
# Standardization and Clinical Relevance of HIV Drug Resistance Testing

**A Report of the Forum for Collaborative HIV Research HIV Drug Resistance Working Group**

**April 2002 – August 2003**


## Background

Reduced viral susceptibility to antiretroviral drugs is a major factor determining treatment response in HIV infected patients. Drug resistance testing is recommended by expert panel guidelines in the US and Europe. Resistance testing technology has been developed to allow routine use of resistance testing for clinical practice as well as drug development using standardized and validated methodologies.

- Genotyping kits: academic laboratories and clinics
- Genotyping through commercial service laboratories
- Phenotyping: through commercial service laboratories

The clinical relevance of reduced HIV drug susceptibility was clearly demonstrated in 1997 through the work of the Resistance Collaborative Group (RCG). At that time, drug resistance was identified as a major problem by many smaller studies but demonstration of an association between baseline susceptibility and clinical outcome was not consistent across studies. The studies were generally small and the analyses for baseline resistance and treatment outcome not standardized. The RCG, a consortium of industry, academic researchers and US regulatory agency representatives reviewed the then current status of prospective and retrospective clinical studies investigating the association between baseline drug resistance and virologic outcome. Appropriate studies were identified and investigators invited to participate in the collaborative effort. The key components of the RCG project were to develop a standardized data analysis plan (DAP) and to derive a common definition of baseline resistance for genotype and phenotype (genotypic and phenotypic sensitivity scores or GSS and PSS).

The RCG recognized the limitations of the approach used: the compromises made by simplifying the definitions of baseline susceptibility were a trade-off for a standardized approach to analysis that allowed the demonstration of clinical relevance. The derivation of the GSS was based on simply counting a set of consensus mutations assuming equal contribution (with very few exceptions) and the PSS was based on arbitrary/technological cut-offs without recognition for the differences for individual drugs.

The findings of the RCG were presented to the FDA at an advisory hearing that included discussions on prevalence of transmission of drug resistance, clinical validation of resistance testing and laboratory/technology issues.


Since this landmark project, significant developments in the interpretation of resistance tests have been made.

**Progress in the area of genotype interpretation:**

- Rules based genotypic algorithms of various levels of complexity, generally derived by consensus of expert panels or expert interpretation
- Interpretations based on relational databases (e.g. virtual phenotype)
- Neural network approaches
- Algorithms based on virologic outcome are available for some drugs
- Studies comparing the ability of individual algorithms (not derived using clinical outcome data) to predict clinical outcome
- Major effort to compare the output of algorithms and to simplify the "cross-talk" between the various rules based systems (Stanford Database)

Investigators have begun to develop algorithms relating the baseline genotype to clinical outcome. Examples include:

- Narval Study (various drugs)
- Abacavir
- Tenofovir
- Lopinavir/r

**Progress in the area of phenotype interpretation:**

- Recognition that generic technical cut-offs are not necessarily the relevant cut-off
- Description of normal distribution for "wild-type" viruses
- Recognition that clinically relevant cut-offs are unique to individual drugs
- Derivation of these cutoffs using clinical databases

Examples of defining clinical cut-offs based on virologic outcome databases:

- Abacavir
- Tenofovir
- Lopinavir/r

**Current status of interpretation of resistance testing:**

Interpretation of resistance tests in the clinical setting remains a key problem to date. In the clinical setting, what is known through drug


development studies may not always be applicable to individual patients due to the nature of the studies used for derivation of algorithms or clinical cut-offs. The heterogeneity of the patient population will continue to increase due to increasing number of options for treatment combinations. For example, many of the protease inhibitor resistance studies were performed using single PIs, whereas ritonavir boosting is now the norm and dosing schedules for boosted PI regimen are not standardized. The ideal "add on" of one drug type studies for measuring the contribution of susceptibility to one particular drug is not a feasible proposition in most cases. Thus, larger databases may be required to tease out the individual drug effects. Drug development is focusing increasingly on substances that are active against viruses with reduced susceptibility towards one or more drug/drug class. Description of activity against drug resistant viruses will require standardized language. Interpretation of genotype and phenotype resistance testing will be increasingly important when assessing the expected contribution of these drugs to suppression of viruses with a history of drug exposure.

