Low Intrapatient Variability in ARV Plasma Concentrations is Associated with Low Viral Load – Findings from a Longitudinal HIV Study with Ingestible Sensor Monitoring

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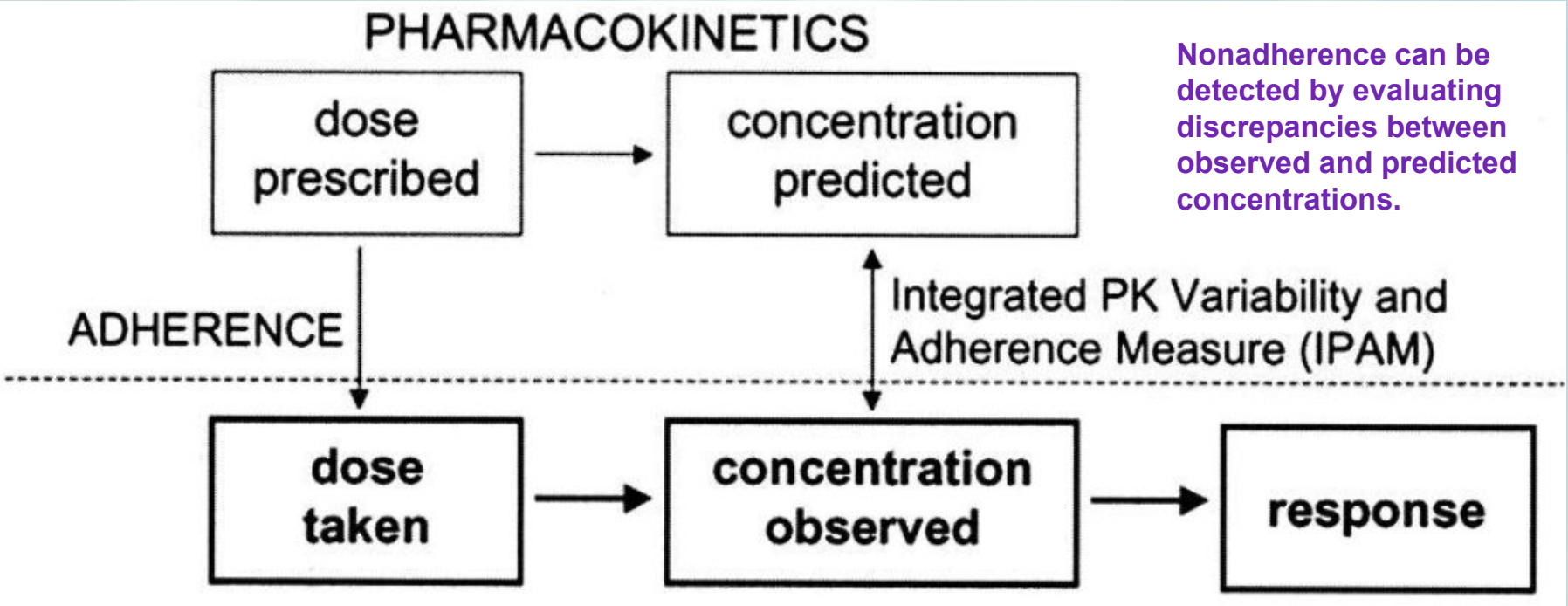
Pharmacokinetics (PK) and Adherence

Plasma concentration

Plasma concentration refers to **the concentration of an agent in the plasma which is derived from full blood**. Plasma concentrations are used to define major PK parameters.

PK - adherence



Nonadherence can be detected by evaluating discrepancies between observed and predicted concentrations.

