FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIVIRAL DRUGS ADVISORY COMMITTEE

8:05 a.m.

Monday, October 4, 1999

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Gaithersburg Holiday Inn
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Gaithersburg, Maryland

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ALSO PRESENT:

THOMAS FLEMING, PH.D.

C O N T E N T S

P R O C E E D I N G S

(8:05 a.m.)

DR. HAMMER: Good morning. Would you please take your seats? We are about to start.

I would like to officially open the October 4th session of the Antiviral Drugs Advisory Committee. Our session and duty this morning is to discuss the applicability of perinatal interruption transmission trials for HIV and their applicability to the U.S. clinical setting and implications for drug approvals.

I'd like to start by having people around the table introduce themselves for the record. Dr. Kweder?

DR. KWEDER: I'm Sandra Kweder. I am the acting Office Director for Office of Drug Evaluation IV.

DR. RARICK: Good morning. I'm Lisa Rarick. I'm the Division Director for Reproductive and Urologic Drugs in CDER.

DR. JOLSON: Good morning. I'm Heidi Jolson. I'm the Director of the Division of Antiviral Drug Products.

DR. BIRNKRANT: Debra Birnkrant, Deputy Director, Division of Antiviral Drug Products.

DR. KUKICH: Stanka Kukich, medical team leader, FDA.

DR. BAYLOR: Melisse Baylor. I'm a reviewer,

FDA.

DR. HANDELSMAN: Ed Handelsman, pediatrician, Kings County Hospital, Brooklyn.

DR. WILFERT: Cathy Wilfert, pediatrician, Duke University Medical Center and the Pediatric AIDS Foundation.

DR. DIAZ: Pamela Diaz, pediatrician, infectious disease, Chicago Department of Public Health.

MS. STOVER: Rhonda Stover, FDA.

DR. HAMMER: Scott Hammer, infectious disease, Columbia University.

DR. MASUR: Henry Masur, infectious disease, Clinical Center, NIH.

DR. LIPSKY: Jim Lipsky, Director, Clinical Pharmacology, Mayo Clinic, Rochester, Minnesota.

DR. POMERANTZ: Roger Pomerantz, infectious disease, Thomas Jefferson University.

DR. HAMILTON: John Hamilton, adult infectious diseases at Duke.

DR. WONG: I'm Brian Wong from infectious diseases at Yale.

DR. FLETCHER: Courtney Fletcher from the College of Pharmacy at the University of Minnesota.

DR. D'AGOSTINO: Ralph D'Agostino, biostatistics from Boston University.

DR. GULICK: Roy Gulick from Cornell University, infectious disease.

DR. KUMAR: Princy Kumar, infectious diseases at Georgetown University.

DR. MATHEWS: Chris Mathews, University of California, San Diego, Department of Medicine.

DR. HAMMER: Thank you.

I'd like to turn now to Rhonda Stover who will read the conflict of interest statement.

MS. STOVER: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions.

In accordance with 18 United States Code 208, full waivers have been granted to Drs. Scott Hammer, John Hamilton, Henry Masur, and Princy Kumar. A copy of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information Office, room 12A-30 of the Parklawn Building.

In addition, we would like to disclose that Dr. Kumar's employer has financial interests in Glaxo-Wellcome which do not constitute financial interests within the meaning of 18 United States Code 208, but which could create the appearance of a conflict. The agency has determined, notwithstanding these interests, that the interests of the government in Dr. Kumar's participation outweighs the concern that the integrity of the agency's programs and operations may be questioned. Therefore, Dr. Kumar may participate fully in today's discussions.

In the event that the discussions involve any products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous involvement with any firm whose products they may wish to comment upon.

DR. HAMMER: Thank you.

Dr. Heidi Jolson will now make some introductory comments.

DR. JOLSON: Good morning and welcome to this morning's open session. I'd like to additionally extend a

welcome to this morning's consultants and guest speakers on today's topic.

In the next few minutes, I'll focus my comments on two areas: first, to provide the objective and context for this morning's meeting; and second, to comment on the multi-disciplinary nature of today's issue and, in particular, the composition of this morning's advisory committee.

