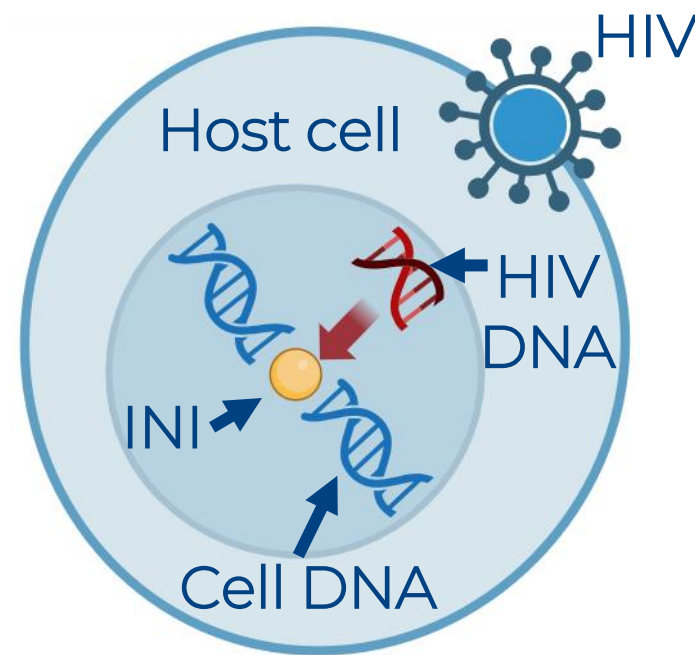


Introduction

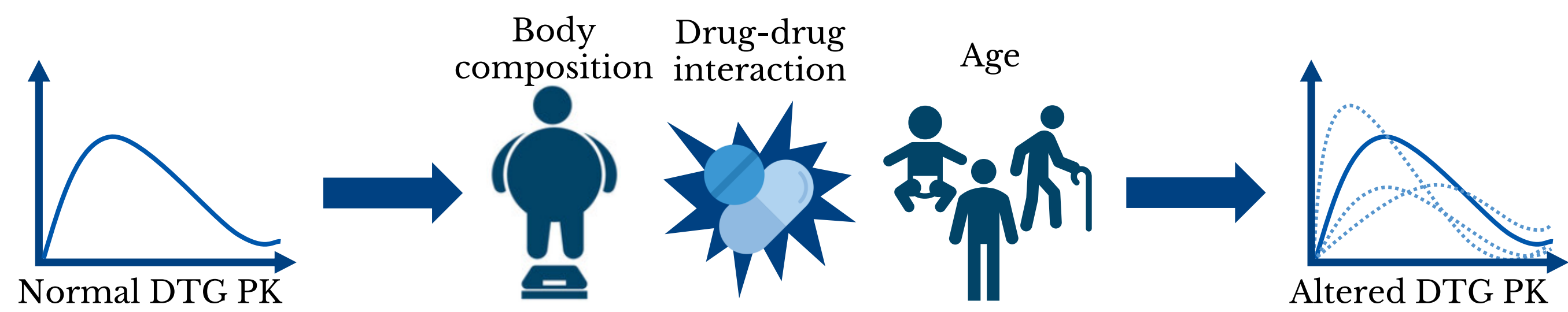
Background

HIV and Dolutegravir (DTG)

- Different classes of antiretrovirals (ARVs) can sustainably suppress HIV viral replication.¹
- Integrase inhibitors (INIs) are first-line agents for the treatment of HIV because they are highly effective and well tolerated.²
- DTG, an INI, is recommended by the World Health Organization (WHO) as a first- and second-line agent in all populations.³



DTG Pharmacokinetics (PK)



- Understanding these sources of variability is crucial to ensuring adequate DTG exposure, given the potential effects of both low and high concentrations.
- Therapeutic drug monitoring (TDM) can play a role in optimizing DTG therapy, particularly in individuals at risk of altered drug exposure.
- Population pharmacokinetic (PopPK) modeling offers a powerful tool for characterizing DTG disposition across diverse patient groups, helping to refine dosing strategies and optimize treatment outcomes.

Objective

- This narrative review synthesizes existing DTG PopPK models, highlighting key PK parameters and covariate effects.

Methods

Search strategy

Sources and search criteria

- A literature search of published PopPK studies on DTG was conducted in Embase⁴ and Medline⁵ (from inception to January 13, 2025).
- Keywords related to: 'PopPK', 'Non-linear mixed effect', and 'dolutegravir'.

Inclusion criteria	Exclusion criteria
Studies on the development or revision of a human plasma DTG PopPK model.	Insufficient details on the PopPK model.

Data extraction

- Data on study design, populations, PopPK models, covariates, and simulations were extracted.