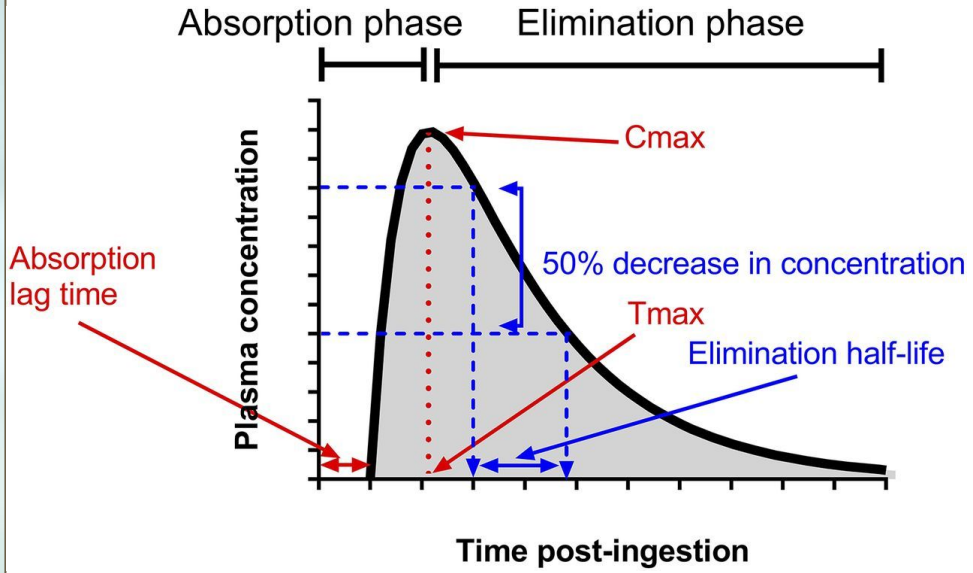
Brundage, R. C., Yong, F. H., Fenton, T., Spector, S. A., Starr, S. E., & Fletcher, C. V. (2004). Intrapatient variability of efavirenz concentrations as a predictor of virologic response to antiretroviral therapy. Antimicrobial agents and chemotherapy, 48(3), 979–984. https://doi.org/10.1128/AAC.48.3.979-984.2004

Drug exposure and viral response

- **Variability in response** to ART is attributed to
  - Virologic outcomes
  - Immunologic outcomes
  - Pharmacologic outcomes
  - Behavioral characteristics
- **Source of variation**
  - Pharmacokinetics
  - Adherence
  - Expected (analytical error, time dependencies, model)

