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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UCLA

Adherence 2023 • June 11-13 • Puerto Rico
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)
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.

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
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.

Study design

Excluded (n=6)
1. Not accepting incoming calls
2. Withdrawn due to behavior
3. Difficult blood draw
4. Compensation related
5. Real-time monitoring related

Screened for eligibility (n=136)

Analysed (n=54)
8. Lost to follow-up (5 during the COVID-19 pandemic)
1. Deceased

Analysed (n=58)
3. Lost to follow-up (2 during the COVID-19 pandemic)
1. Deceased
1. Incarcerated

Allocated

Enrolled & Randomised (n=130)

Assignment to ingestible sensor arm (n=65)
- Completed baseline/study onboarding (n=57)
  - 5 withdrew
    - 2 lost to follow-up
      - 1 due to COVID-19

Assignment to usual care arm (n=65)
- Completed baseline/study onboarding (n=58)
  - 4 lost to follow-up
    - 1 due to COVID-19
    - 1 deceased

Follow-Up

16-week intervention with ingestible sensor (n=57)
- Excluded from analysis (n=3)
  - 1 due to adverse event
  - 1 traveled out of country
  - 1 lost due to COVID-19

28-week follow-up under usual care (n=58)

Discontinued intervention [other than death] (n=5)
- Included in analysis (n=2)
  - 1 moved out of state
  - 1 incarcerated

June 2018
California issued a COVID-19-related lockdown on March 19, 2020
October 2020
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

Co-encapsulation arv + ingestible sensor pill

Dose prescribed → Self-reported adherence → Dose taken

Predict by IPAM score → Plasma concentration → Pharmacodynamics → Response

Viral suppression

evaluating discrepancies between observed and predicted concentrations.

Pharmacokinetics (ADME):
Absorption → Distribution → Metabolism → Elimination

#ADHERENCE2023
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

<table>
<thead>
<tr>
<th>Study Week</th>
<th>Dosage = 10mg</th>
<th>Dosage = 25mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
<td>Usual Care</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Concentration (ng/mL)
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

<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.

**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.
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><strong>0.25 (0.09, 0.72)</strong>**</td>
<td><strong>0.40 (0.17, 0.97)</strong>*</td>
</tr>
<tr>
<td>age</td>
<td>0.99 (0.95, 1.04)</td>
<td>0.98 (0.94, 1.02)</td>
</tr>
<tr>
<td>baseline log10 RNA (per unit change)</td>
<td>1.85 (1.19, 2.87)****</td>
<td>1.61 (1.07, 2.43)*</td>
</tr>
<tr>
<td>baseline log2 CD4% (per unit change)</td>
<td>1.03 (0.84, 1.25)</td>
<td>0.96 (0.82, 1.13)</td>
</tr>
</tbody>
</table>

* <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 understand 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

UCLA

- Honghu Liu, PhD (PI)
- Jason Shen, PhD
- Di Xiong, MS
- Yilan Huang, MS
- Linyu Zhou, MS

THE LUNDQUIST INSTITUTE

- Eric Daar, MD (mPI)
- Katya Corado, MD
- Lisa Siqueiros
- Mario Guerrero, MD
- Investigational Drug Services

Nebraska Medical Center

- Courtney Fletcher, Pharm.D.
- Veenu Bala, PhD
- Kayla Campbell, DNP

Yale

- Mark Rosen, MD

Research reported in this talk is supported by R01MH110056 and T32MH080634