Globally mother-to-child transmission of HIV is an enormous public health problem, and I believe that development of effective and feasible prevention strategies will be one of society's most challenging issues for the next century.

Recalling that FDA's mission is the regulation of drug products within the United States, today's session will be devoted to just one aspect of this complex global issue: the question of how drugs can be developed for perinatal HIV prevention with the goal of providing important information about their safety and efficacy and approved product labeling in this country.

While you will hear this morning that rates of perinatal HIV transmission have been reduced in the United States through a variety of strategies, mother-to-child transmission has not been eliminated and all patient populations are not being equally reached.

Additionally, while there are 14 antiretrovirals that have received FDA approval for treatment of HIV, only 1 of these products, zidovudine, carries specific product labeling to guide physicians in how to safely and effectively use this product in pregnant women and their children to reduce the likelihood of perinatal transmission. Because in practice many other antiretrovirals are used by pregnant women, there is clearly a need for more data and guidance on their safe and effective use for this population in product labeling.

The recent publication of the HIVNET 012 results for short-course nevirapine in women presenting in labor in Uganda raises a broad question for the agency. How can the results of this and similar foreign-based trials be applied to clinical practice in the United States, and by extension, can data from trials that were conducted to answer specific public health questions, appropriate for their particular nation, be used to support product labeling in this country?

The questions posed to the committee will address particular aspects of the applicability of these data, including differences in population and breast feeding practices, interpretability of comparator regimens, and the adequacy of follow-up for safety.

To help focus our discussion this morning and

to provide relevant background, we will begin with a series of invited presentations. First, Dr. Catherine Wilfert will discuss the epidemiology of mother-to-child transmission in the United States and will review the current U.S. Public Health Service task force recommendations. Next, Dr. Lynne Mofenson will provide an overview of previously conducted and ongoing clinical trials in this field. Dr. Stefan Wiktor will then provide commentary on issues unique to clinical trial conduct in developing nations.

Following our invited speakers, Drs. David Morse and Debra Birnkrant, both from the Division of Antiviral Drug Products, will provide commentary on antiretroviral safety issues for both mother and child and FDA regulatory considerations for the use of foreign data to support U.S. product labeling.

Before I close, I'd like to additionally comment on the composition of the advisory panel this morning. The division recognizes that effective prevention of perinatal HIV transmission requires a multi-disciplinary clinical approach, involving collaboration at a minimum between the pregnant woman, her delivering health care provider, other specialists in HIV management, and the child's health care provider. In formulating today's advisory panel, our intention and goal was to provide

representation from all of these areas with the objective of reflecting the multi-disciplinary clinical approach.

Unfortunately, due to an unexpected conflict of interest issue that arose just before the weekend, two invited consultants and two of our regular members were deemed ineligible to participate at this meeting by the Commissioner's office. Regrettably, this included an obstetrical perinatal transmission expert, and because lack of this expertise is a notable and unfortunate omission from the panel, I wanted to bring the circumstance to your attention.

Therefore, in this morning's discussion and in your consideration of our questions, please feel free to charge the division with the responsibility for soliciting input from relevant experts in obstetrics on particular matters.

Additionally and on very short notice, Dr. Lisa Rarick, Director of FDA's Division of Reproductive and Urologic Drug Products, graciously agreed to join us this morning as a resource to the committee on general obstetrical issues, and I want to thank her for her assistance.

Thank you for your attention and we look forward to a productive session and your guidance on these very important issues.

Dr. Hammer.

DR. HAMMER: Thank you very much.

I'd like to welcome Dr. Wilfert who will give us a discussion on the epidemiology of mother-to-child transmission of HIV in the U.S. and a review of the U.S. Public Health Service task force recommendations.

DR. WILFERT: Thank you, Dr. Hammer.

As most of you will appreciate, as soon as you see the first slide, I'm in a sense standing in for the folks who did this epidemiology, which is the Centers for Disease Control.

If I might have the first slide, please. I apologize because they sent me some of this material on Friday afternoon, which defeated my efforts to have them made into honest-to-goodness slides which are in the back of the room here.

