Clinical Trial Simulations of Effectiveness of Reduced-Dose Efavirenz Therapy: Impact of adherence, pharmacogenetics and rifampin co-administration

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Background

- Effectiveness of low dose efavirenz (400 mg) is currently being evaluated in clinical trials as a viable strategy for cost-effective HIV treatment in resource limited settings.
- Extensive knowledge on EFV pharmacokinetics, efficacy and DDI is already available
- Virological outcome from efavirenz + rifampin is unclear
- Virological outcome from low dose efavirenz + rifampin is not known
Prediction of HIV Clinical Outcome is Multi-dimensional and Complex

- Population model capturing inter- & intra-subject variability
- Enzyme induction
- DDI
- PK
- Treatment Rules
- PD, Viral Dynamics
- Adherence (Compliance)
- Dose

- Efficacy, Resistance
- Prescribed vs actual doses
- Drug holidays, Dose timing errors

Patient Demographics

Patient’s genotype
Aims & Methods

• To evaluate effectiveness of low dose efavirenz therapy
• To assess the effect of real world adherence, pharmacogenetics and rifampin co-administration
• **Methods**: extensive clinical trial simulations
  – incorporating an exhaustive efavirenz knowledge-base including:
    • true adherence patterns
    • pharmacokinetics
    • pharmacodynamics
    • pharmacogenetics
    • risk of resistance development
    • expected drug-drug interaction with the commonly co-administered TB drug rifampin.
Simulation framework

Adherence
Patient demographics
PK model
PKPD relationship
Clinical trial outcome
Clinical Trial Simulation (CTS) : Adherence

Adherence data:

- Models for adherence
  - Binomial distribution (yes/no)
  - Markov models

- Real world (MEMS) data
  - AARDEX group contributed random sample of MEMS data from >200 patients on ARV
MEMS data
Effect of adherence on a PK profile

PK projection assuming Steady State (IDEAL) or TRUE dosing histories

Occasional toxicity

Periodic loss of effectiveness; emergence of drug resistant HIV

MEMS data impact

Example of an adherent patient

Simple pharmacokinetics
Literature is informative and consistent on EFV pharmacokinetics

Things to consider:
• Auto-induction: initial 2-3 weeks of continuous therapy
• Effect of genotype
• Effect of rifampin
# PK meta analysis, literature reports

**Table A1.** General PK model parameters CL, V, and Ka based on selected research reports

<table>
<thead>
<tr>
<th>Clearance, CL (L/h)</th>
<th>Volume of distribution, V (L)</th>
<th>Absorption rate constant, Ka (h⁻¹)</th>
<th>Study size and patient population demographics</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>Mean CV (%)</td>
<td>Mean CV (%)</td>
<td>Mean CV (%)</td>
<td></td>
</tr>
<tr>
<td>9.6</td>
<td>44</td>
<td>291</td>
<td>101</td>
<td>(n=128) HIV-positive, 97% Caucasian</td>
</tr>
<tr>
<td>10.8</td>
<td>42</td>
<td>282</td>
<td>~10</td>
<td>(n=139) HIV-positive, multiple genetics</td>
</tr>
<tr>
<td>8.8</td>
<td>~20</td>
<td>418</td>
<td>~20</td>
<td>(n=1216) HIV-positive, multiple countries</td>
</tr>
<tr>
<td>9.2</td>
<td>~15</td>
<td>317</td>
<td>~10</td>
<td>(n=21) healthy adult subjects</td>
</tr>
<tr>
<td>11</td>
<td>~15</td>
<td>350</td>
<td>~30</td>
<td>Summary estimate from meta analysis based on six efavirenz PK studies*</td>
</tr>
<tr>
<td>10</td>
<td>30</td>
<td>300</td>
<td>0.65</td>
<td>Parameter estimate values used for simulations in this report</td>
</tr>
</tbody>
</table>

Note: exact values used where available in original reports. Other data estimated from graphs made available.