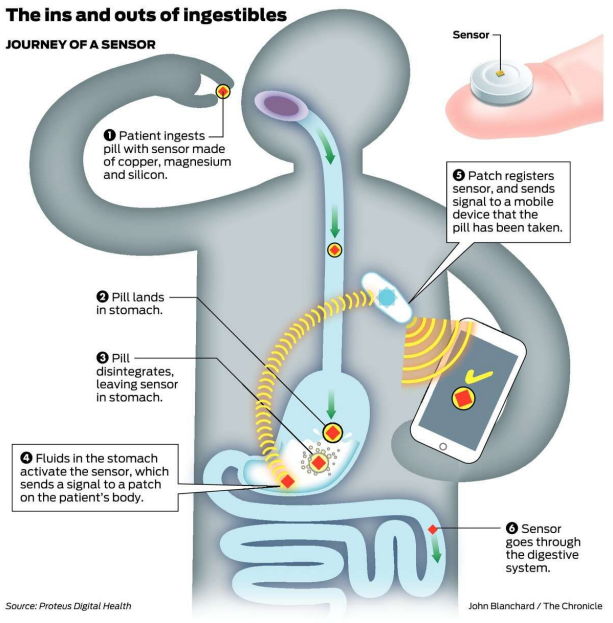
Pharmacokinetics

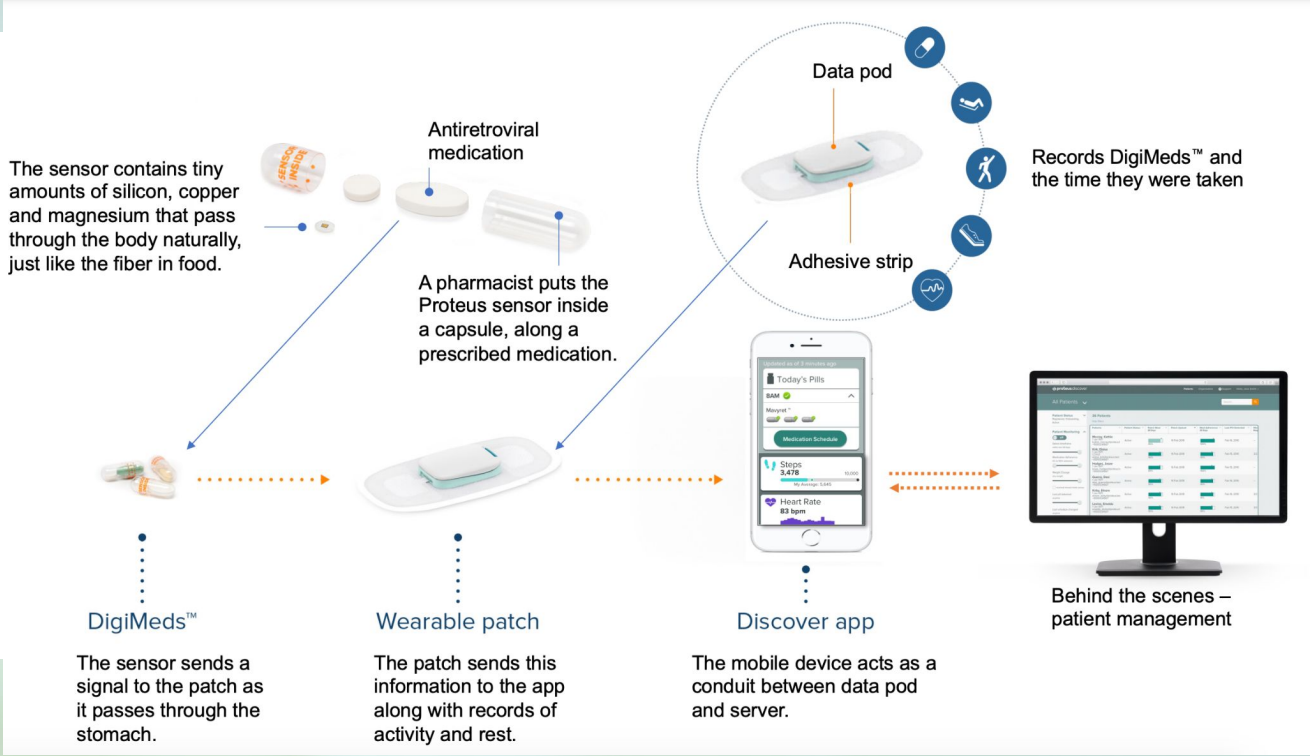
- **A**bsorption – how the drug get into the body
- **D**istribution – where the drug goes into the body
- **M**etabolism – how the body chemically modify the drug
- **E**limination – how the body gets rid of the drug



Plasma concentration-time profile after oral administration of a single dose.

