Dose Individualization in HIV Therapy

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<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Efficacy Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s</td>
<td>30</td>
</tr>
<tr>
<td>Analgesics (Cox-2)</td>
<td>80</td>
</tr>
<tr>
<td>Asthma</td>
<td>60</td>
</tr>
<tr>
<td>Cardiac Arrhythmias</td>
<td>60</td>
</tr>
<tr>
<td>Depression (SSRI)</td>
<td>62</td>
</tr>
<tr>
<td>Diabetes</td>
<td>57</td>
</tr>
<tr>
<td>Incontinence</td>
<td>40</td>
</tr>
<tr>
<td>Migraine (acute)</td>
<td>52</td>
</tr>
<tr>
<td>Oncology</td>
<td>25</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>48</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>48</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>50</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>60</td>
</tr>
</tbody>
</table>

The Sources of Variability in Response

Concentration-Controlled Combination Antiretroviral Therapy (GCRC # 540)

RANDOMIZE

**Standard Therapy**
- ZDV, 600 mg/day
- 3TC, 300 mg/day
- IDV, 2400 mg/day

**Controlled Therapy**
- ZDV, $C_{ss} \geq 0.17$ mg/L
- 3TC, $C_{ss} \geq 0.40$ mg/L
- IDV, $C_{min} \geq 0.13$ mg/L

6 months of therapy; participants with plasma HIV RNA < 200 copies/mL can continue therapy for 6 more months
ZDV, 3TC, and IDV Concentrations

![Graphs showing Zidovudine, Lamivudine, and Indinavir concentrations in conventional and concentration-controlled conditions.]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Standard</th>
<th>Concentration Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>9/17 (53%)</td>
<td>16/16 (100%) *</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>11/17 (65%)</td>
<td>16/16 (100%) *</td>
</tr>
<tr>
<td>Indinavir</td>
<td>3/17 (18%)</td>
<td>14/16 (88%) *</td>
</tr>
</tbody>
</table>

Percent with Undetectable HIV RNA

Pharmacokinetic Variability
What Do We Need to Know

- How much is expected?
  - Interpatient
  - Intrapatient

- How much is too much?
  - Exposure-response relationships

- Can we control for, or accommodate the effects of pharmacokinetic variability?
  - Adherence
  - Pharmacokinetic strategies
  - Pharmacodynamic strategies
Dose Optimization and Individualization

- Questions
  - Is there a role for dose individualization?
  - Is there a role for age-specific dosing?
  - Is there a role for pharmacogenomics?
  - Is there a role for compartment/tissue targeted dosing?
Predictive Value of EFV Concentrations for Viral Suppression and CNS Adverse Effects

Efavirenz Population Pharmacokinetics

![Graph showing efavirenz concentrations over time](image)
Pharmacokinetics, Dynamics, and Adherence

Brundage RC...Fletcher CV. Antimicrob Agents Chemo 2004;48:979-84
Subjects Sorted by Ascending Integrated PK and Adherence Measure (IPAM)

Brundage RC…Fletcher CV. Antimicrob Agents Chemo 2004;48:979-84
Time to Failure (HIV-RNA > 400) vs. Adherence Score

Brundage RC…Fletcher CV. Antimicrob Agents Chemo 2004;48:979-84

<table>
<thead>
<tr>
<th>n</th>
<th>fail</th>
<th>fail rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>7</td>
<td>23%</td>
</tr>
<tr>
<td>19</td>
<td>10</td>
<td>53%</td>
</tr>
</tbody>
</table>

p<0.003
PK/PD of Dolutegravir

Maximum Effect ($E_{\text{max}}$) Model of Dolutegravir
Exposure vs. Response

Dose Optimization and Individualization

- Questions
  - Is there a role for dose individualization?
  - Is there a role for age-specific dosing?
  - Is there a role for pharmacogenomics?
  - Is there a role for compartment/tissue targeted dosing?
Tenofovir disoproxil fumarate (TDF)
- Safe and effective; widely used for treatment of HIV-infection,
- Limited plasma and intracellular PK data in children.

TFV plasma and intracellular TFV-DP PK were quantified in 47 HIV-infected children and adolescents (8.6-25 yrs).
These data were pooled with those of 55 HIV-infected adults (25-60 yrs).
Non-linear mixed effects modeling was used to describe the PK and explore the influence of covariates (e.g. age, renal function).
An indirect, stimulation of response model was used to describe the formation of TFV-DP.

