Dynamic Association between Intra-patient Variability in ARV Plasma Concentration and HIV RNA Viral Suppression - Findings from a longitudinal HIV study with Ingestible Sensor Monitoring

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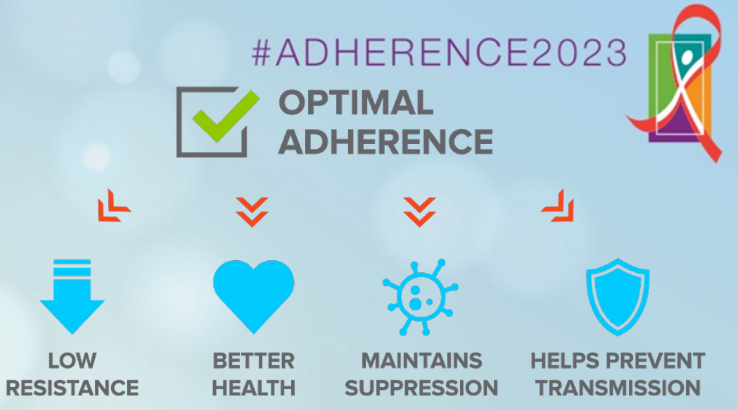
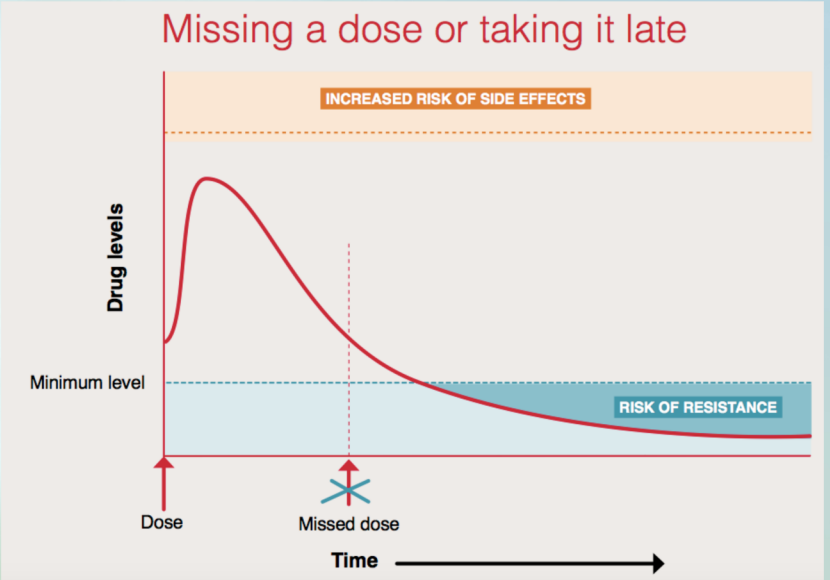
Adherence to ART

Measure adherence

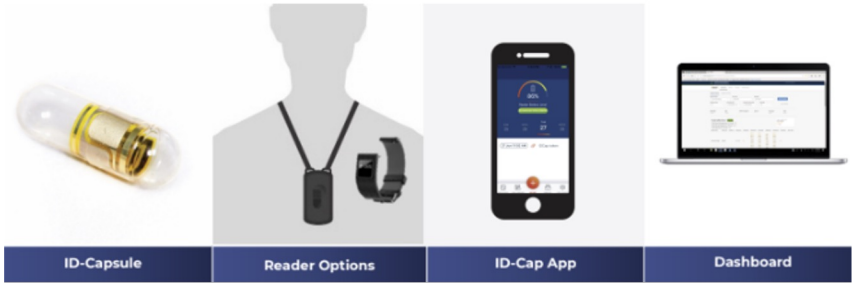
- Self-report questionnaires
- Directly observed therapy
- **Electronic devices**
- Pick-up/refill rates
- New sampling methods (e.g. dried blood spot)
- Sampling matrices (e.g. hair, saliva and urine)





Adherence to medication

Medication Event Monitoring Systems (MEMS)



etectRx™

Overview of the proteus digital health feedback

The sensor contains tiny amounts of silicon, copper and magnesium that pass through the body naturally, just like the fiber in food.

