DATE: September 27, 1999

TO: Antiviral Drugs Advisory Committee Members and Consultants

FROM: Debra Birnkrant, M.D.
Deputy Division Director
Division of Antiviral Drug Products

SUBJECT: Overview of the October 4, 1999, Meeting of the Antiviral Drugs Advisory Committee

The Division is looking forward to your participation in the upcoming meeting of Antiviral Drugs Advisory Committee.

The October 4th advisory committee meeting will address issues related to drug development for the prevention of mother-to-child transmission (MTCT) of HIV. The morning session is an open meeting and is designed to address general issues related to all antiretrovirals, both approved and investigational, under development for this indication. During the morning session invited speakers will present an overview of the epidemiology and current Public Health Service recommendations regarding maternal health considerations and prevention of MTCT, an overview of published clinical trials, and an international perspective on the conduct of foreign clinical studies. FDA reviewers will address safety/toxicology issues and other regulatory considerations. Broad questions will be posed to the committee related to evaluating new regimens to prevent perinatal transmission, given the broad acceptance of PACTG 076; questions concerning the applicability of data from studies conducted in developing countries to the U.S. population will also be discussed. The morning's discussion will help us to advise many sponsors about their development plans for prevention of MTCT.

The morning session will set the stage for the afternoon session, which is closed to the public. It is closed because Boeringher Ingelheim will be presenting their development plan for short-course neviripine for the prevention of MTCT. They will discuss the results from the completed HIVNET 012 trial, as well as present information from their ongoing trials of short-course neviripine. Although results of HIVNET 012 have been publicly presented, the subject matter for the closed session is confidential.

We have formulated specific questions that will help to ensure a productive discussion to assist this sponsor in formulating a strategy for preparing a future marketing application for their product.

Attached please find two background documents that will address the respective sessions. Two sets of questions are also appended, as are cited publications.

MEMORANDUM

Date: September 27, 1999

To: Antiviral Drugs Advisory Committee Members and Consultants

From: Medical Review Team
Division of Antiviral Drug Products

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

Subject: Background information for the open session of the Antiviral Drugs Advisory Committee of October 4, 1999
Prevention of Mother-to-Child Transmission of HIV

Introduction

On the morning of October 4, we will ask you to provide comment on a number of issues regarding the perinatal transmission of HIV. Much of the discussion will focus on the applicability of outcome data from foreign studies of mother-to-child transmission (MTCT) of HIV to patient care in the United States.

Clinical Background

As you are aware, mother-to-child transmission of HIV-1 accounts for more than 90% of the pediatric AIDS cases in the United States. To date, there have been more than 8,000 cases of AIDS reported in children in the U.S., and it is estimated that more than 15,000 children in the U.S. have been infected with HIV-1. In early 1994 the results of the Pediatric AIDS Clinical Trials Group (PACTG) study 076 were announced. PACTG 076, a randomized, placebo controlled study in the United States and France, showed a 68% reduction in mother-to-child transmission of HIV by the use of oral zidovudine, starting after 14 weeks gestation, intravenous intrapartum zidovudine, and oral zidovudine given to the infant for 6 weeks after delivery. Within 6 months, the U.S. Public Health Service (USPHS) recommended the use of zidovudine for the prevention of perinatal transmission of HIV. The PACTG 076 regimen was rapidly incorporated into clinical practice and the effects were seen almost immediately. Lindegren et al. estimated that while 1,650 HIV infected infants were born in 1991, that number fell to 895 in 1995 and to 480 in 1996. Several studies have reported a rate of mother-to-child transmission as low as 3-5% (Fiscus, et al.), and the PACTG 076 regimen plus cesarean section before the onset of labor has been shown to reduce the transmission rate to as low as 1% (The International Perinatal HIV Group).

Numerous mechanisms have been developed to provide long term follow up of the infants exposed to antiretroviral drugs perinatally. At the present time, most of the information available is from perinatal exposure to zidovudine; little information is available concerning intrauterine or neonatal exposure to other antiretroviral drugs.

Many of the infants who were part of the PACTG 076 trial are being followed as part of the PACTG 219 study. Other infants have been followed in the Women and Infants Transmission Study, the Perinatal AIDS Collaborative Transmission Study, and the Pediatric Spectrum of Disease Study.

