Development of an In-Silico Platform to Explore HIV Incidence Across Different Regions and Its Application to PrEP Clinical Trials for Treatment Design and Optimization

Pharmacometrics & Systems Pharmacology group UNAV

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INTRODUCTION & OBJECTIVES

Human immunodeficiency virus (HIV) remains a **major global public health** challenge, affecting millions worldwide, with the highest prevalence in Africa and other resource-limited regions.

Despite effective antiretroviral therapies, **no cure exists**, and prevention strategies such as **pre-exposure prophylaxis (PrEP)** are essential. Daily oral regimens often face adherence challenges, reducing effectiveness. This has motivated the development of different new agents, where models can guide dose optimization and support the design of more effective PrEP strategies.[1,2]

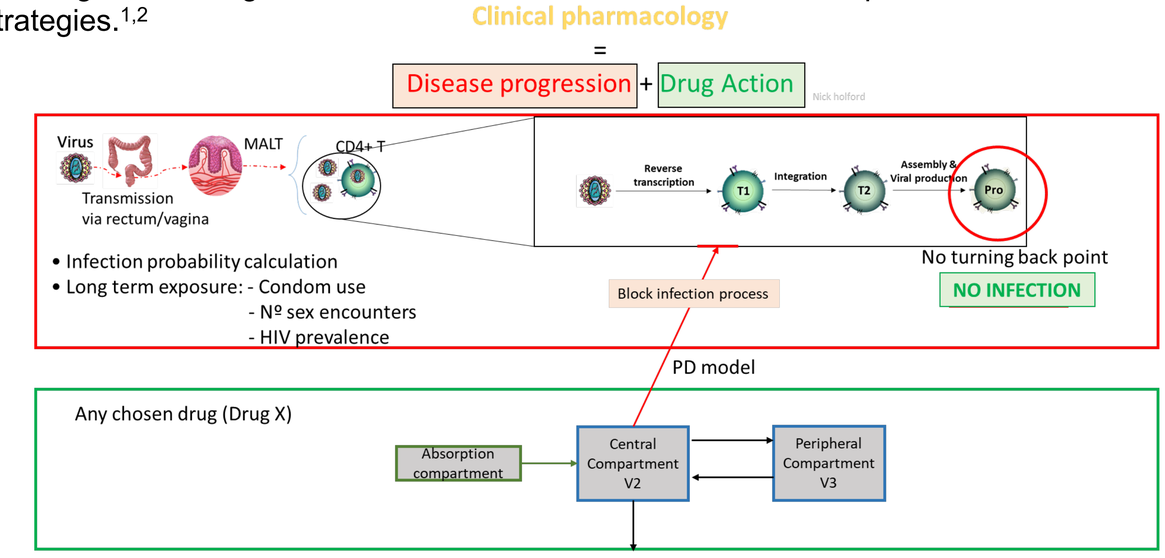


Figure 1. Visual representation of the full model following the pathophysiology of infection

OBJECTIVES

To develop an **in-silico platform** capable of simulating **HIV incidence** across diverse populations, allowing the assessment of covariates such as **risky sexual encounters**, **condom use** and **partner HIV status**, enabling also the evaluation of **PrEP interventions**. The platform aims to **support clinical trials** by providing insights into treatment optimization and potential outcomes.

- ✓ Create an encounter model to simulate cohorts
- ✓ Validate the model with the background incidence
- ✓ Adapt the model to drug X
- ✓ Use the model to simulate clinical trials

MATERIALS & METHODS

Viral dynamics model

The model considers viral dynamics at the cellular level based on the work from Duwal et al.[3], where **infection** is established if the virus completes a **full replication cycle**. Viral elimination and progression through each stage are treated as discrete reactions, allowing calculation of the probability of extinction at each step. To establish infection, at least **1 virus** needs to progress to **last stage**.