TFV Concentrations and Oral Clearance by Age Group

Mean Plasma TFV and Intracellular TFV-DP Concentrations by Age Group

### Differences in Children-Adolescent and Adult Plasma and IC TFV Kinetics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>&gt; 25 years</th>
<th>&lt; 25 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>N and Age (median)</td>
<td>N=102 subjects; 21 years (range, 9 to 60 years)</td>
<td></td>
</tr>
<tr>
<td>PLASMA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma CL/F (L/h)</td>
<td>42.3</td>
<td>57.6</td>
</tr>
<tr>
<td>INTRACELLULAR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$K_{in}$ (h$^{-1}$)</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>$EC_{50}$ (ng/mL)</td>
<td>116</td>
<td>69</td>
</tr>
<tr>
<td>$K_{out}$ (h$^{-1}$)</td>
<td>0.0081</td>
<td>0.0099</td>
</tr>
<tr>
<td>Intracellular $T^{1/2}$ (h)</td>
<td>86</td>
<td>70</td>
</tr>
<tr>
<td>$E_{max}$ (fmol/10^6)</td>
<td>1200</td>
<td></td>
</tr>
</tbody>
</table>

- Children and adolescents achieved higher TFV-DP concentrations despite lower plasma exposure.
- An increased sensitivity to phosphorylation is suggested as a mechanism based on a lower $EC_{50}$. 
Questions

- Is there a role for dose individualization?
- Is there a role for age-specific dosing?
- Is there a role for pharmacogenomics?
- Is there a role for compartment/tissue targeted dosing?
Isoniazid (INH)

- Used for the treatment and prevention of TB for over 50 years.
- In adults, INH chemoprophylaxis has been associated with a marked reduction in the risk of TB disease.¹
- INH is the only agent recommended for TB prophylaxis in children.²,³
  - The WHO recommended dose for children is 5 mg/kg/day.
  - 10 mg/kg/day was effective at preventing TB in a recently published study in 263 HIV-infected older children.⁴
- There are no data on the PK of INH in infants, the appropriate dose of INH in infants, or INH PK from administration of a crushed tablet.

INH PK and PG Objectives

- Characterize INH PK in infants randomized at 91-120 days of life to INH 10–20 mg/kg/d orally QD or placebo (enrolled in P1041) using population PK techniques.
- Determine N-acetyltransferase-2 (NAT2) genotype and evaluate if acetylator genetics explains INH PK, and if there is a concordance between NAT2 genotype and acetylator phenotype (INH CL/F) in infants.
- Evaluate the effects of other covariates, such as HIV infection, sex and body weight on INH PK.
- Develop a enzyme maturation PK model that can separate the effects of
  - (1) body size,
  - (2) enzyme maturation and genotype, and
  - (3) bioavailability on INH PK.
INH Concentration-Time Data

INH PK in Children

- INH CL/F was dependent NAT2 genotype, with a concordance observed between NAT2 genotype and acetylator phenotype (INH CL/F).
  - A different NAT2 enzyme maturation pattern was found for each of the three acetylation groups:
    - Fast: 14.25 L/h at 3 mo to 22.84 L/h at 24 mo;
    - Intermediate: 10.88 L/h at 3 mo to 15.58 L/h at 24 mo.
    - Slow: flat at 7.35 L/h at 3 mo to 24 mo.

- INH CL was also dependent upon age and body weight.
- INH relative bioavailability increased from 0.72 at 3 mo to 0.95 at 24 mo.
- The dose of 10-20 mg/kg (avg 14.5 ± 2.8) was safe and well tolerated, and PK was similar to data in older (median 3.8 y) children and adults.
Simulations of INH Cmax
(INH Dose of 14.5 mg/kg/d)