For a variety of reasons, not all HIV-infected pregnant women receive the full PACTG 076 regimen, and it is not known which component is the most critical in the prevention of perinatal transmission of HIV. Since the results of PACTG 076 have been published, several investigators have retrospectively examined transmission rates in mother-infant pairs who have receive only part of the PACTG 076 regimen. Fiscus et al. reported a transmission rate of 10.7% when zidovudine is begun intrapartum as compared to 30.9% with no therapy and 3.2% with the full PACTG 076 regimen. Wade et al. reported similar results; when zidovudine was begun during the prenatal period, the transmission rate was 6.1%, while the transmission rate was 10% in cases where zidovudine was begun in the intrapartum period and 26.6% when no zidovudine was given.

Approved Therapy

Zidovudine, as administered per PACTG 076, was found to be safe and effective and was approved by the FDA for use in the prevention of perinatal transmission of HIV in August, 1994. It remains the only antiretroviral with approval for this indication. This zidovudine regimen quickly became the standard of care in the U.S. and numerous published articles attest to the successful implementation of this regimen in decreasing the number of HIV-infected births since 1994.

A USPHS consensus panel of experts was convened in 1997 and released new recommendations in 1998 regarding the use of multiple antiretroviral drugs in pregnant women infected with HIV. These recommendations (Attachment 1) are based on the opinion of a panel of experts and provide guidelines for the practice of medicine, but do not necessarily reflect the approved indications of the antiretroviral drugs discussed in the guidance document. In addition, off label use of antiretrovirals for prevention of perinatal HIV transmission is described in the Antiretroviral Pregnancy Registry, a voluntary reporting mechanism funded by the pharmaceutical industry. This registry was originally designed to detect major teratogenic effects of antiretroviral drugs and describes the use of 10 different antiretrovirals given either alone or in combination to pregnant women during 761 pregnancies as of January 1999.

It is understood that individual physicians prescribing drugs off label must use clinical judgement based on a drug's labeling and other available information under the practice of medicine. However, the FDA can only approve drugs for new indications or uses after substantial evidence of safety and efficacy for the new indication or use is submitted to the FDA and reviewed. When drugs are used for off label purposes, the FDA believes that it is in the public interest to encourage the sponsor to submit the necessary data to support the inclusion of safety and efficacy information in an updated drug label.

Regulations Concerning Foreign Data

Because many MTCT trials are conducted outside of the U.S., we would like to familiarize you with the pertinent citations outlined in the Code of Federal Regulations (see Attachment 2) regarding the use of foreign data to support a marketing application.

In general, the FDA accepts data from foreign clinical studies provided that the studies are well designed, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community (CFR 312.120). The regulations further state that data obtained in foreign studies and included in an application for marketing approval in the U.S. are acceptable as long as that data are applicable to the U.S. population and to medical practice in the U.S. (CFR 314.106)

Issues for discussion

Based on your experience and the information conveyed in the presentations, we will ask you to provide advice on the applicability of data obtained in foreign trials of the prevention of perinatal transmission of HIV to the practice of medicine in the United States. The following questions address issues concerning the use of data obtained from studies conducted in foreign countries and in the United States. We appreciate your participation and look forward to your comments on the following questions.

1. Given the broad acceptance of PACTG 076, please provide advice regarding how new regimens should be evaluated.

2. Please discuss clinical situations and special populations in whom regimens containing all or part of the PACTG 076 regimen are not feasible.
   a. Specifically, in your experience what is the frequency of an HIV-infected woman without prenatal care presenting in labor?
   b. What do you consider to be the optimal regimen for the prevention of MTCT in an untreated HIV-infected woman who presents in labor?

3. If studies of MTCT performed in non-U.S. settings use comparator regimens that differ from regimens commonly used in the U.S., then to what extent and in what ways do you find the results of such studies applicable to your clinical practice?

4. If studies of MTCT are conducted in areas where recommendations concerning breast-feeding differ from those in the U.S., then how does the practice of breast-feeding affect the usability and interpretation of the data?

5. What duration of follow up is needed to adequately assess the safety of MTCT prevention strategies? Do you have any suggestions regarding follow up approaches?

6. Please discuss study design approaches that would provide useful information about prevention of MTCT in your community's clinical practice setting.

7. What other types of information should be obtained from trials for the prevention of MTCT?

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Fiscus SA, Schoenbach VJ, Wilfert C. Short courses of zidovudine and perinatal transmission of HIV. N Eng J Med 1999; 340: 1040-1041.

Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. N Eng J Med 1998; 339:1409-1414.

Summary Table from the USPHS Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant Women Infected with HIV-1 for Maternal Health and for Reducing Perinatal HIV-1 Transmission in the United States.