Overview of the proteus digital health feedback system





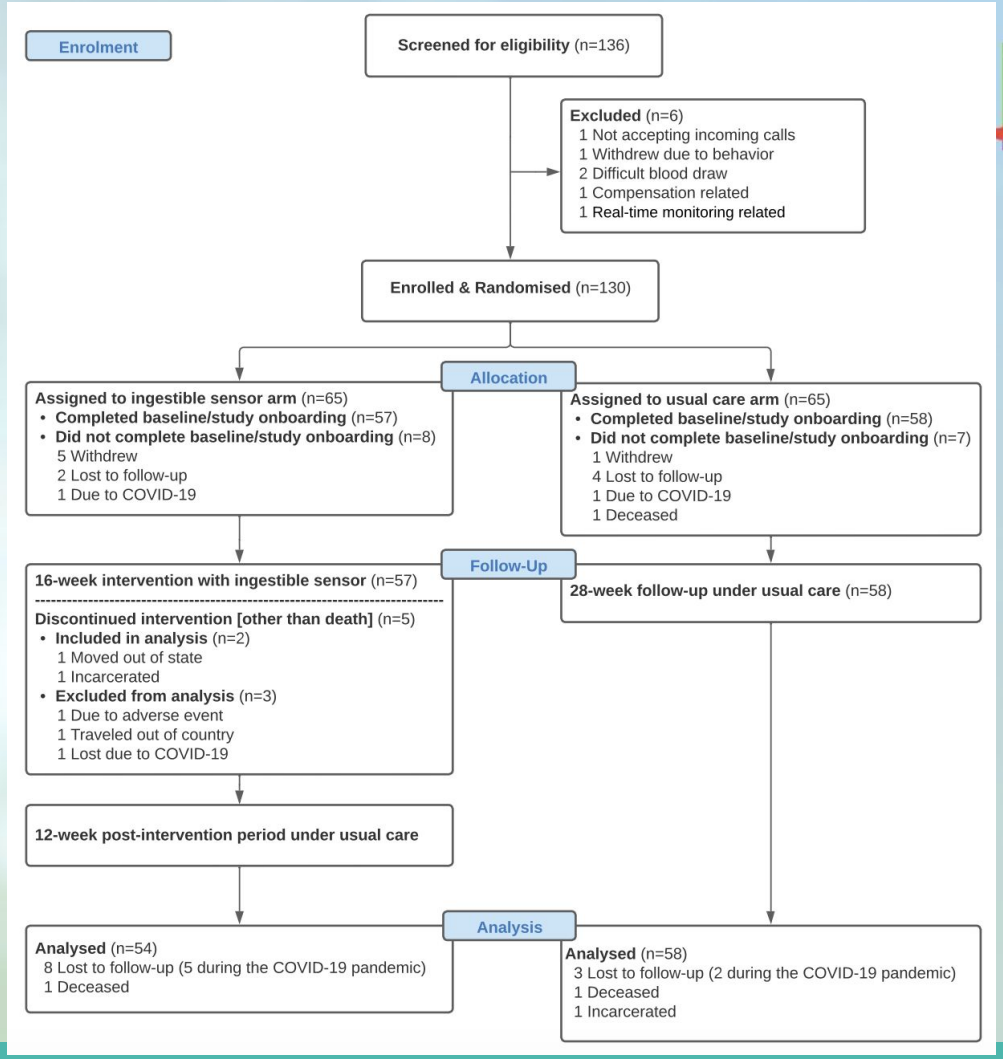
Study Design

Inclusion criteria: HIV-infected individuals (≥18 years) who were in care and had difficulty adhering to their recommended regimens

- Self-reported adherence <90%
- Gaps in treatment
- Missing appointments (>2, not rescheduled)
- VL elevated in the past six months.

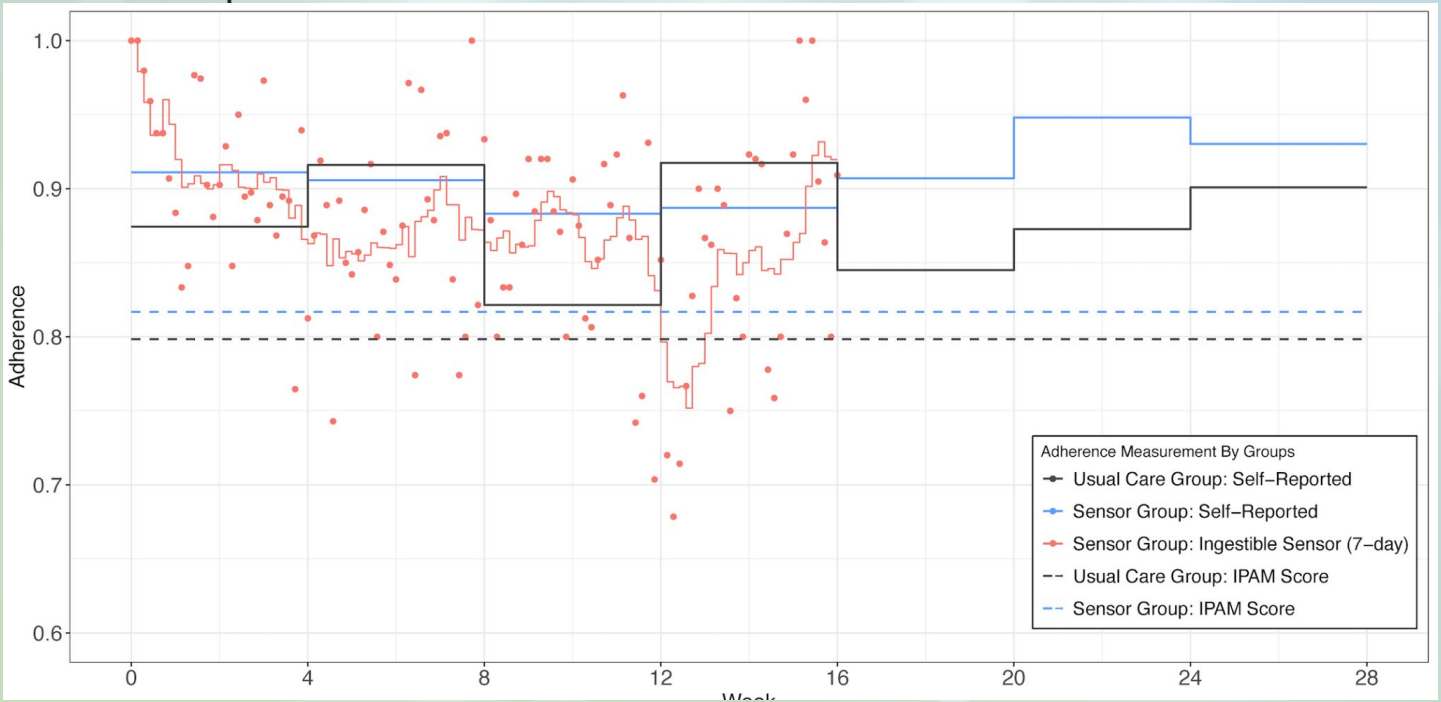
Randomization: Before baseline since extra time was needed for co-encapsulation process. Stratified by,

