Adherence to Medications

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13th International Workshop on Clinical Pharmacology of HIV Therapy
Adherence to medications is essential for therapeutic success

Effective Therapies

Adherence to medications

Effective Disease Management

« Drugs don’t work in patients who do not take them »

C Everett Koop, former US surgeon general
Adherence to Medications

The process by which patients take their medications as prescribed.

It is composed of 3 parts:

→ **Initiation**
→ **Implementation (execution)**
→ **Discontinuation**

**Persistence** is the length of time between initiation and discontinuation of dosing.

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**Vrijens et al., BJCP, 2012**
Perfect BID dosing

~12 hours interdose interval
A patient with delayed morning intake during weekends
Worsening regimen execution, then complete discontinuation.
Short Persistence (5 months)
# Assessment of drug dosing history

<table>
<thead>
<tr>
<th>Methods that reveal aggregate dose omissions but cannot show when omissions occurred (Sparse Sampling)</th>
<th>Continuous assessment over time (Rich sampling)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods that allow easy censorship of the data by the patient (Biased method)</td>
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<tr>
<td>• Pill counts</td>
<td>• Patient diary</td>
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<tr>
<td>• Retrospective questionnaire</td>
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<tr>
<td>Reliable methods</td>
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<tr>
<td>• Therapeutic drug monitoring (TDM)</td>
<td>• Medication Event Monitoring System</td>
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<tr>
<td>• Pharmacy refill data</td>
<td></td>
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</tbody>
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Modified from Vrijens & Urquhart, 2005 *Journal of Antimicrobial Chemotherapy*
Presented at the 13th Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain

Pre-Electronic Methods are Unreliable

Pill Counts Overestimate Adherence

Patients were given 160% drug supply


Figure 3. Distributions of the estimated proportion of capsules taken (PCT) at 1 month and 6 month visits. 6 groups combined

Self Reports Overestimate Adherence

EM-measured adherence correlates best with clinical outcomes (viral load)

Levine et al.; 2006; health Psychology

Diagnosing potential noncompliance. Physicians' ability in a behavioral dimension of medical care.


- predict only 35% of the nonadherers
- half of their predictions of nonadherence were incorrect

No better than a coin-toss!

Bias in 31% of the samples clustered in 66% of the subjects
Pre-electronic methods are sparse

Each patient took 75% of prescribed doses during a 3-month period
Pre-Electronic Methods confound the outcome analysis

A traditional ITT study

A pharmacometrically driven study

Pill counts used for drug accountability

Without Electronic Monitoring, precise estimation of treatment discontinuation is difficult
Longitudinal illustration of the taxonomy

16,907 participants from 95 clinical studies

Perfect adherence

Decrease in adherence due to discontinuation of treatment (nonpersistence)

% of patients engaged with the dosing regimen

Decrease in adherence due to nonexecution

% of patients who dosed correctly

Blaschke, Osterberg, Vrijens, Urquhart, Annual Review, 2012
Persistence: time to treatment discontinuation

Overall, 40% of patients will have discontinued the prescribed drug after 12 months

Blaschke, Osterberg, Vrijens, Urquhart, Annual Review, 2012
Variable adherence is a major source of Variance in Drug Response

- Manufacturing & distribution: CV = 20%
- Prescribing
- Dispensing
- Adherence: CV = 50%
- PK: CV = 50%
- PD: CV = 30%
- Drug response

HIV subset; n= 2777 (QD=1245 ; BID=1532)

Methodology published in Hypertensive subset by Vrijens et al. in BMJ 2008

Perfect adherence
Shortfall in adherence due to treatment discontinuation
Persistence
Adherence/Compliance

Shortfall in adherence due to poor execution of the dosing regimen

10-20% daily
Patient execution of the dosing regimens (QD vs BID)

HIV subset, N=2777

<table>
<thead>
<tr>
<th>Time</th>
<th>QD patients</th>
<th>BID patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td>90%</td>
<td>82%</td>
</tr>
<tr>
<td>3 months</td>
<td>89%</td>
<td>79%</td>
</tr>
<tr>
<td>6 months</td>
<td>89%</td>
<td>77%</td>
</tr>
<tr>
<td>1 year</td>
<td>88%</td>
<td>76%</td>
</tr>
<tr>
<td>2 years</td>
<td>92%</td>
<td>77%</td>
</tr>
</tbody>
</table>
Patients Vary Dosing Intervals and Keep the Dose Constant

Occasional toxicity

Periodic loss of effectiveness & emergence of drug resistance (HIV)

Blaschke, Osterberg, Vrijens, Urquhart, Annual Review, 2012

Presented at the 13th Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain
Better regimen execution does not imply better outcomes