The first slide just gave you the numbers that says that perinatal transmission accounts for 90 percent of acquisition of infection in infants in the United States and actually worldwide. The majority of the others are unknown as opposed to some mysterious mode of transmission, and it is because either the follow-up is incomplete or the information not obtained from the infants and/or a very small number of children who acquire infection by sexual abuse. So, for the purposes of this meeting, we're

actually considering that the vast majority of transmission in this country is due to perinatal transmission.

In the United States, the distribution of infection as recorded for children under 13 years of age and reported through 1998 is depicted on this slide. The colors of the states are those states where HIV reporting occurs, the orange states, or in the case of Texas where pediatric only HIV infection is reported, and the white states where it is not required.

Of interest I think is obviously that there continue to be a number of states with large numbers of HIV infection in the northeast, although New York, which is the largest, I believe has just changed to HIV reporting so that they report AIDS and HIV infection.

You may not be able to read these numbers. The white squares are AIDS and the blue numbers are HIV infection, but you will see from another slide that the concentration of children reported with either AIDS or HIV infection is in the southeast and the northeast of the United States and in California on the west coast.

Here are the number of infections reported, AIDS infection reported in children in 1998, some 382 which, as most of you know, represents a substantial decrease from earlier years in the epidemic, with the obvious concentrations of children being reported in 1998

as being in the northeast and Florida, California, and Texas.

I think it's important to keep in mind that there are clearly specific areas where transmission still occurs. Those areas help us to know how difficult it is to reach everyone and are part of our problem in trying to figure out how to continue the decrease in HIV infection in the United States.

If we look at the occurrence of HIV in women in the United States, I'm going to emphasize the interrelationship of the epidemic in women and children because it's obvious with 90 percent or more of transmission occurring to children, that the epidemic in women is directly related to what happens in children. The constant increase, so that the proportion of infected women is 25 percent, is clear from this slide by the end of 1998. The blue bars depict some decrease in the reported numbers of cases which I would expect my adult colleagues to tell me represents better treatment of persons with HIV infection and a decline in the reported AIDS cases. But this is obviously a tremendous change from the beginning of the outbreak where the proportion of women was substantially smaller.

The women who acquired infection in the beginning of the epidemic were intimately related to the

drug-using epidemic in the United States. At the present time, heterosexual transmission, if you combine sex with men who are at risk and/or using drugs, the proportion of women who acquire infection through sexual contact is reported as 38 percent, almost 40 percent. The proportion of women who use drugs is reported as 29 percent, and there are a couple of caveats about this information.

The first is that this is reported AIDS and the acquisition of infection by these women occurred some time ago. If you looked at 1998 in the acquisition of HIV, you might guess that some of these lines would have shifted somewhat.

The second caveat is that the definition of reporting of sexually acquired disease might be regarded as a little stringent: partners known to have risk factors, multiple sex partners, et cetera. So, the unknown category on this slide or not identified because of insufficient information undoubtedly also includes some women who acquired their infection heterosexually.

The reason that I am placing emphasis upon this is an attempt to have people believe that you can acquire HIV infection in the United States and not be an intravenous drug user, and that continues to be a perception amongst some of the care providers for women, which may be transmitted to the patients from the

standpoint of having women accept counseling and testing.

This shows you very clearly where the women with reported AIDS are in the United States and that relates directly to where the reported children are in the United States who have acquired infection from their mothers. The southeastern United States is heavily involved in this epidemic. From the beginning it has been predominantly heterosexual; that is, the majority of women have acquired their infection by that route.

Now, there is a slide that hasn't appeared here, and I wonder if it fell through. Unfortunately, it is the key to this whole discussion and I do not know if I can get at it. So, why don't we put the first transparency up and see if I can do it on this slide.

Here is the number of perinatally acquired AIDS cases by half-year of diagnosis and age from the Centers for Disease Control in children who are under 13 years of age. It's perfectly clear that the epidemic peaked, in terms of the numbers of children infected, in 1992-1993, and subsequently declined. The greatest decline has occurred in the children on the red line who are less than a year of age and the children from 1 to 5 years of age, and we all appreciate that that's related to the observation that zidovudine diminishes transmission. It also is clear and will be even clearer from the next slide

that the plateauing of the reported number of cases probably began in 1992 when, in fact, zidovudine treatment was becoming available for pregnant women.