- Single/multiple tablet regimen
- Detectable/undetectable VL



Adherence measures

- Ingestible sensor – measured adherence
- Plasma concentration adherence
- Self-reported adherence



PK - timing and dosage

- **Blood samples at**
  - **Baseline:** before(0), 2 hour, 6 hour - follow an observed dose
  - **Follow up:** week 4, 8, 12, 16, 20, 24, 28
- All of these study participants were receiving a **TAF –** tenofovir alafenamide - containing regimen
- The TAF dose is **25mg** once daily except for those receiving Genvoya, where the TAF dose is **10mg**.

One compartment model

- Population PK model using nonlinear mixed-effects approach (**NLME**)
- Use first-order conditional estimation (**FOCE**)
- Extended least square (**ELS**) - interaction between inter-, intra-, and residual error
- **Model selection:** likelihood function (**-2LL**) and visual inspection (**GOF plot**)
- **Final Model:** One-compartment PK linear model with a proportional error and random effects of person and time
- **Software:** Phoenix WinNolim 8.3 for PK/PD analysis

Pharmacokinetic parameters

- Intra-patient variability
- Clearance, volume of distribution, absorption rate were estimated in the model
- **Concentration predictability score** is defined as,

$$\frac{\text{Observed concentration}}{\text{Predicted concentration}} \in [0.6, 1.4]$$

- **IPAM** – % of ratio within this range over study period

IPAM score

Group	No. of subjects	IPAM statistics	
		Mean ± SD	Range
All	81	0.82 ± 0.26	0.00-1.00
High (> 0.8)	52	0.97 ± 0.06	0.83-1.00
Low (≤ 0.8)	29	0.55 ± 0.24	0.00-0.80

Use the 33rd percentile of the IPAM in the population (0.8) as the cut-off.

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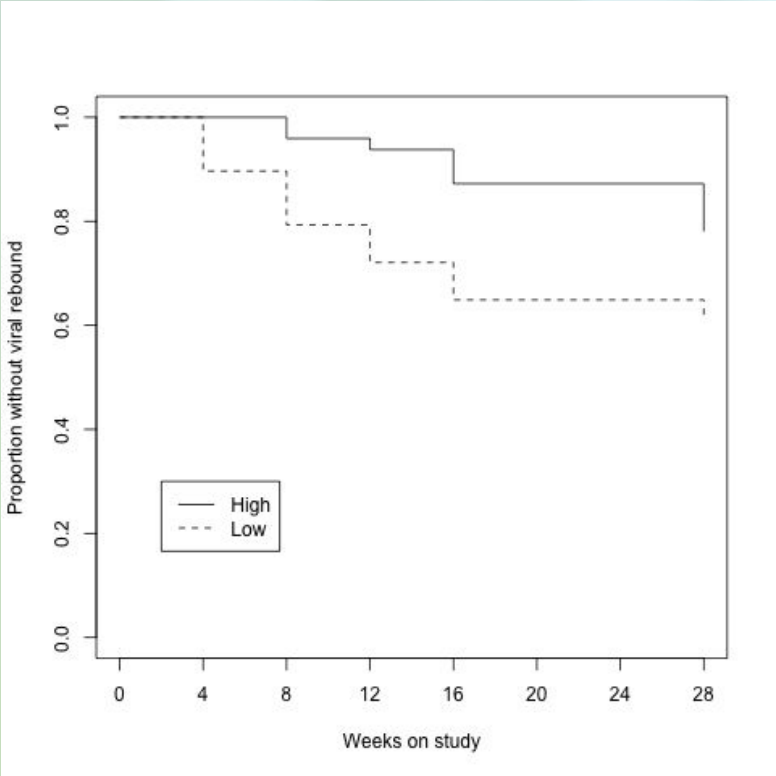
IPAM score - Time to first viral rebound