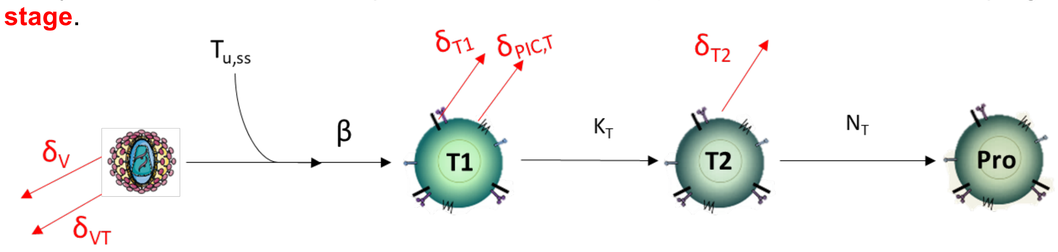


Figure 2. Schematic model representation. *$T_{u,SS}$ is the uninfected total cells for T cells, δ represents a clearance parameter, δ_V virus clearance, δ_{VT} virus clearance due to unsuccessful infection, δ_{T1} death rate of T1 cell, $\delta_{PIC,T}$ death due to unsuccessful integration and δ_{T2} death rate of T2 cell.β represents the infectivity parameter of direct infection. Lastly K_T represents the integration rate and N_T the viral production rate.*

The infection probability **(P_{inf})** is the complement of the extinction probability **(P_{ext})** $P_{\text{inf}}(Y_0) = 1 - P_{ext}(Y_0)$

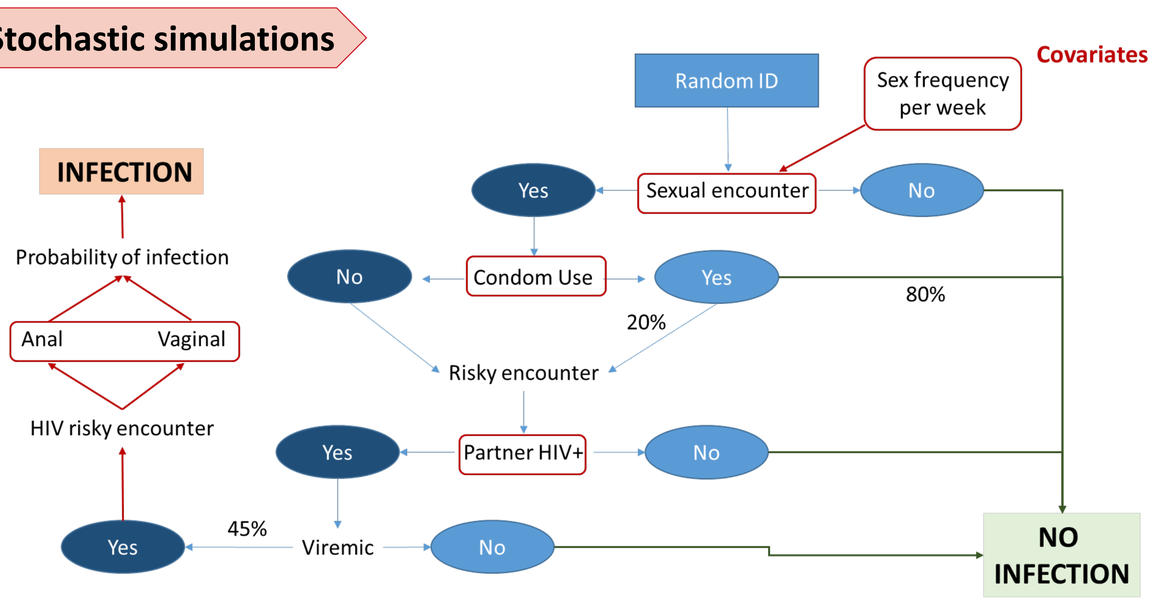
The probability of extinction it is derived into one-step transition probabilities, calculated as the **ratio of successful events to total events**, based on the rate constants defined in the model, i.e.:

V → ø $P(Y_1 = 0 | Y_0 = \hat{V}) = \frac{a_1(ø)}{a_1(ø)+a_{61}(ø)}$ Being a_1 parametrized from the model presented above

For example; Clearance of free virus → $a_1(ø) = (\delta_V + \delta_{VT} \cdot T_{u,SS}) \cdot V$

The probability of extinction of a virus is $P_{ext} = \prod_i^n JP$ where JP represents the joint probability of the virus being cleared at different stages