TABLE 3. Clinical scenarios and recommendations for the use of antiretroviral drugs to reduce perinatal human immunodeficiency virus (HIV) transmission

Clinical scenario	Recommendations*
Scenario #1 HIV-infected pregnant women who have not received prior antiretroviral therapy.	HIV-1–infected pregnant women must receive standard clinical, immunologic, and virologic evaluation. Recommendations for initiation and choice of antiretroviral therapy should be based on the same parameters used for persons who are not pregnant, although the known and unknown risks and benefits of such therapy during pregnancy must be considered and discussed. The three-part zidovudine (ZDV) chemoprophylaxis regimen should be recommended for all HIV-infected pregnant women to reduce the risk for perinatal transmission. The combination of ZDV chemoprophylaxis with additional antiretroviral drugs for treatment of HIV infection should be a) discussed with the woman; b) recommended for infected women whose clinical, immunologic, and virologic status indicates the need for treatment; and c) offered to other infected women (although in the latter circumstance, it is not known if the combination of antenatal ZDV chemoprophylaxis with other antiretroviral drugs will provide additional benefits or risks for the infant). Women who are in the first trimester of pregnancy may consider delaying initiation of therapy until after 10–12 weeks' gestation.
Scenario #2 HIV-infected women receiving antiretroviral therapy during the current pregnancy.	HIV-1–infected women receiving antiretroviral therapy in whom pregnancy is identified after the first trimester should continue therapy. For women receiving antiretroviral therapy in whom pregnancy is recognized during the first trimester, the woman should be counseled regarding the benefits and potential risks of antiretroviral administration during this period, and continuation of therapy should be considered. If therapy is discontinued during the first trimester, all drugs should be stopped and reintroduced simultaneously to avoid the development of resistance. If the current therapeutic regimen does not contain ZDV, the addition of ZDV or substitution of ZDV for another nucleoside analogue antiretroviral is recommended after 14 weeks' gestation. ZDV administration is recommended for the pregnant woman during the intrapartum period and for the newborn—regardless of the antepartum antiretroviral regimen.

TABLE 3. Clinical scenarios and recommendations for the use of antiretroviral drugs to reduce perinatal human immunodeficiency virus (HIV) transmission — Continued

Clinical scenario	Recommendations*
Scenario #3 HIV-infected women in labor who have had no prior therapy.	Administration of intrapartum intravenous ZDV should be recommended along with the 6-week ZDV regimen for the newborn. In the immediate postpartum period, the woman should have appropriate assessments (e.g., CD4+ count and HIV-1 RNA copy number) to determine whether antiretroviral therapy is recommended for her own health.
Scenario #4 Infants born to mothers who have received no antiretroviral therapy during pregnancy or intrapartum.	The 6-week neonatal ZDV component of the ZDV chemoprophylactic regimen should be discussed with the mother and offered for the newborn. ZDV should be initiated as soon as possible after delivery—preferably within 12–24 hours of birth. Some clinicians may choose to use ZDV in combination with other antiretroviral drugs, particularly if the mother is known or suspected to have ZDV-resistant virus. However, the efficacy of this approach for prevention of transmission is unknown, and appropriate dosing regimens for neonates are incompletely defined. In the immediate postpartum period, the woman should undergo appropriate assessment (e.g., CD4+ count and HIV-1 RNA copy number) to determine if antiretroviral therapy is required for her own health.

*Discussion of treatment options and recommendations should be noncoercive, and the final decision regarding the use of antiretroviral drugs is the responsibility of the woman. A decision to not accept treatment with ZDV or other drugs should not result in punitive action or denial of care. Use of ZDV should not be denied to a woman who wishes to minimize exposure of the fetus to other antiretroviral drugs and who therefore chooses to receive only ZDV during pregnancy to reduce the risk for perinatal transmission.

ATTACHMENT 2

Rules concerning the use of data obtained in foreign studies as noted in the Code of Federal Regulations

Introduction to Section 312.120 Foreign clinical studies not conducted under an IND
This section describes the criteria for acceptance by FDA of foreign clinical studies not conducted under an IND. In general, FDA accepts such studies provided they are well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community. Studies meeting these criteria may be utilized to support clinical investigations in the United States and / or marketing approval.

Section 314.106

(a) *General.* The acceptance of foreign data in an application generally is governed by 312.120 of this chapter.

(b) *As sole basis for marketing approval.* An application based solely on foreign clinical data meeting U.S. criteria for marketing approval may be approved if: (1) The foreign data are applicable to the U.S. population and U.S. medical practice; (2) the studies have been performed by clinical investigators of recognized competence; and (3) the data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA is able to validate the data through an on-site inspection or other appropriate means. Failure of an application to meet any of these criteria will result in the application not being approvable based on the foreign data alone. FDA will apply this policy in a flexible manner according to the nature of the drug and the data being considered.