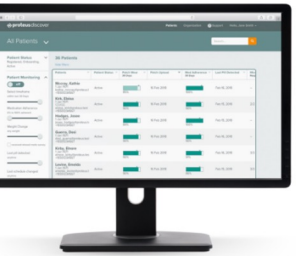
Antiretroviral medication

A pharmacist puts the Proteus sensor inside a capsule, along a prescribed medication.

Data pod

Adhesive strip

Records DigiMeds™ and the time they were taken



Behind the scenes – patient management

DigiMeds™

The sensor sends a signal to the patch as it passes through the stomach.

Wearable patch

The patch sends this information to the app along with records of activity and rest.

Discover app

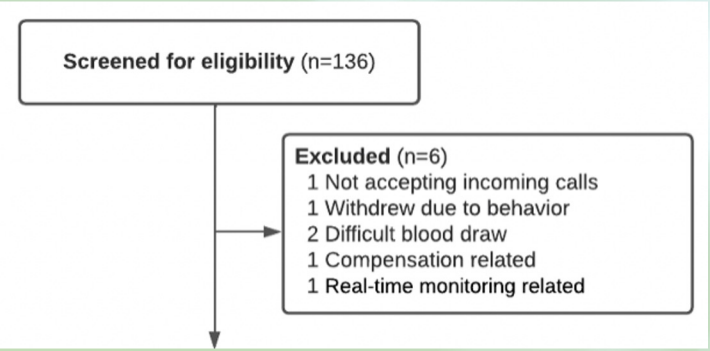
The mobile device acts as a conduit between data pod and server.

