIV** were collected from an **observational** PK study (NCT03923231) within the VirTUAL consortium at two Ugandan and one South African site.
- A larger, intensive PK study in **standard adults with HIV** (NCT04121195) served as the **main cohort**.⁴
- NONMEM (v7.5.1)** – FOCE-I, was used to perform the analysis, using fixed parameters (**MAXEVAL=0**) from the model developed with data from **standard adults with HIV** from the main cohort.⁵

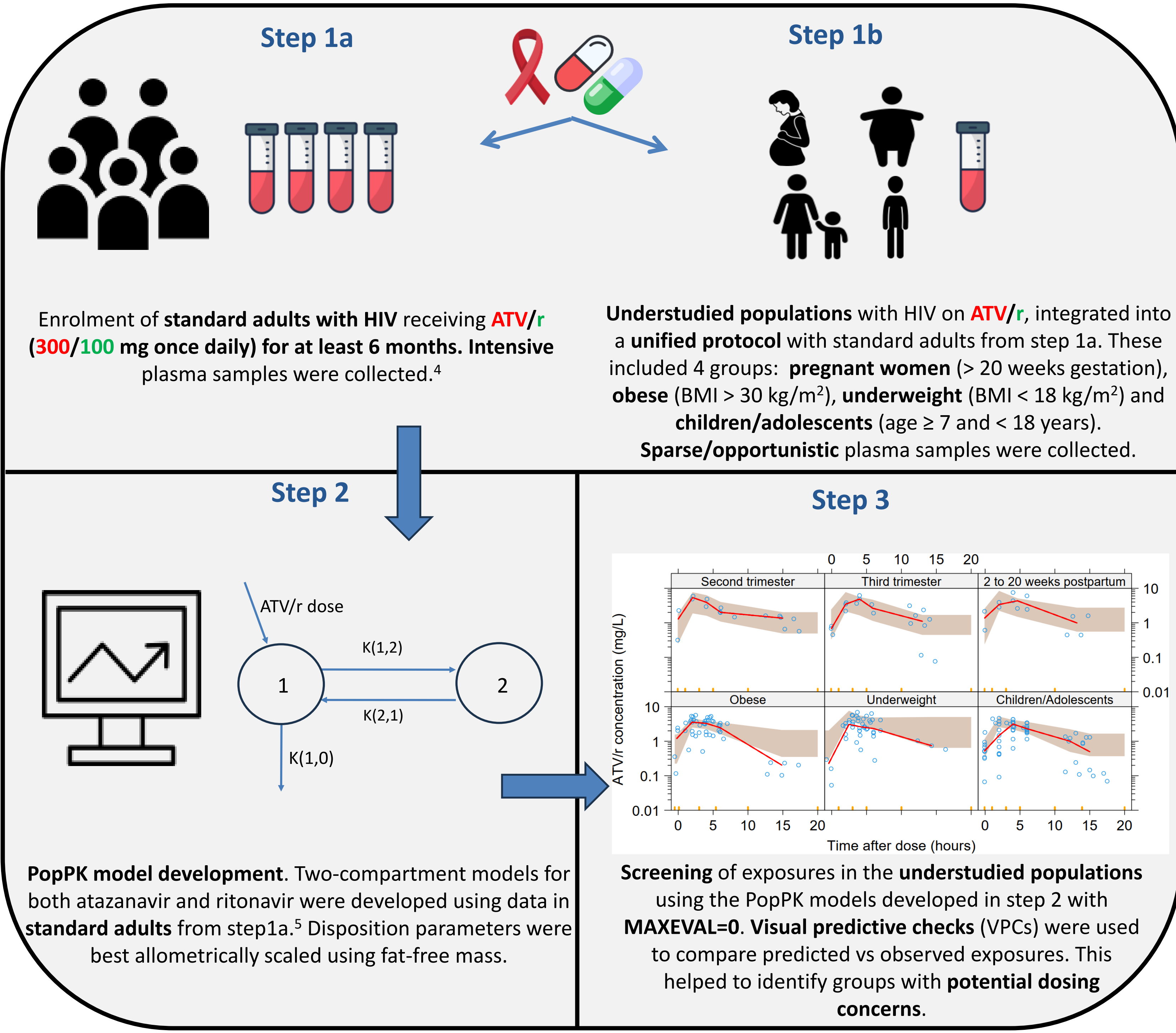


Figure 1. Study workflow summary. BMI: Body Mass Index.