* Including: Pfister *et al.* 2003, Arab-Alameddine 2009 (n=393), Csajka 2003 (n=719), Kappelhoff 2005a (n=1009), Kappelhoff 2005b (n=1728)
## Effect of genotype, literature reports

<table>
<thead>
<tr>
<th>Estimated REDUCTION in clearance rate for CYP2B6 homozygote vs. wild type</th>
<th>Description of study findings</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>30%</td>
<td>Clearance for EFV estimated to be 30% less for CYP2B6 patients</td>
<td>Denti et al. (2012)</td>
</tr>
<tr>
<td>22%</td>
<td>Hepatic clearance of EFV estimated 28% higher in white non-Hispanics than in African Americans and Hispanics (P = 0.03)</td>
<td>Pfister et al. (2003)</td>
</tr>
<tr>
<td>25 to 50% (medium alt. slow metabolizers)</td>
<td>Intermediate and slow metabolizers found to have clearance of 7.2 L/h and 4.0 L/h vs. baseline 9.4 L/h</td>
<td>Nyakutira et al. (2008)</td>
</tr>
<tr>
<td>more than 20%</td>
<td>CYP2B6 516G-&gt;T polymorphism reduced the clearance by &gt; 20%. Other polymorphisms in this gene estimated to have lower influence.</td>
<td>Sanchez et al. (2011)</td>
</tr>
<tr>
<td>25-30%</td>
<td>Parameter estimate value used for simulations in this report</td>
<td></td>
</tr>
</tbody>
</table>

## Effect of rifampin, literature reports

<table>
<thead>
<tr>
<th>Estimated INCREASE in clearance rate when used concurrently with rifampin</th>
<th>Description of study findings</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-26%</td>
<td>Among healthy volunteers rifampin caused 26% vs. 20% reduction in mean efavirenz AUC, and peak concentration respectively.</td>
<td>Benedek et al. (1998)</td>
</tr>
<tr>
<td>22%</td>
<td>The combination of efavirenz and rifampin has been shown to reduce the area under the concentration-time curve (AUC) of efavirenz by 22%.</td>
<td>Lopez-Cortez et al. (2002) Rekić et al. (2011)</td>
</tr>
<tr>
<td>18%</td>
<td>The geometric mean AUC ratio of on/off rifampin was 0.82 (0.72 0.92). However, large individual and confounding variations were recorded</td>
<td>Kwara et al. (2011)</td>
</tr>
<tr>
<td>20-25%</td>
<td>Parameter estimate value used for simulations in this report</td>
<td></td>
</tr>
</tbody>
</table>
Efavirenz-Rifampin interaction

**RIFAMPIN facts:**
- Rifampin is common inducer of most CYP-mediated drugs
  - Most of the studies report increased EFV CL with rifampin
- Rifampin autoinduces own disposition enzymes
- Higher doses of RIF are being tested (TBM)

**EFAVIRENZ facts:**
- Several dose levels are being considered
- EFV is auto-inducer of own disposition enzymes
- Complex pharmacogenetics
- Relation between auto-induction and dose is unknown

**Multiple DDIs:**
RIF-EFV, EFV-INH
Multi-dimensional problem

EFAVIRENZ

Dose

Pharmacogenetics

Time

DDI
Clinical Trial Simulation (CTS): Pharmacokinetics

Genotype
- Effect of CYP2B6 mutation on CL
- Weight
- TB co-infection
Clinical Trial Simulation (CTS) : PKPD relationship

Adherence | Patient demographics | PK model | PKPD relationship | Clinical trial outcome

\[
\frac{d}{dt} T = \lambda - d_T T - [1 - \gamma(t)]k T V
\]

\[
\frac{d}{dt} T^* = [1 - \gamma(t)]k T V \lambda - \delta T^*
\]

\[
\frac{d}{dt} V = N \delta T^* - c V
\]

<table>
<thead>
<tr>
<th>Metric</th>
<th>( \lambda )</th>
<th>( d_T )</th>
<th>( k )</th>
<th>( \delta )</th>
<th>( N )</th>
<th>( c )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (( \mu ))</td>
<td>8.8</td>
<td>5.6E-4</td>
<td>2.7E-7</td>
<td>1.3E-2</td>
<td>508</td>
<td>0.44</td>
</tr>
<tr>
<td>( CV_{\text{population}} )</td>
<td>45%</td>
<td>308%</td>
<td>52%</td>
<td>83%</td>
<td>100%</td>
<td>42%</td>
</tr>
<tr>
<td>( CV_{\text{patient}} )</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Wu et al. (2005) adapted from Perelson & Nelson (1999)
Clinical Trial Simulation (CTS): Resistance development