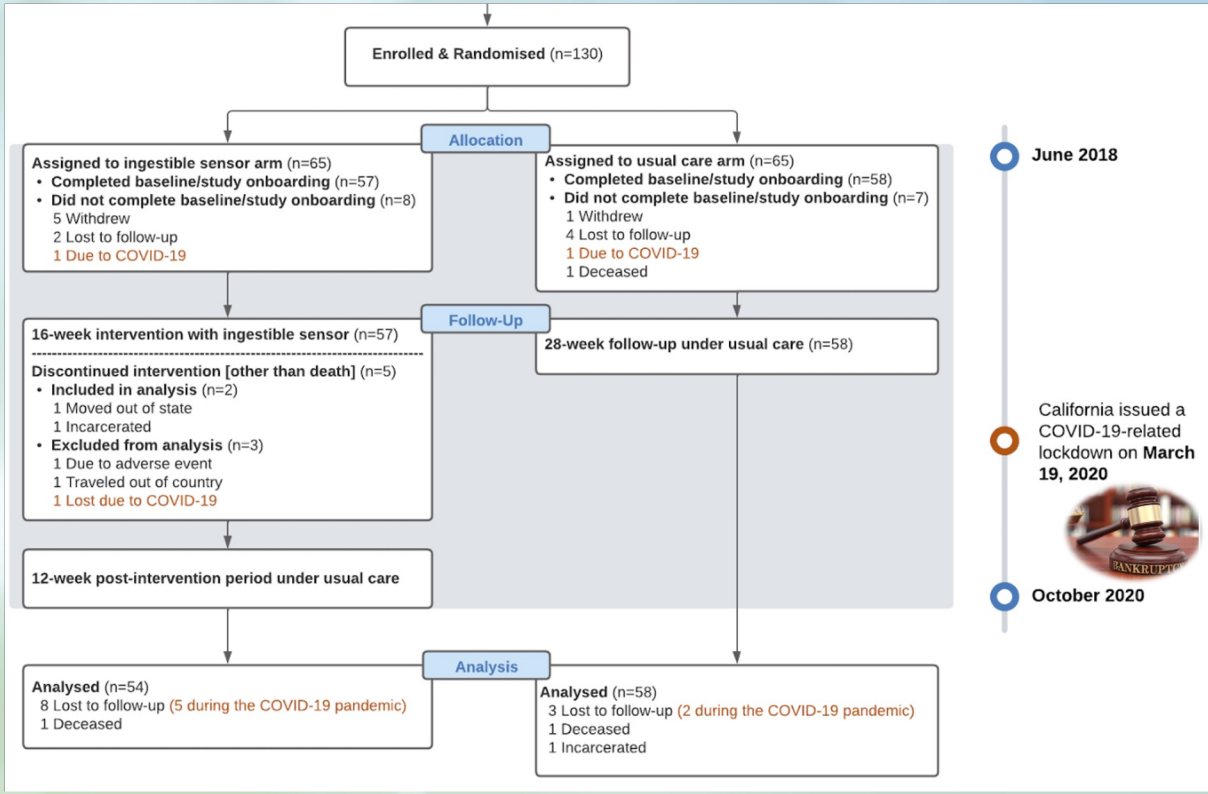
Otsuka proteus DIGITAL HEALTH

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 6 months.



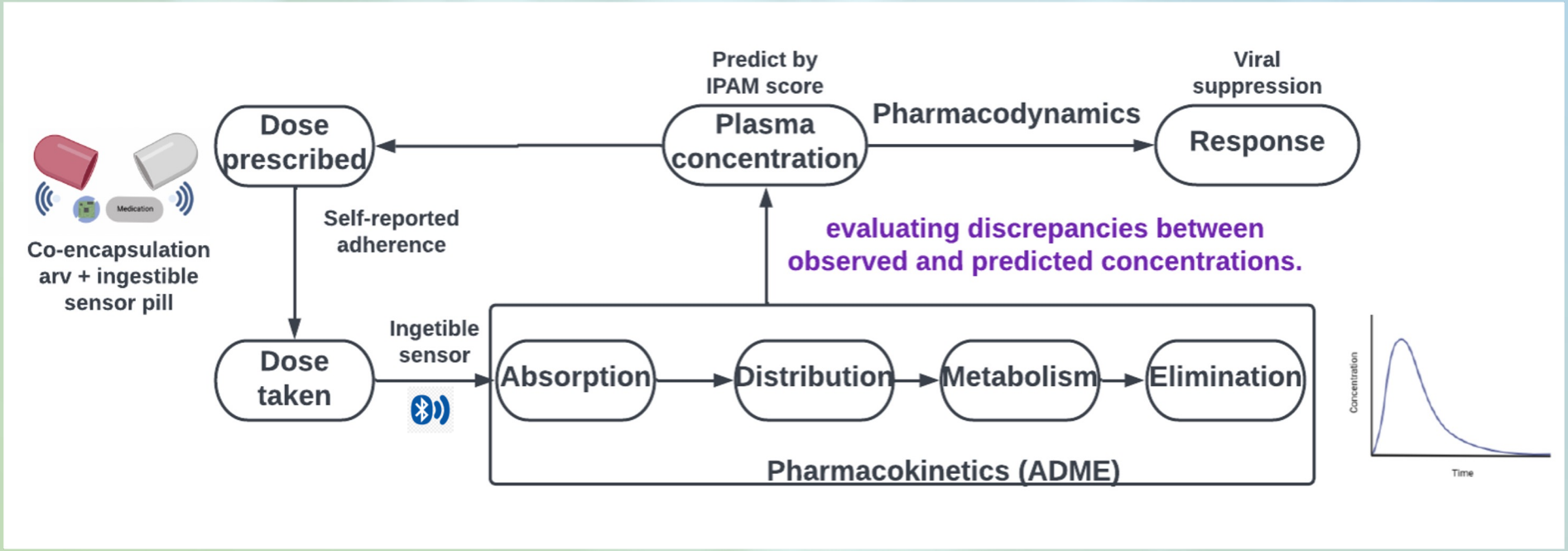


Pharmacokinetics (PK) and Adherence

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.