Results

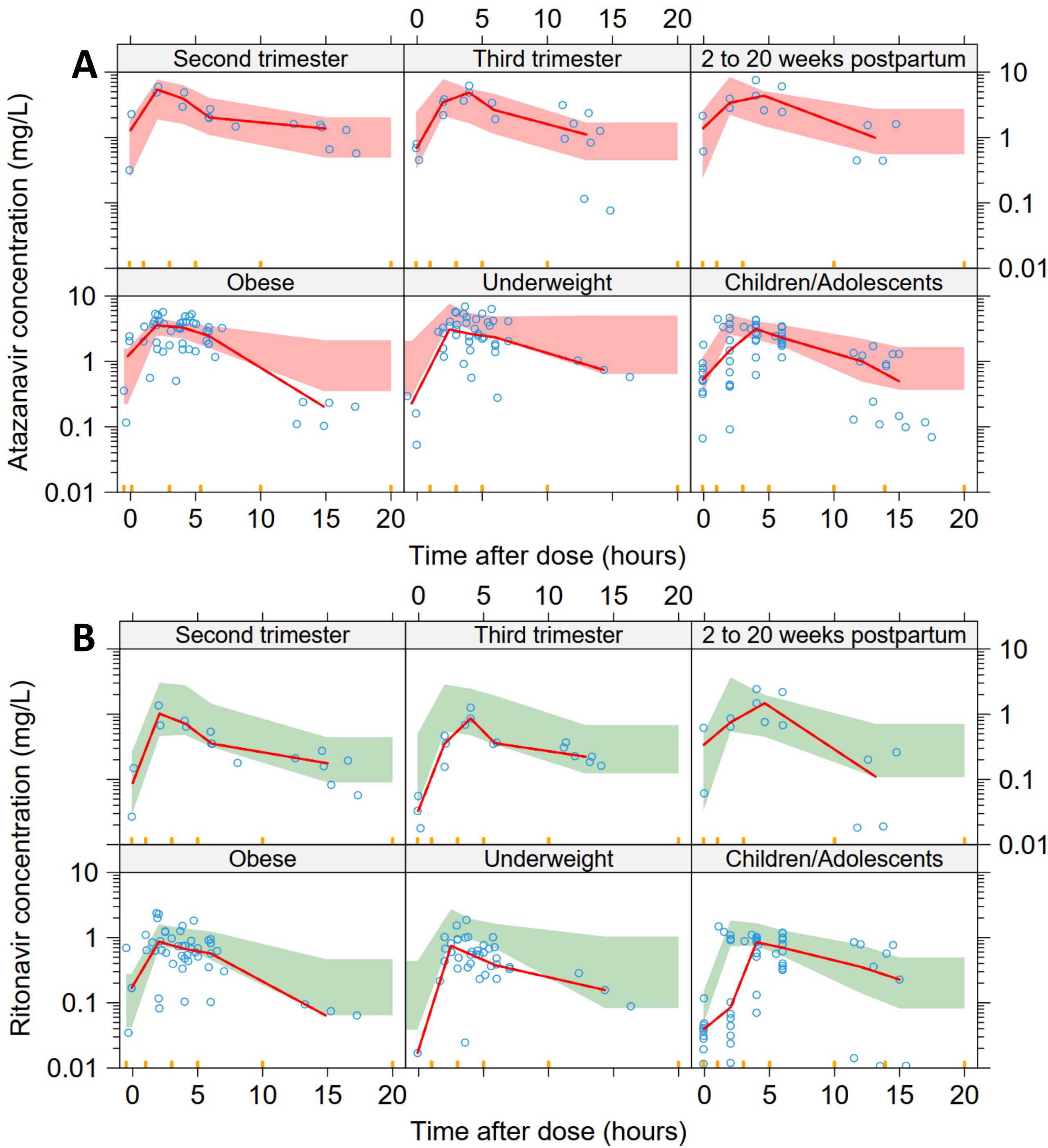


Figure 2. VPCs of atazanavir concentrations (panel A), and ritonavir concentrations (panel B) versus time after dose generated using fixed parameters (**MAXEVAL=0**) from the model developed in standard adults with HIV.⁵ The y-axis is plotted in the log-scale. Only the 50th percentile is shown due to limited observed data.

Summary of ATV/r exposures

- Pregnant women:** Exposures observed at both **antepartum** and **postpartum** were **inline** with model predictions for atazanavir and ritonavir. However, **ritonavir exposures were slightly lower at antepartum** compared to postpartum, likely due to **increased CYP3A4/5** activity during pregnancy.⁶
- Obese individuals:** Observed exposures matched model predictions for both drugs—**no concern for dosing adjustment**.
- Underweight individuals:** Exposures observed were **lower than predicted** for both atazanavir and ritonavir, possibly due to reduced bioavailability.⁷
- Children/adolescents:** Showed **delayed absorption** for both drugs, suggesting formulation and/or age related effects.⁸

Conclusions

- By integrating multiple populations into a **unified protocol** and leveraging **PopPK modelling**, we used **sparse/opportunistic sampling** to screen for differences in ATV/r PK across **understudied groups**—**expediting evidence** generation where traditional studies are often slow or unfeasible.