Estimation of the comparative therapeutic superiority of QD and BID dosing regimens, based on integrated analysis of dosing history data and pharmacokinetics

Laetitia Comte - Bernard Vrijens - Eric Tousset - Paul Gérard - John Urquhart

« The BID advantage »
Cumulative frequency of each type of dosing errors

HIV subset, N=2777

- More than 18 hours
- More than 30 hours
- More than 54 hours
- More than 78 hours

QD
BID
More missed doses on weekends and in the evenings

QD HIV subset, N=1245

- **Wobblers**
- **PM Dosers (>75% of doses after 3:00PM)**
- **AM Dosers (>75% of doses before 3:00PM)**

Major problems on Friday & Saturday evenings
55% of residual PK variability is explained by EM

Successful Projection of the Time Course of Drug Concentration in Plasma During a 1-Year Period From Electronically Compiled Dosing-Time Data Used as Input to Individually Parameterized Pharmacokinetic Models

Bernard Vrijens, Eric Tousset, Richard Bode, Richard Bortz, Steve Mayer, and John Urquhart

Journal of Clinical Pharmacology, 2005; 45: 461-467
©2005 the American College of Clinical Pharmacology

The Odds that Clinically Unrecognized Poor or Partial Adherence Confuses Population Pharmacokinetic/Pharmacodynamic Analyses

Bernard Vrijens1,2, Robert Gross3 and John Urquhart1,4,5


Intensive PK day

4 trough concentrations

Log(Concentration)

EC50

~1 year

Time (hours)

0 2000 4000 6000 8000
Learn important PK/PD facts from adherence variability

Modelling the association between adherence and viral load in HIV-infected patients

Bernard Vrijens\textsuperscript{1,2,*}, Els Goetghebeur\textsuperscript{1,3}, Erik de Klerk\textsuperscript{2}, Richard Rode\textsuperscript{4}, Steve Mayer\textsuperscript{4} and John Urquhart\textsuperscript{2,5}

STATISTICS IN MEDICINE

Presented at the 13\textsuperscript{th} Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain

Onset of drug action

OFFSET
Comparison between PIs

Deterioration probabilities

Data from a cross-study comparison

Vrijens et al. – Basic Clin Pharma & Toxicol. 2005
Rich sampling is required for precise assessment

Decreased Adherence to Antiretroviral Therapy Observed prior to Transient Human Immunodeficiency Virus Type 1 Viremia

Thomas J. Podsadecki,1 Bernard C. Vrijens,2 Eric P. Tousset,2 Richard A. Rode,1 and George J. Hanna1
1Abbott Laboratories, Abbott Park, Illinois; 2Ardex, Zug, Switzerland

(See the editorial commentary by Gallant, on pages 1729–31.) • JID 2007:196 (15 December) • 1773
The Adherence Gap

Consequences are:
- decrease of study power (increase of type II errors)
- underestimation of « true efficacy » for a patient taking the drug as prescribed
- underestimated risk of adverse effects

Blaschke, Osterberg, Vrijens, Urquhart, Annual Review, 2012

Presented at the 13th Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain

10 Big PhRMA Companies

- Problem & Opportunity
- Met the Challenge
- Problem & Opportunity


R. Lalonde, PaSiPhic, 2011, San Luis Obispo
In practice, what needs to be done about adherence?

Variable adherence to prescribed therapy

Variable drug exposure

Noise (residual unexplained variance)

Learning
Reliable measure of drug exposure

Signal
(variation due to identified and interesting cause)
- Dose-response
- Forgiveness
- ...

Confirming
How much adherence is enough?

FIX the adherence problem!

In Trial Medication Management
Effect of intervention through a pharmaceutical care program on patient adherence with prescribed once-daily atorvastatin

Bernard Vrijens PhD, Ann Belmans MSc, Katelijne Matthys PhD, Erik de Klerk PhD and Emmanuel Lesaffre PhD

Vrijens, et al., Pharmacoepidemiology and Drug Safety, 2006

Presented at the 13th Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain
Feedback based on realistic and accurate dosing history data (EM-feedback, n=18 studies) is the cornerstone to manage patient adherence to medications.

Individual patient example

« What can be measured can be managed »

Deming WE

Demonceau et al., FP7 funded project ABC & submitted, 2012
Interested in patient adherence:

European Society for PAtient Adherence, COMpliance & Persistence
WWW.ESPACOMP.eu

Ascertaining Barriers for Compliance (ABC)
WWW.ABCproject.eu

The largest open-source database of drug dosing histories of ambulatory patients.
www.iAdherence.org

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