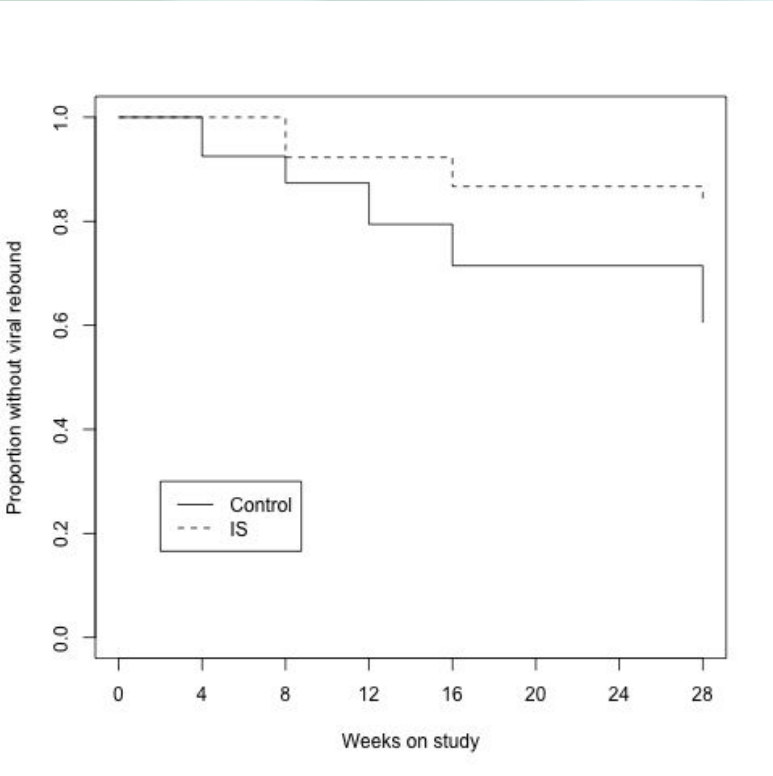


IPAM	Rebound	Total	Rate
High (> 0.8)	10	52	0.19
Low (≤ 0.8)	11	29	0.38

- Viral rebound >50 copies/ml
- Proportion without viral rebound
- A two-sample log rank test statistic between the two groups yielded a P value of 0.048.