Stochastic simulations



Study population

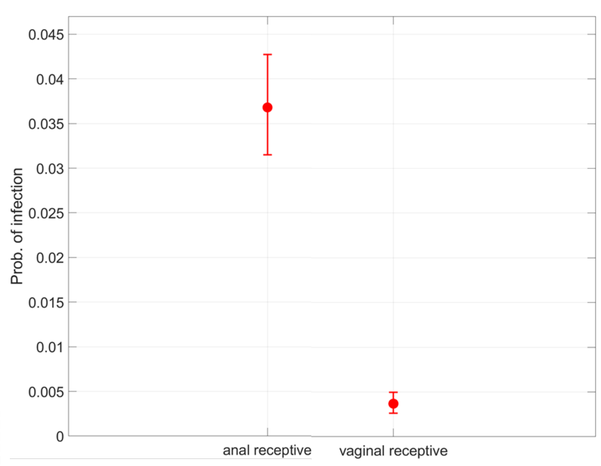
- Adolescent girls and young women
- Median age 25 years (22-30)
- 99% black
- 80/20 vaginal / anal

Region	HIV Prevalence (adults 15–49)	Condom Use	Sexual Frequency (per week)
South Africa (40.5%)	17–19%	60%	1.4
Zimbabwe (24.2%)	11–13%	40%	2
Uganda (18.6%)	5–7%	45%	3
Malawi (7.0%)	8–10%	40%	2
Eswatini (5.0%)	27–28%	40%	2
Botswana (2.9%)	20–22%	50%	2
Kenya (1.9%)	3–4%	50%	2

The model randomly determines region and subsequently condom use & sex frequency for each simulated individual

RESULTS

Infection probability



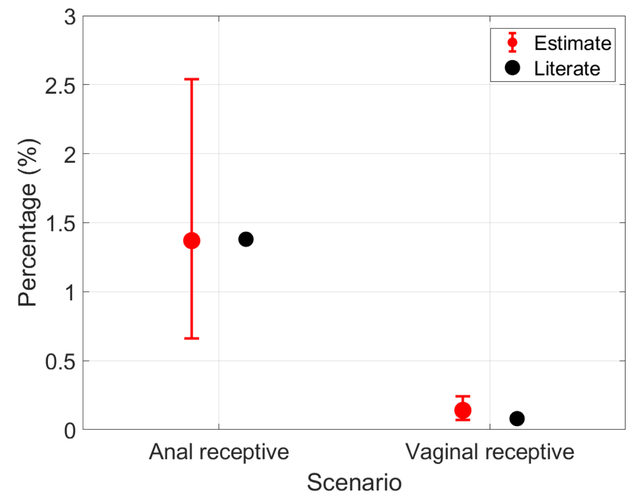


Figure 3. Infection probability and probability of transmission

Route	Literature Estimate (%)	Model Estimate (%)
Anal receptive	1.38[4]	1.37 (0.66, 2.54)
Vaginal receptive	0.08[4]	0.14 (0.07, 0.24)

Table 1. Transmission percentages stratified by sex type and comparing model estimates and literature data

Model predictions are very **consistent with the literature**. Probability of infection only varies due to differences in T cell and number of transmitted virions. It was estimated HIV transmission probability by route, assuming an HIV-positive donor with sufficient viremia. The estimates are **sensitive to model changes**. A higher vaginal transmission value (~3%) is plausible in low-income settings, and receptive anal transmission may be higher, supporting the model's validity.

Incidence

Population simulation
1 year
Generated population characteristics
Women (80% vaginal receptive, 20% anal receptive)
Repeat for 100 simulations
Total cases: 70
Population Incidence: 3.284 (2.568, 4.225) per 100 PY.
Literature data: Incidence 3.38[5] per 100 PY.

