

## MEMORANDUM

**Date:** December 4, 2000

**From:** Therapy for Treatment-Experienced Patients Working Group  
Division of Antiviral Drug Products

**Through:** Heidi Jolson, M.D., M.P.H.  
Director, Division of Antiviral Drug Products

**Subject:** Background Package for January 11, 2001 Advisory  
Committee

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### Introduction

On January 11, 2001, the Antiviral Drug Products Advisory Committee will meet to consider issues pertinent to clinical trial design in the development of antiretroviral agents for HIV infected, heavily treatment experienced adults and children with limited therapeutic options. As the number of treatment experienced patients with limited therapeutic options increases, so does the need for new agents that are effective in these patients. The Division has convened this meeting to have an open discussion about the numerous challenges of studying new agents in these treatment-experienced patients. A further goal of this meeting is to facilitate and promote the development of new therapies for patients who are most in need of new therapeutic options. For purposes of the discussion, the relevant population has been defined as patients who have had a loss or lack of virologic response to at least 2 HAART regimens that, in total, have included at least one member of each of the approved antiretroviral drug classes (protease inhibitors, nucleoside and nonnucleoside reverse transcriptase inhibitors). This definition has been chosen for the meeting to focus discussion on a patient population for whom designing comparative trials is problematic.

### The Success of HAART in Clinical Practice

Following the introduction of HAART, marked decreases in AIDS-related morbidity and mortality have been observed. More patients are living longer and are therefore being exposed to an increasing number of regimens and drug combinations. Despite the improvement in morbidity and mortality, many patients experience a failure of HAART treatment for a variety of reasons including the development of resistance, inappropriate antiretroviral selection, poor patient adherence, lack of tolerability and adverse events, or intra-patient variation in drug exposure parameters.

Although the method to assess efficacy has varied among different clinical trials, as has the combination of antiretroviral agents studied, between 40-80% of antiretroviral naïve patients in clinical trials have achieved suppression of HIV below the assay limit of detection. In contrast, analyses of the ability of HAART to achieve durable viral suppression in American and Western European patients has been less successful. In general, HAART regimens in clinical practice achieve durable virologic suppression in patients less than half of the time. The success rates of subsequent regimens, often reflective of underlying resistance, are even lower.

The success of “rescue” or “salvage” therapy in heavily pretreated patients has been examined primarily in small cohorts of patients and uncontrolled trials. The majority of the rescue regimens have included ritonavir and saquinavir, at varying doses. Although treatment histories were variable, as were the definitions of virologic success, in general the results were disappointing. The success rates reported in these cohorts may be more similar to clinical practice and underscore the need to develop agents that are better tolerated and effective in both naïve and treatment-experienced patients.

### **Clinical Trial Design for the Evaluation of Antiretroviral Agents**

In order for a new antiretroviral agent to be approved for marketing, efficacy and safety must be demonstrated in two adequately powered and well-controlled clinical trials. Historically, we have generally recommended that these studies be double-blind, randomized, placebo or active controlled trials of antiretroviral treatment-naïve and -experienced subjects of 48 weeks duration. The contribution of the new drug to the antiviral effect must be quantifiable, which is usually achieved by incorporating a placebo control or by demonstrating comparable efficacy to an antiretroviral with a treatment effect that has been well-defined for the population of interest.

The difficulty arises when trying to apply these comparative trial designs to drug development for the heavily treatment-experienced patient population. A few of these difficulties are as follows:

- The treatment-experienced patient population is more heterogeneous than the naïve population by virtue of the fact that each patient has a unique treatment history and drug resistance profile. Thus, it is unlikely that there exists a regimen that can be used uniformly across a treatment group. Differences in treatment history and drug resistance profiles may necessitate the stratification of patients based on these variables.
- Identification of an acceptable comparator drug or regimen is difficult. In this setting, the use of placebos may be perceived as unethical, and patients may be less likely to enroll when there is a substantial likelihood that they will receive placebo, or they may drop out of the study early if they discover they

are on placebo. Due to the necessity of using multiple agents in order to achieve some antiviral effect, blinding and the use of dummy active controls only adds to an already significant pill burden.