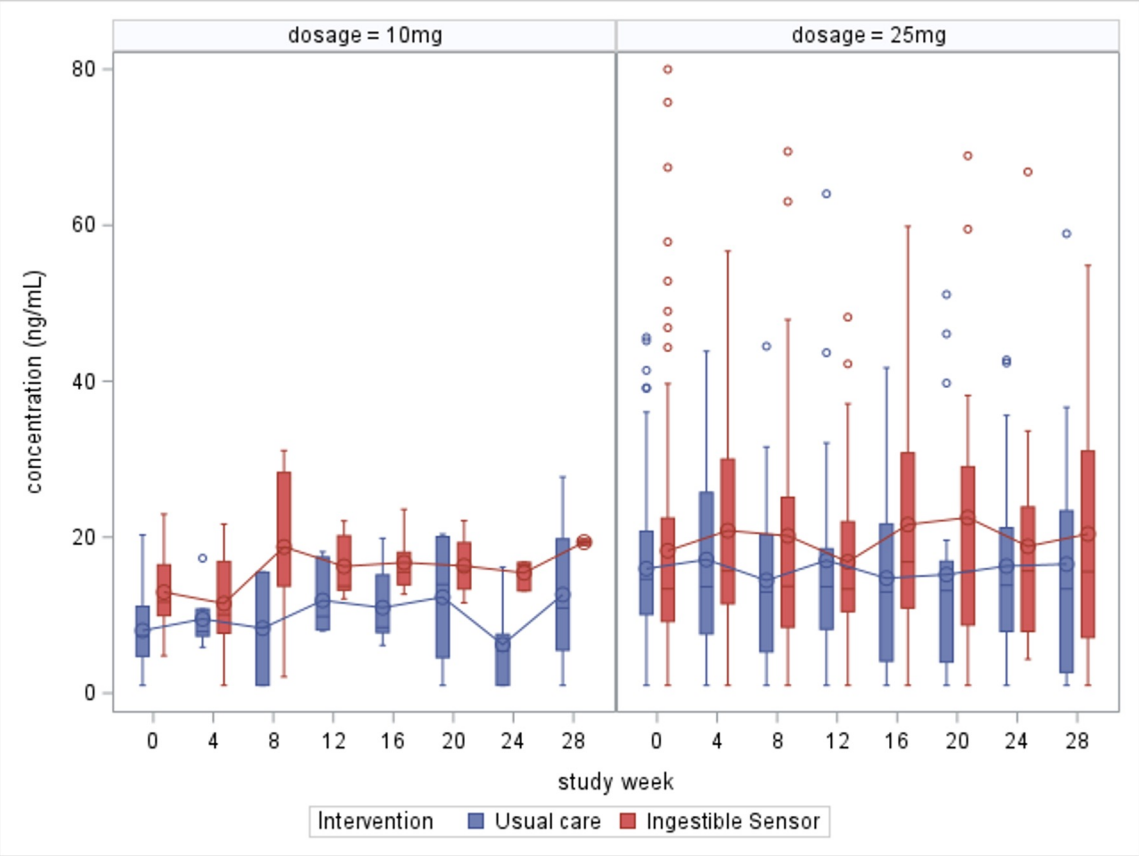
Overview of adherence and PK/PD



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**.