Unpublished results

Intervention - Time to first viral rebound

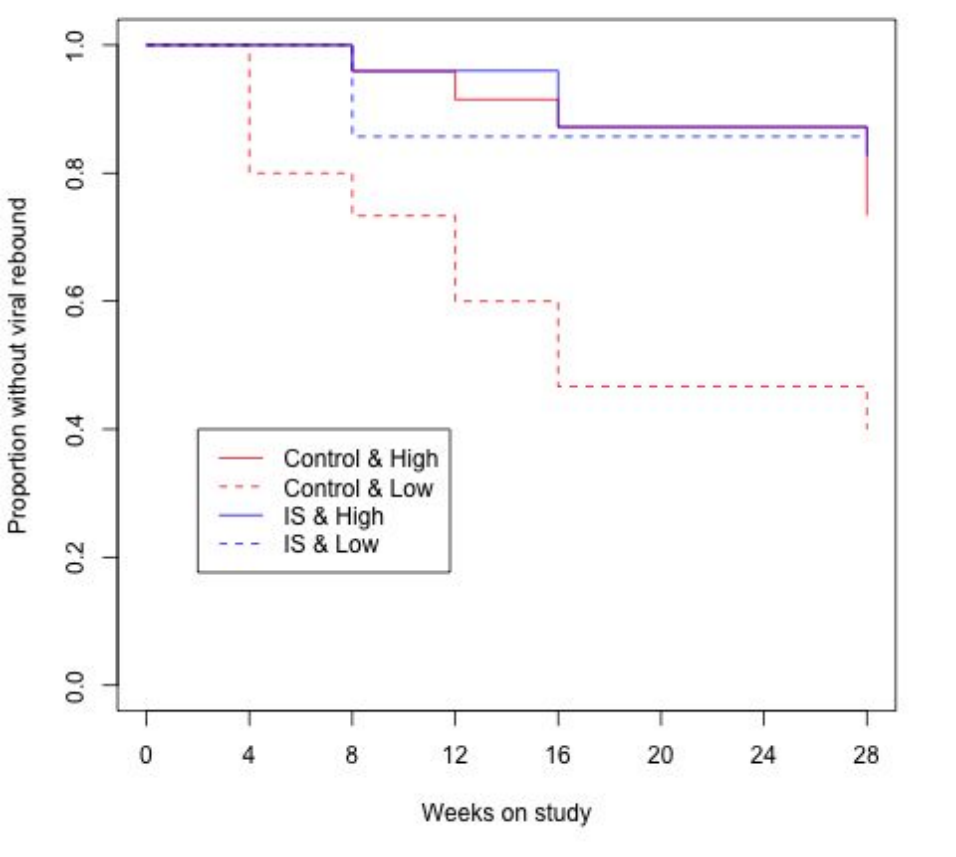


Group	Rebound	Total	Rate
Control	15	40	0.38
IS	6	41	0.15

- Proportion without viral rebound
- A two-sample log rank test statistic between IS vs Control yielded a p-value of 0.029.

Unpublished results

Intervention & IPAM score - Time to first viral rebound



Group	Rebound	Total	Rate
IS & High	4	27	0.15
IS & Low	2	14	0.14
Control & High	6	25	0.24
Control & Low	9	15	0.6

- Log rank test statistic between four groups yielded a p-value of 0.004.

Unpublished results

Cox regression model - time to first VL rebound

- High-IPAM score group – longer time to the first viral rebound (p<0.01),
- The adjusted risk ratio, high vs low, is 0.25 with 95% CI (0.09, 0.72).

Model	Intervention phase (16 weeks)	Study period (28 weeks)
Simple model	**Risk ratio (95% CI)**	
Intervention (IS vs Control)	0.41 (0.14, 1.18)	0.36 (0.14, 0.92)*
IPAM (High vs Low)	0.29 (0.11, 0.80)*	0.42 (0.18, 0.99)*
Adjust covariates		
Intervention (IS vs Control)	0.33 (0.11, 0.99)*	0.29 (0.11, 0.79)*
IPAM (High vs Low)	**0.25 (0.09, 0.72)****	0.40 (0.17, 0.97)*
age	0.99 (0.95, 1.04)	0.98 (0.94, 1.02)
baseline log10 RNA (per unit change)	1.85 (1.19, 2.87)**	1.61 (1.07, 2.43)*
baseline log2 CD4% (per unit change)	1.03 (0.84, 1.25)	0.96 (0.82, 1.13)

*** <0.05, ** <0.01, ***<0.001**

Unpublished results

Discussions

- **Intrapatient variability** of drug concentration over time can be used as a predictor for adherence and virological outcomes
- **IPAM score** is a pharmacologically based measure of intrapatient variability of drug concentration
- High **IPAM score** is associated with improved virologic (low VL rebound rate and long the time to rebound) and immunologic outcomes (high CD4)

Future work

- Predict **longitudinal** plasma concentration to better understanding the dynamics of drug response
- Design **dose-adjust strategies** to achieve target drug exposures and to reduce intrapatient variability, e.g. concentration-controlled ART
- Develop a **proactive and integrative approach** to improve adherence and drug response

Collaborators

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