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.

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

- **Absorption** – how the drug get into the body
- **Distribution** – where the drug goes into the body
- **Metabolism** – how the body chemically modify the drug
- **Elimination** – 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

The ins and outs of ingestibles

1. Patient ingests pill with sensor made of copper, magnesium and silicon.
2. Pill lands in stomach.
3. Pill disintegrates, leaving sensor in stomach.
4. Fluids in the stomach activate the sensor, which sends a signal to a patch on the patient’s body.
5. Sensor goes through the digestive system.
6. Patch registers sensor and sends signal to a mobile device that the pill has been taken.

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

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

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.

Records DigiMeds™ and the time they were taken

Behind the scenes – patient management
**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

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of subjects</th>
<th>IPAM statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>All</td>
<td>81</td>
<td>0.82 ± 0.26</td>
</tr>
<tr>
<td>High (&gt; 0.8)</td>
<td>52</td>
<td>0.97 ± 0.06</td>
</tr>
<tr>
<td>Low (≤ 0.8)</td>
<td>29</td>
<td>0.55 ± 0.24</td>
</tr>
</tbody>
</table>

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

IPAM score - Time to first viral rebound

- 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.

<table>
<thead>
<tr>
<th>IPAM</th>
<th>Rebound</th>
<th>Total</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (&gt; 0.8)</td>
<td>10</td>
<td>52</td>
<td>0.19</td>
</tr>
<tr>
<td>Low (≤ 0.8)</td>
<td>11</td>
<td>29</td>
<td>0.38</td>
</tr>
</tbody>
</table>
Intervention - Time to first viral rebound

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Rebound</th>
<th>Total</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>15</td>
<td>40</td>
<td>0.38</td>
</tr>
<tr>
<td>IS</td>
<td>6</td>
<td>41</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Unpublished results
### Intervention & IPAM score - Time to first viral rebound

<table>
<thead>
<tr>
<th>Group</th>
<th>Rebound</th>
<th>Total</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>IS &amp; High</td>
<td>4</td>
<td>27</td>
<td>0.15</td>
</tr>
<tr>
<td>IS &amp; Low</td>
<td>2</td>
<td>14</td>
<td>0.14</td>
</tr>
<tr>
<td>Control &amp; High</td>
<td>6</td>
<td>25</td>
<td>0.24</td>
</tr>
<tr>
<td>Control &amp; Low</td>
<td>9</td>
<td>15</td>
<td>0.6</td>
</tr>
</tbody>
</table>

- 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).

<table>
<thead>
<tr>
<th>Model</th>
<th>Intervention phase (16 weeks)</th>
<th>Study period (28 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention (IS vs Control)</td>
<td>0.41 (0.14, 1.18)</td>
<td>0.36 (0.14, 0.92)*</td>
</tr>
<tr>
<td>IPAM (High vs Low)</td>
<td>0.29 (0.11, 0.80)*</td>
<td>0.42 (0.18, 0.99)*</td>
</tr>
<tr>
<td>Adjust covariates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention (IS vs Control)</td>
<td>0.33 (0.11, 0.99)*</td>
<td>0.29 (0.11, 0.79)*</td>
</tr>
<tr>
<td>IPAM (High vs Low)</td>
<td>0.25 (0.09, 0.72)**</td>
<td>0.40 (0.17, 0.97)*</td>
</tr>
</tbody>
</table>

- 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
Acknowledgement

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