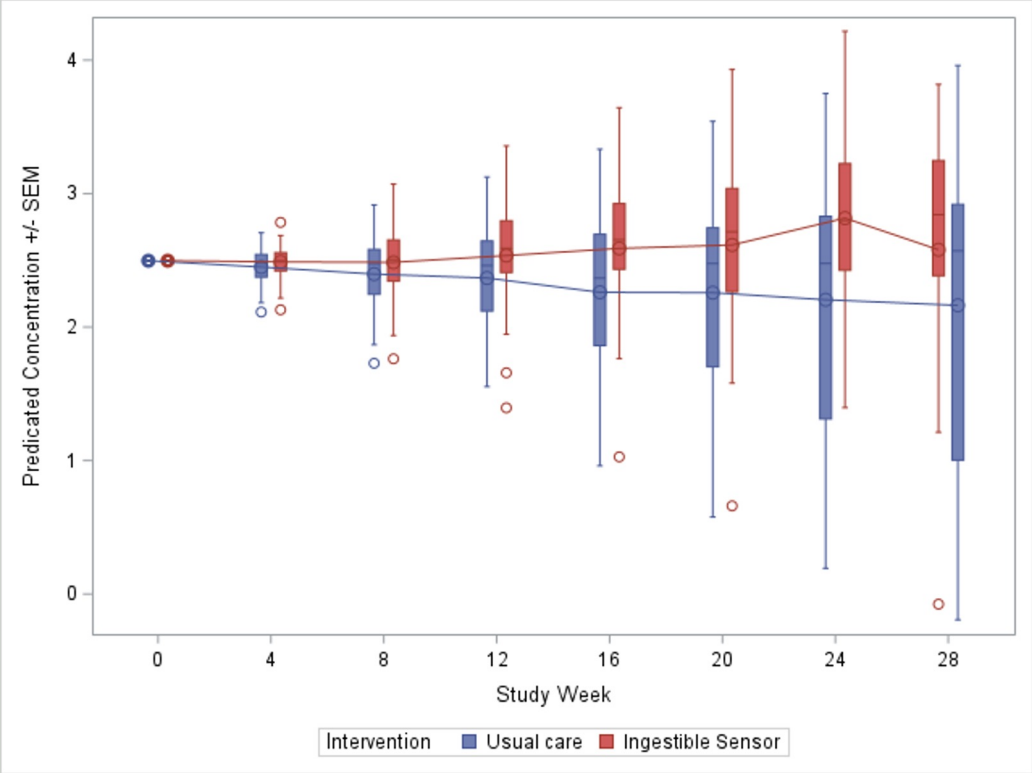
The plasma concentration by dosage



One compartment linear PK model

- **Final Model:** One-compartment PK linear model with a proportional error and random effects of person and time
- 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**)
- **Software:** Phoenix WinNolim 8.3 for PK/PD analysis

Predicted concentration over time



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

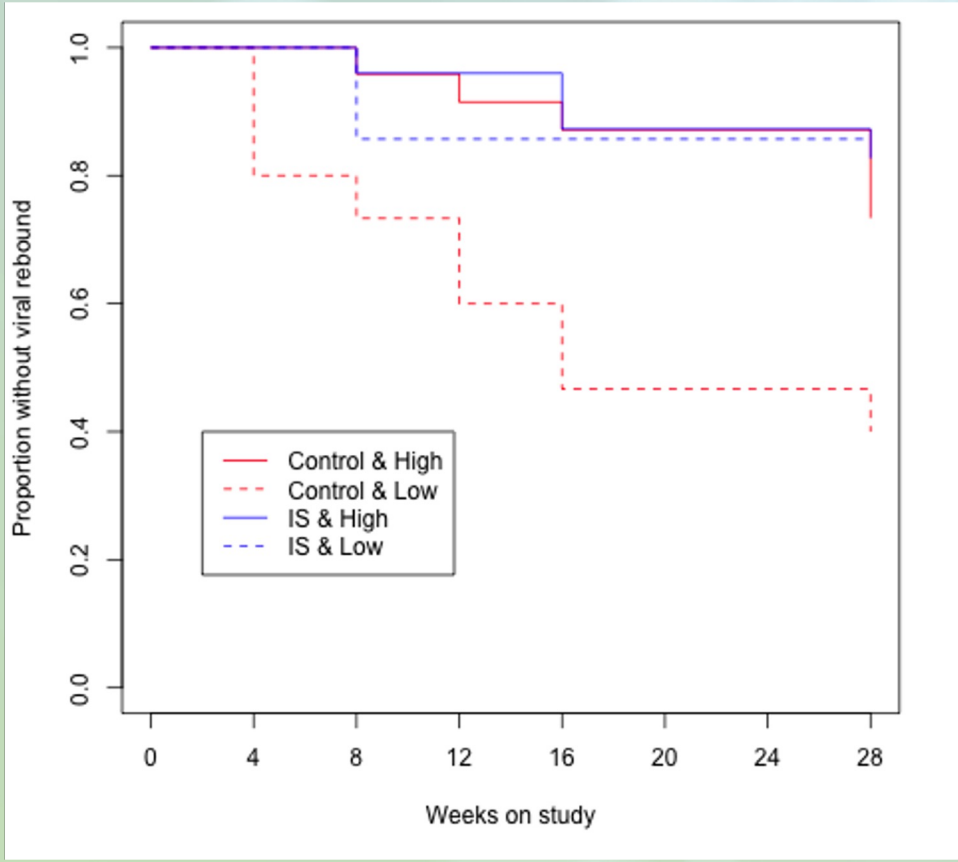
IPAM score

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.

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

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

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