- Increasing IC$_{50}$ over time
- IC$_{50}$ at steady state is 100 x the initial IC$_{50}$ (baseline)

\[
IC_{50}(t) = \begin{cases} 
I_0 + \frac{I_r - I_0}{I_r} & \text{for } 0 < t < t_r \\
I_r & \text{for } t \geq t_r
\end{cases}
\]

Huang & Rosencranz (2003)
Clinical Trial Simulation (CTS): Clinical trial outcome

- Adherence
- Patient demographics
- PK model
- PKPD relationship
- Clinical trial outcome

• Definition of viral failure

Viral failure defined if patient has viral load of > 200 (or 100, 50) HIV RNA copies per mL after 24 wks

CTS endpoint: proportion of patients failing the therapy
Technical details & Simulation Tool

TECHNICAL DETAILS:

- Parameters from non-linear mixed effects (variability)
- Systems of large number of differential equations
- Matlab and C++ implementation

CLINICAL TRIAL SIMULATION TOOL

- Simulations help decision makers refresh decision-making skills, conduct experiments, and play.
- They provide low-cost laboratories for learning.
- Actions can be repeated under the same or different conditions. One can stop the action to reflect.
- Decisions that are dangerous, infeasible, or unethical in the real system can be explored, and the time delays in the learning loop through the real world are dramatically reduced.
Results: EFV 600 mg vs 400 mg

Summary

• Failures are expected even with 600 mg dose
• Real adherence profiles are doubling failure rates
• CYP2B6 poor metabolizers have best likelihood of favorable virological outcome
Results: EFV 600 mg vs 400 mg + RIF

Summary

- Failures are expected even with 600 mg dose
- Rifampin is increasing failure rates
- Results are more favorable for slow metabolizers
Pharmacokinetic results

Proportion of patients with trough < 1 mg/L

PM + Rifampin
EM + Rifampin
PM
EM

Dose (mg qd)
Summary

- A reduced-dose (400 mg) efavirenz treatment alternative requires very high adherence (>90%) levels to be effective. This is an unrealistic expectation in the real world.

- Patients on rifampin therapy are less well-suited to receive a reduced-dose regimen, regardless of adherence level.

- Patients with CYP2B6 polymorphic genotype maintain low viral load after receiving 400mg dose (cost-effective?)

- The outcome of the clinical trials is function of all of the above (adherence + rifampin + inherent variability, genotype + virological dynamics + resistance+...)

Thanks

**AARDEX**
- John Urquhart
- Bernard Vrijens
Results: 600 mg vs 400 mg
CYP2B6 wild type
Results: 600 mg vs 400 mg
CYP2B6 wild type + Rifampin
Results: 600 mg vs 400 mg
CYP2B6 homozygote + Rifampin

CYP2B6 mutant + rifampin

<table>
<thead>
<tr>
<th>Dose</th>
<th>Full adherence</th>
<th>Real (MEMS)</th>
<th>Low adherence (80%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>600</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

% Failure

30
Discussion & Future directions

• True genotype-phenotype relationships may not be fully apparent until the gene product is fully expressed. Is there relationship between phenotype/genotype subtypes and discontinuation rates or adverse events?

• Does phenotype/genotype directly/indirectly influence adherence patterns and ultimately, resistance profiles and outcomes?

• Incorporation of the cost effectiveness analysis?
  – Evaluate cost and the outcome (impact, result, effect, benefit, health gain …) of competing interventions
  – Expressed as: years of life gained, quality-adjusted life years gained (QALYs), new diagnoses, infections averted, and deaths averted.
Potential Collaborations

• Integrate HIV disease-progression models with Pre-Exposure Prophylaxis (PrEp) models?
  – address key questions about access, adherence, and patient outcomes in community settings.

• Explore and devise treatment strategies for HIV/TB co-infection
  – High dose rifamycins-based treatments

• Provide general pharmaco-statistical support and tools, any other interests….