

**Emerging Issues in HIV Clinical Trials for new ARVs Roundtable
Washington DC
Background Paper
September 30, 2010**

Meeting Background

The Forum for Collaborative HIV Research's (Forum) role is to foster consensus on issues in development of new and effective HIV treatment strategies. The Forum has held three prior meetings as new ARV classes have been discovered and the field of HIV clinical trials has matured. In 1999, a workshop on the "Challenges of Clinical Trial Design in Assessing the Effects of Anti-HIV Therapy in Heavily Pretreated Patients" brought greater recognition to the issue of the need for inclusion in pharmaceutical clinical trials of people for whom current ARV treatment is no longer working¹. In 2004, a second workshop was held on issues of study design for patients with documented three- or four class ARV drug resistance. The conclusions of the workshop were: i) these patients were heterogeneous and not all were candidates for clinical trials; ii) open-label expanded access programs, which allow for simultaneous use of multiple new drugs, are acceptable options for certain patients; iii) the lessons learned from past studies should help to optimize future study designs for these patients; and iv) close collaboration between all stakeholders is paramount for the successful development of new therapies and effective treatment strategies². In 2008, the Forum convened a meeting to discuss the current status and research challenges in designing studies in treatment-experienced and treatment-naïve patients. A consensus was reached on the need to design studies that minimized the risk of functional monotherapy in treatment-experienced patients³. Historically, treatment experienced patients had been defined by the number of drugs to which they were resistant. One conclusion was that the classification of treatment experienced patients should be based on the number of available active drugs so that construction of a suitable optimized background therapy (OBT) for randomization was possible³. And, with the development of new antiretrovirals that achieve complete virologic suppression, the virologic endpoint should be set at < 50 copies/ml rather than measured by reduction in baseline viral load³.

Meeting Rationale

Currently, with over 30 drugs on the market – some in the form of drug combinations in a single pill – developers of new ARVs are faced with a dilemma: how to assess the contribution of an investigational HIV agent in the presence of a fully suppressive OBR. The September 30th, 2010 roundtable is the 4th in the series organized by Forum and is co-convened with FDA to address this dilemma. This meeting is an opportunity for stakeholders to identify key issues in new ARV

development and propose novel approaches or innovative ideas for the conduct of HIV clinical trials in this new age.

Background Developments in Complex Clinical Trials

In preparation for the roundtable, discussions were conducted with representatives from regulatory agencies, academia, pharmaceutical manufacturers and patient advocates to identify important issues in HIV clinical trials for new ARVs. Key issues for treatment experienced and naïve patients are outlined in this document.

General Developments in Clinical Trials

Defining Non-Inferiority

- 1) Non-inferiority trials aim to show that the efficacy difference between the test and active control treatments are very small, as defined by a pre-specified, stringent non-inferiority margin. Determination of this margin is complicated due to variations in OBT used and their response rates over time. The clinical justification for permissible lower bound of the inferiority margin that will be tolerated in a trial must be identified before study initiation.
- 2) The influence of non-inferiority testing and the chosen margin on sample size may be larger than for a comparative superiority study if the drug were potentially superior. Given achievement of complete virologic suppression, superiority studies may no longer be possible.
- 3) Recent experience with comparative non-inferiority studies will be discussed as a part of an effort to address these concerns.

Adaptive Design

- 1) Adaptive designs are commonly viewed as a panacea for dealing with issues that need to be examined in clinical trials. The agenda will include a background discussion of adaptive design and examples from other areas of investigation including concerns related to Type I error as set forth in FDA guidance.
- 2) Can ARV studies benefit from adaptive designs? Adaptations such as endpoint driven studies or progressive stratification can allow for post-initiation identification of efficacy in preplanned subsets, the impact of resistance, proper dosing and appropriate control of optimized background therapy, as a few examples.

Treatment Experienced Patients

New Models for Clinical Trials

- 1) Patient advocates have developed an interesting model that may simplify decision making for developers of new ARVs. The decision tree advocates decoupling safety from efficacy studies and conducting smaller non-randomized, single arm efficacy studies using different approaches. At the same time, a larger, randomized safety study could be undertaken with comparison groups kept intact for a longer period of time so that better safety and efficacy data can be obtained for a new investigational agent.
- 2) The FDA would like to receive feedback on a proposed new model for accelerated approval based on the two-part hybrid trial design to assess the short-term contribution (1-2 weeks) and durability (24 weeks) of an investigational agent at different doses/dose regimens. In this design, safety over the 24 week trial period is also assessed.
- 3) Industry will propose some models at the meeting for feedback.

Issues that Impact Trials

1) **Patient enrollment:**

Use of non-traditional sites for the conduct of registration trials: The experience of community physicians in enlisting more patient diversity in trials.

2) **Changes in optimized background regimen:**

Some protocols have allowed:

- No switches (switch=failure).
- One in class substitution due to documented toxicity issue.
- OBT substitutions (in class or across class) permitted per protocol for documented toxicity reasons are permitted on or before the first trial visit without penalty. If OBT substitutions for toxicity reasons occur after the first trial visit, then patients are considered virologic failures if they have HIV RNA > 50 copies/mL at the time of switch.

How can study integrity be maintained while allowing participants to modify treatment based on toxicity?

3) **Viral load assays:**

Given the recent concerns for differences in viral “blips” with the available viral load assays, there is a need for discussion on ways to manage these blips.

4) **Trial endpoints:**

What is the potential for new or different endpoints in heavily treatment experienced patients when suppressive therapies aim to keep viral load undetectable and still try to understand the

contribution made by the study drug when log drops from baseline may not be statistically significant:

- Mean change
- Proportion < 50 copies/mL
- Proportion < 200 copies/mL (ACTG)

Treatment Naïve Patients

New treatment options continue to be needed for initial HIV treatment. Issues in this population include:

- 1) Should low CD4 count or other criteria exclude treatment-naïve patients from dose finding trials?
- 2) Should biomarkers (e.g. inflammatory) be evaluated in treatment-naïve trials to permit assessment of correlation with long-term safety? If yes, which biomarkers should receive priority?

REFERENCES:

1. Forum for Collaborative HIV Research. The challenges of clinical trial design in assessing the effects of anti-HIV therapy in heavily pre-treated patients. *Annals of the Forum for Collaborative HIV Research*. 1999; 2:1-42.
2. Struble K, Murray J, Cheng B, Gegeny T, Miller V, Gulick R. Antiretroviral therapies for treatment-experienced patients: current status and research challenges. *AIDS*. 2005; 19(8):747-756.
3. Chan-Tack KM, Struble KA, Morgensztejn N, et al. HIV clinical trial design for antiretroviral development: moving forward. *AIDS*. 2008;22(18):2419-2427.