Use the model to explore the effect of the variables

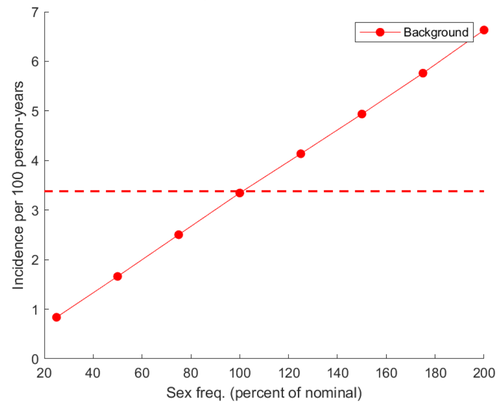


Figure 4. Effect of sex encounters on background incidence

Example: drug X

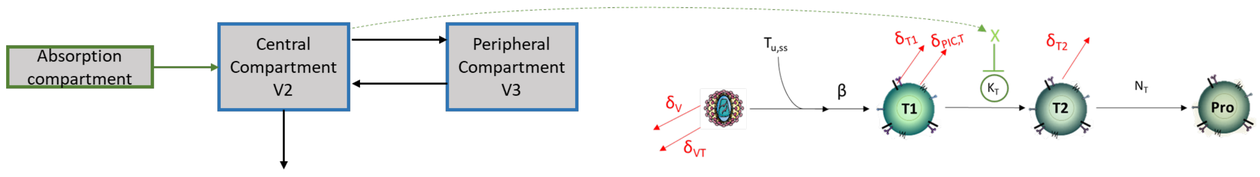
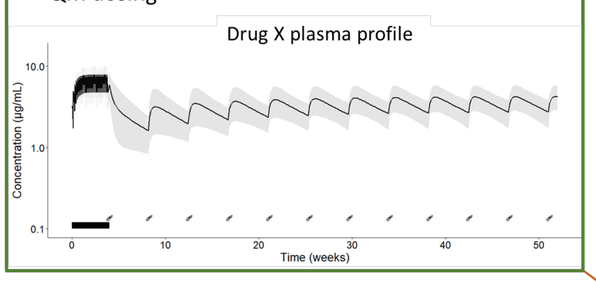
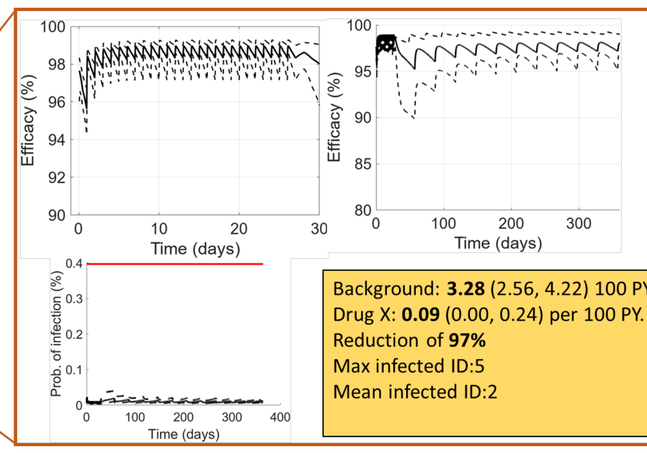


Figure 5. PKPD model scheme for drug X.

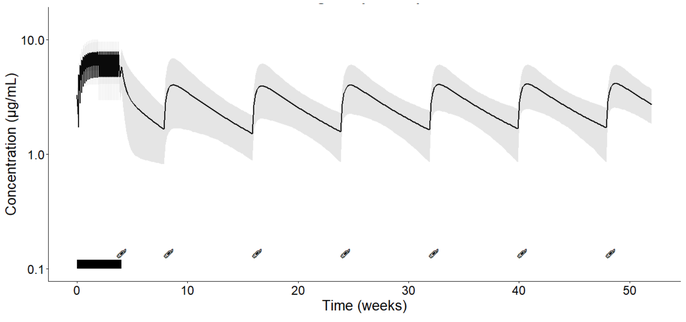
Selected dose regimen:
- Oral loading dose
- QM dosing





Background: **3.28** (2.56, 4.22) 100 PY.
Drug X: **0.09** (0.00, 0.24) per 100 PY.
Reduction of **97%**
Max infected ID:5
Mean infected ID:2

Explore another dose regimen



Background: **3.33** (2.56, 4.03) 100 PY.
Drug X: **0.1** (0.00, 0.24) per 100 PY.
Reduction of **97%**
Max infected ID:7
Mean infected ID:2

Clinical trial results:
4 infections detected, 1 at enrollment and 1 with low drug exposure

The model matches the trial results

CONCLUSIONS

- ✓ The model accurately simulates **HIV incidence** across diverse virtual populations by incorporating behavioural and biological factors such as **condom use, sexual act type, partner HIV status and sexual frequency.**
- ✓ The model allows the Integration of different drugs and drug regimens enhancing its ability to predict prophylactic protection, **consistent with clinical trial observations**. Allowing the exploration of mutant strains too (based on in vitro EC50 values)
- ✓ The analysis confirms **the drug** as a **highly efficacious long-acting PrEP option**. Allowing to perform different scenarios (missed doses, different regimens) to explore the outcomes

Strong asumptions

- Simplified PK (PBPK in order to know concentration at exposure sites)
- Simplified viral dynamics
- Sexual acts are considered as random independent acts (repeated partners, network, status,…)
- Some biological processes and Inflammation, other STD are not considered in the model this can increase the probability of infection.

REFERENCES