- The efficacy endpoint of time to loss of virologic suppression may be too stringent a criterion to assess the virologic response in this group of patients in phase 2 and 3 studies. Other endpoints such as mean change from baseline in viral load or CD4 cell counts may be more appropriate. Focusing attention on the CD4 cell count allows determination of the immunologic benefit of a drug, and may be quite important especially if the virologic benefit is less impressive. Assessment of a drug's effect on clinical outcome is especially important in treatment-experienced patients with more advanced HIV disease. An additional endpoint issue is what study duration is appropriate, as a durable virologic suppression to 48 weeks may be unrealistic in heavily pretreated patients.
- Dose-finding studies in treatment experienced patients may be necessary to identify differences in the antiviral activity among patients with well-characterized resistance mutations to currently available antiretroviral agents.
- The safety assessment is complicated as well due to the differing agents used in the background regimens and their uncertain contributions to the adverse events.

Thus, almost every aspect of clinical trial design for the development of antiretroviral agents needs to be addressed and redirected for the heavily treatment experienced patient population.

### **General Meeting Plan**

The primary objectives for the committee deliberations are to discuss issues relating to the identification of appropriate control arms, possible trial designs, and study endpoints for this patient population. During the planning for this meeting, the Division requested members of industry and the community to submit written comments, proposals, and suggestions pertinent to this issue for inclusion in the discussion. We would like to invite you to consider preparing original trial design approaches for discussion at the meeting.

The following sections include the draft agenda and questions for January 11<sup>th</sup>. Also attached are several articles focusing on therapeutic issues in HIV infected antiretroviral experienced patients. Please review these materials to prepare for what we anticipate will be a thorough and vigorous discussion. We look forward to your contribution to this thought-provoking and productive meeting.

## **Draft Agenda and Advisory Committee Questions**

- 8:30 Welcome  
 8:35 Conflict of Interest Statements  
 8:45 Introduction/Opening Remarks –  
 Heidi Jolson, M.D., M.P.H, Division Director, DAVDP

### ***Trial Design Issues***

- 9:00 **Therapeutic Challenges for Antiretroviral Experienced Patients: A Clinical Perspective**  
 Douglas Ward, M.D.
- 9:15 **Overview of Trial Design Options: Adults**  
 Martin Schecter, M.D.
- 9:45 **Overview of Trial Design Options: Pediatrics**  
 Colleen Cunningham, M.D.
- 10:00 **Trial Design Options – Patient Perspective**  
 Carlton Hogan
- 10:15 Break
- 10:30 **FDA Presentation**
- 10:50 **Questions to the Committee**
1. What type of information would you most like to see from studies conducted in treatment experienced adults and children? Please comment on the use of studies in these populations to support efficacy for registration vs. their use for addressing more focused questions, such as drug interactions, dosing, or virologic response according to baseline susceptibility.
  2. Please comment on the strengths and weaknesses of the trial design options presented.
  3. What control arm(s) could be used for studies in this patient population?
    - a. For placebo or no treatment controls how long is it feasible to continue a randomized comparison? Please also comment on the clinical criteria for early switching from randomized therapy.
    - b. What is the role of resistance testing for constructing background regimens?
    - c. What constitutes an optimal background regimen?
  4. Please comment on the advantages and disadvantages for conducting open-label studies instead of double-blind studies in this patient population?

- 12:00 Lunch
- 1:00 Open Public Hearing
- 2:00 Continue Questions to the Committee

### ***Endpoint Issues***

- 2:45 **Response Rates in heavily pretreated patients**  
Roy Gulick, M.D.
- 3:15 **Statistical Considerations for Endpoints in heavily pretreated patients**  
Victor DeGrutolla, Ph.D.
- 3:45 **Questions to the Committee**
  - 5. What are the most appropriate study endpoints for trials in heavily pretreated patients? Please comment on the strengths and weakness of virologic, immunologic and clinical endpoints. In addition please discuss the relevance of virologic endpoint metrics other than below the limit of assay detection.
  - 6. Please discuss the role of shorter-term trials (e.g., 16 weeks) in assessing the safety and efficacy of new antiretrovirals in treatment-experienced patients. In your discussions please consider the needs to establish longer-term safety.
- 5:30 Adjourn