## Problem Statement

- Data sets from published studies are frequently too small for more generalized analysis
- Data sets frequently too small for generation of clear breakpoints for specific drugs
- Clinical resistance data does not available for all drugs (e.g. "old" drugs)
- Different analytic approaches used
  - ✓ Definition of baseline resistance
  - ✓ Definition of treatment outcome
  - ✓ Derivation of algorithm or phenotypic cut-off
- More comprehensive approach to analysis is required
  - ✓ Exploratory
  - ✓ Cross validation
  - ✓ Confirmatory analysis
  - ✓ Training vs. test sets
- Different statistical approaches used in the published studies, including for example (not an exhaustive list):
  - ✓ Linear or logistic regression
  - ✓ Recursive partitioning
  - ✓ Neural nets


Regulatory Perspective

The FDA perspective and needs (as presented at the Forum for Collaborative HIV Resistance Planning Committee Meeting, April 30, 2002) are as follows:

- CDER
  - ✓ guidance for resistance testing in drug approval
  - ✓ definition of clinical breakpoints (phenotype) for old and new drug labels
  - ✓ relevance of mutations for old and new drug labels
  - ✓ commitment for continued collaboration as new drugs enter the market

- CBER
  - ✓ Update clinically relevant mutational algorithm (guidance document published in August 2001)

The EMEA/CPMP perspective and needs are as follows:

- "Points to consider" document is evolving
- Investigation of drug resistance is an essential part of drug development
- Response data needs to be related to resistance data

The opportunity for collaboration

- Public and private partnership
- Inter-industry collaborations (e.g. FDA submitted datasets)
- Public and private databases
- Opportunity to collaborate in small groups and larger, more ambitious collaborations

## Strategy -- Approach

Various approaches to this project are available; they can generally be described as fitting between the following two models:

- RCG model
  - ✓ Common data analysis plan + many sets of independent analyses
- Large common/collaborative database
  - ✓ Pooling of relevant data from various sources into one + carrying out centralized analyses


The planning committee for this project has opted to take a combination of these approaches. Data sets from within industry and academia have been identified that have and can continue to serve for exploratory analyses and others can be enlisted for confirmatory/validation studies. In addition, existing collaborative initiatives will be encouraged and the Forum will facilitate growth within the existing collaborations and initiating new collaborations as required for the aims and objectives of this project. We expect a major outcome to be the recognition of the advantage that the multitudes of approaches that have contributed to the development in this field have brought and that novel ideas will be generated as a result of this unique opportunity for collaborative discussions among the world's leaders from within industry and academia in the resistance field.

## Strategy -- Structure

The Forum has convened an international planning committee consisting of key representatives from government agencies (research, regulatory and health services), academia and industry (diagnostic and pharmaceutical). In order to structure the various areas of discussion, five working groups have been established, each chaired by members of the planning committee.

- Genotype working group
- Phenotype working group
- Analysis and statistics working group
- Technology, laboratory and reporting working group
- Reimbursement working group

The working groups include members from the planning committee and additional individuals representing datasets or specialized expertise (e.g. the analysis/statistics group).

## Aims and Objectives

The overarching aims of this project are:

- To improve patient management through better use of drug resistance test information and through better access to drug resistance testing
- To collaborate in an ongoing process with industry and regulatory agencies for the purpose of consistent application of


drug susceptibility information in drug development and drug labeling

Specific objectives:

- Identify clinical databases suitable for the generation of genotypic algorithms and phenotypic cut-offs
- Develop analytic approaches for the derivation of virologic response associated definitions of resistance for each antiretroviral drug
- Establish collaboration amongst the various constituencies to facilitate the performance of the required analyses
- Review current regulatory aspects related to standardization and quality assurance including laboratory as well as genotype interpretation issues
- Present and publish the overall findings to the relevant government drug and technology approval agencies (FDA and EMEA)
- Make recommendations for how best to establish a continuous and long-term evaluation of clinically defined HIV drug resistance