- Pregnant and obese individuals**, had **reassuring exposures**. However, **ritonavir at antepartum** may need **closer attention** due to slightly lower exposure.
- Underweight and children/adolescent** groups showed **atypical PK profiles** and may benefit from **further investigation** or **dose optimisation**.

Results

Table 1. Participant characteristics (baseline)

	Pregnant women (n = 8)	Obese (n = 7)	Underweight (n = 7)	Children/adolescents (n = 11)	Total (n = 33)
Age (years)	32 (22 – 39)	43 (28 – 49)	29 (21 – 49)	15 (11 – 17)	31 (11 – 49)
Weight (kg)	75.0 (61.5 – 99.4)	93.0 (75.6 – 128)	41.5 (32.0 – 47.5)	46.5 (33.1 – 87.1)	60.8 (32.0 – 128)
Height (m)	1.61 (1.48 – 1.65)	1.55 (1.51 – 1.64)	1.57 (1.46 – 1.63)	1.57 (1.32 – 1.68)	1.57 (1.32 – 1.68)
BMI (kg/m ²)	29.2 (22.9 – 38.6)	37.6 (31.5 – 54.3)	16.8 (13.2 – 18.8)	19.3 (17.1 – 33.1)	24.3 (13.2 – 54.3)
Sex, Females/Males (n)	8/0	7/0	6/1	4/7	25/8
Co-administered NRTIs					
3TC-AZT	2 (25%)	3 (43%)	4 (57%)	0 (0%)	9 (27%)
3TC-TDF	5 (62%)	3 (43%)	1 (14%)	5 (45%)	14 (42%)
FTC-TDF	1 (13%)	1 (14%)	2 (29%)	0 (0%)	4 (12%)
3TC-ABC	0 (0%)	0 (0%)	0 (0%)	6 (55%)	6 (18%)

Data are represented as median (range) or n (%). NRTIs, nucleoside reverse transcriptase inhibitors; 3TC, lamivudine; AZT, zidovudine; TDF, tenofovir; FTC, emtricitabine; ABC, abacavir.

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