Results

Search – Results

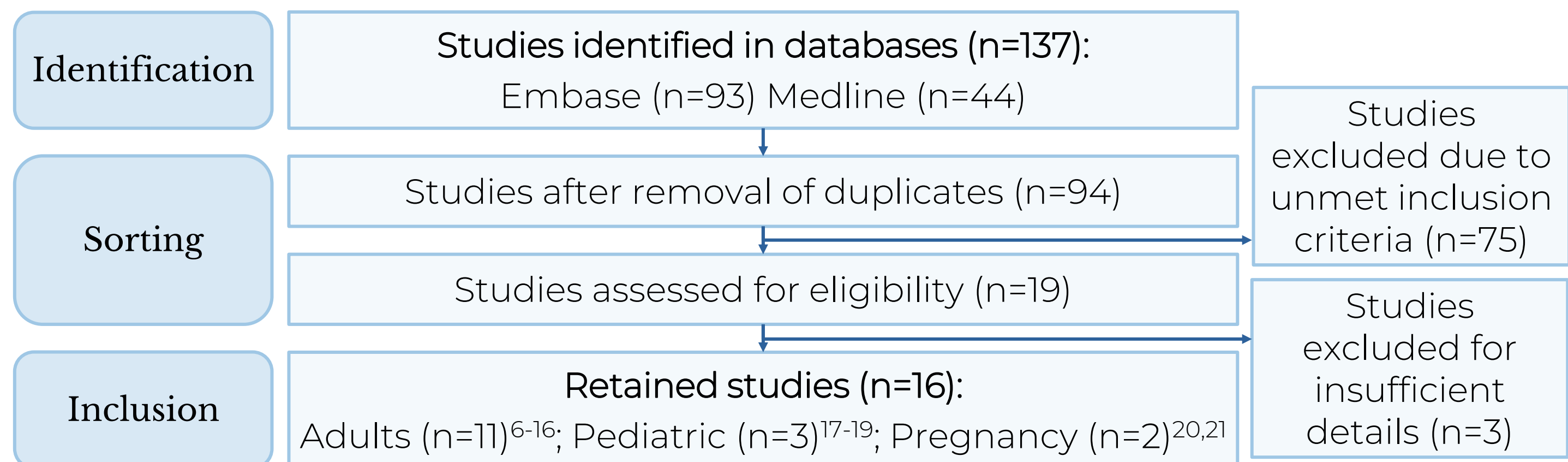


Figure 1: *PRISMA* Chart of the review

Study design and populations

Study design

- Most studies used data from clinical trials, but some also used TDM data, cohort data, and electronic medical records.
- Study type: Prospective (n=7) and retrospective (n=9).
- Some adult studies focused on drug-drug interactions (DDIs) between DTG and rifampicin (RIF) (n=3), RIF and rifabutin (RFB) (n=1), or antimalarial drugs (n=1).

Table 1: Population characteristics

Characteristic	Adult ^a	Pediatric ^a	Pregnant ^b	Infant ^b
N subjects	279 [26-676]	153 [42-239]	28-31	18-22
N PK samples	782 [211-3 357]	455 [358-2 650]	533-552	65-70
Median age (years)	38.8 [28.5-51.0]	10.9 [6.0-15.0]	27-31	38-39
Median weight (kg)	72.0 [55.5-81.5]	27.8 [21.1-50.0]	67.0-83.4	3.1-3.3

^a Median (min-max).

^b Reported values (only two studies in these populations).

Results (continued)

Models

Table 2: Model parameters

	N compartments	CL/F (L/h)	Total Vd (L)	ka (h ⁻¹)
Adults ^a	1: n=7; 2: n=4	0.93 [0.71-2.82]	16.82 [12.40-20.20]	1.68 [1.41-2.24]
Pediatric ^{a,b}	1: n=3; 2: n=1	0.91 [0.72-1.03]	13.60 [8.66-16.60]	0.85 [0.50-0.95]
Pregnant ^c	1: n=1; 2: n=1	1.50; 0.73	18.50; 26.61	1.08; 0.75

Abbreviations: CL/F, apparent clearance; ka, absorption rate constant; Vd, volume of distribution.

^a Median [min-max] or n.

^b Abdalla et al.'s model describing unbound DTG PK is not presented.

^c Reported value or n.



Figure 2: Tested and included covariates

Simulations

Adult

- Simulations on DDIs were conducted (DTG + RIF, RFB, or antimalarial drugs).^{8-10,12-14}

Table 3: DDI simulations

DDI	DTG Regimen	C _{min} Target Values
DTG+RIF	50 or 100mg QD or BID	0.064mg/L and 0.3mg/L
DTG+RFB	50mg QD	0.064mg/L and 0.3mg/L
DTG+AL or ASAQ	50mg QD	0.064mg/L

Abbreviations: AL, artemether/lumefantrine; ASAQ, artesunate/amodiaquine; BID, twice daily; C_{min}, minimal concentration; DDI, drug-drug interaction; DTG, dolutegravir; QD, once daily; RFB, rifabutin; RIF, rifampicin.

50mg twice daily was adequate, but 100mg once daily could be better for adherence.

Standard regimens were adequate.

Pediatric

- Simulations on the study regimens were conducted, and one study simulated doses given twice daily.¹⁸

- Recommended doses were adequate, with no benefit from twice daily regimens.

Pregnant

- One study simulated regimens for newborns born to mothers taking DTG or not.²¹

Table 4: Simulated timing of first two DTG doses after birth in newborns

Doses	Exposed newborn	Unexposed newborn
1 st dose (5mg)	24h after birth	At birth
2 nd dose (5mg)	48h after the 1 st dose	48h after the 1 st dose

Summary/Conclusions

Summary

- Sixteen articles were retained: eleven in adults, three in pediatric populations, and two in pregnant women and their infants.
- One- and two-compartment models were used across all populations.
- Significant covariates varied between populations and within the same population.
- Simulations indicated that current DTG regimens are adequate (adult and pediatric).

Conclusions

- DTG PopPK models varied across studies, even within the same population, showing the complexity of DTG PK.
- No PopPK models were identified for elderly or obese individuals, thus indicating a need for PopPK studies in these populations.

Acknowledgements