<table>
<thead>
<tr>
<th>Cmax (mg/L)</th>
<th>3month</th>
<th></th>
<th></th>
<th>24 month</th>
<th></th>
<th></th>
<th>48 month</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SS</td>
<td>FS</td>
<td>FF</td>
<td>SS</td>
<td>FS</td>
<td>FF</td>
<td>SS</td>
<td>FS</td>
</tr>
<tr>
<td>95th</td>
<td>15.19</td>
<td>13.56</td>
<td>12.46</td>
<td>21.31</td>
<td>17.01</td>
<td>14.85</td>
<td>22.22</td>
<td>17.01</td>
</tr>
<tr>
<td>75th</td>
<td>10.74</td>
<td>9.49</td>
<td>8.65</td>
<td>15.00</td>
<td>11.84</td>
<td>10.27</td>
<td>15.62</td>
<td>11.82</td>
</tr>
<tr>
<td>Median</td>
<td>8.84</td>
<td>7.82</td>
<td>7.11</td>
<td>12.36</td>
<td>9.75</td>
<td>8.42</td>
<td>12.87</td>
<td>9.72</td>
</tr>
<tr>
<td>25th</td>
<td>7.01</td>
<td>6.18</td>
<td>5.62</td>
<td>9.81</td>
<td>7.70</td>
<td>6.64</td>
<td>10.22</td>
<td>7.68</td>
</tr>
<tr>
<td>5th</td>
<td>7.01</td>
<td>6.18</td>
<td>5.62</td>
<td>9.81</td>
<td>7.70</td>
<td>6.64</td>
<td>10.22</td>
<td>7.68</td>
</tr>
<tr>
<td>Cmax &lt; 3 mg/L</td>
<td>0</td>
<td>0.2%</td>
<td>0.8%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Dose Optimization and Individualization

- Questions
  - Is there a role for dose individualization?
  - Is there a role for age-specific dosing?
  - Is there a role for pharmacogenomics?
  - Is there a role for compartment/tissue targeted dosing?
Distribution of the PI, DPC681 + RTV

- QWBA demonstrated lowest distribution in the brain and highest in the liver.
- Differential distribution in brain with CNS < CSF.

TFV Tissue Kinetics in Rats by PET

- TFV tissue kinetics evaluated with a fluorine-18 radiolabeled analog
- Lowest distribution: brain, mesenteric LN and testes
- Similar or equivalent distribution: colon and jejunum

Viral Sanctuaries during HAART in a Non-Human Primate Model for AIDS

- Rhesus macaques treated with TDF, FTC, EFV.
- Plasma viral load at necropsy ranged from 11-28 copies/mL.
- vDNA and vRNA were detected during HAART from numerous anatomical compartments.
- The highest levels of vDNA and vRNA were in lymphoid tissues: spleen, lymph nodes and GI tract tissues.

Drug Absorption via Intestinal Lymphatic System

- Physicochemical Properties Associated with Lymphatic System Absorption
  - Molecular weight
  - Particle size
  - Log P (octanol:water partition)
  - Long chain TG solubility

Preclinical PK of Nanoformulated ATV/RTV

**Lymph Node Targeting with a Three Drug anti-HIV Lipid Nanoparticle (LNP)**

<table>
<thead>
<tr>
<th></th>
<th>Lopinavir LNP/free ratio</th>
<th>Ritonavir LNP/free ratio</th>
<th>Tenofovir LNP/free ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma AUC</td>
<td>18.2</td>
<td>14.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Intracellular peripheral MNCs</td>
<td>20.4</td>
<td>&gt;400</td>
<td>70.0</td>
</tr>
<tr>
<td>Intracellular LN MNCs</td>
<td>&gt;485</td>
<td>50.5</td>
<td>0.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tissue or Fluid</th>
<th>TDF conc</th>
<th>TAF conc</th>
<th>TAF:TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>88</td>
<td>80</td>
<td>0.9</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.50</td>
<td>4.34</td>
<td>8.2</td>
</tr>
<tr>
<td>Inguinal lymph nodes</td>
<td>0.28</td>
<td>4.12</td>
<td>15</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.63</td>
<td>8.13</td>
<td>12.8</td>
</tr>
<tr>
<td>Brain</td>
<td>&lt; LOD</td>
<td>&lt; LOD</td>
<td>-</td>
</tr>
<tr>
<td>Ileum</td>
<td>0.50</td>
<td>4.61</td>
<td>9.2</td>
</tr>
<tr>
<td>Prostate</td>
<td>0.24</td>
<td>2.14</td>
<td>9.1</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>0.20</td>
<td>2.05</td>
<td>10.2</td>
</tr>
</tbody>
</table>

* Male beagle dogs.
Dose Optimization and Individualization in HIV Therapy

Questions and Answers

- Is there a role for dose individualization?
  » Yes, because variability in exposure contributes to variability in response.

- Is there a role for age-specific dosing?
  » Yes, because age-related changes in PK and PD may contribute to differences in responses.

- Is there a role for pharmacogenomics?
  » Yes, because genetic-related variability in PKPD contributes to variability in response.

- Is there a role for compartment/tissue targeted dosing?
  » Probably, to achieve effective concentrations in protected or reservoir sites.
In short, after all this discussion, the only principle of drug dosage which survives is that the dose must be adjusted to the individual patient.

Dawson WT. Ann Intern Med 1940;13:1594-1613