Here is the curve that demonstrates through June of 1999 the decreases in perinatally acquired AIDS cases in the United States. This is obviously an incredible accomplishment for this country, and I think it's important to appreciate that nationwide this represents an almost 70 percent decline in perinatally acquired AIDS.

Recognize that this is AIDS, not HIV infection which is being reported and recorded on this graph, and that's important because there's probably a lag period, a matter of months often, but a lag period for the decrease in the number of cases.

Recognize also that the greatest decrease is in the less than 1-year-olds, which I just showed you on the slide, which is approximately an 80 percent decline and a decrease in the 1- to 5-year-olds of approximately 60 percent.

Now, let's talk about the epidemiology, and I'll say a few general things about the transmission to children.

First of all, receiving antenatal care in the United States is variable. If you look at national

statistics, you will get numbers which are cited in the materials given to you about approximately 1 percent of women not receiving antenatal care. Unfortunately, because of its variability, if you look specifically at HIV-infected women or HIV-infected women who are intravenous drug users, you will learn that there are rates of 15 percent or 35 percent or even 50 percent of these women who do not actually get perinatal care or don't have the diagnosis made until they walk in the door. Now, this is of the HIV-infected population, not of all pregnant women in the United States. But I emphasized in the beginning that there were some geographic variability. There are variabilities in the women who get antenatal care and the women who have the diagnosis made. So, it's important to appreciate that the blanket statements and our attempts to reach people still have some holes in them.

Of the children born to women who tested positive and whose testing was done either by the time of birth or before the time of birth, I think this slide shows very clearly that the number of HIV-infected children in green bars at the bottom has decreased, that the number of uninfected children obviously has increased.

I might just say a word about the indeterminate babies. It is that either the follow-up is incomplete or the samples not obtained to define their status. It's not

because we don't know how to determine their status, and the closer they are to the time of the acquisition of infection the more "indeterminate babies" there actually are. This is part of our general surveillance system and it is not perfect from the standpoint of follow-up of infants.

But I think it's completely clear that on a national basis, as reported in that other slide, that the women whose diagnosis is made you might assume are receiving zidovudine based upon the decrease in transmission to their babies, and the next slide actually substantiates that impression.

This is the receipt of zidovudine among perinatally exposed and infected children born from 1993 to 1998 whose mothers tested positive before birth or by the time of birth from 32 states. I think there are a couple of things to appreciate from these bars.

The first would be that the green bars, which represent any zidovudine treatment have dramatically increased from 1993 to 1998, so that it approaches 90 percent of the women who have the diagnosis made actually receiving zidovudine therapy. I think this tells us that when the diagnosis is made, the offering of antiretroviral therapy and the acceptance is actually very high, that it's likely there's a bigger problem in missing women and not

making the diagnosis or making it very late than there is in the acceptance of antiretroviral therapy.

The second thing to note are the yellow bars on the very end which is labeled "other antiretroviral therapy" which doesn't mean instead of zidovudine, but means anything, i.e., combination therapy, in addition to zidovudine. By the end of 1998, it had almost reached 40 percent. In North Carolina, Dr. Fiscus' most recent analysis of our data says it's closer to 60 percent of women who receive something in addition to zidovudine during the course of their pregnancies.

The other several bars indicate missing part of the three-part regimen; that is, if every mother-infant pair received all three parts of the regimen, all the bars would be the same height with a difference between the gray and white bars and the green bars represent mothers or infants who have missed part of the regimen. Usually the intrapartum administration of intravenous zidovudine is the easiest to miss because of unexpected rapid delivery because of not appreciating at the moment that the mother needed intravenous therapy because of difficulty establishing the line, the intravenous access. But be that as it may, the majority -- i.e., 90 percent -- of women who have the diagnosis made are actually receiving treatment.

That's the end of the overheads. Now, let's

see what slides materialize in the projector.

Now, let me say just a word about the guidelines before ending.

The guidelines appeared in 1998, and Dr. Mofenson can correct me, but I believe we are in the process of trying to assemble groups to reconsider the guidelines as we speak. The reasons for that will become apparent as I run rapidly through these, which I know are also in your handout materials.

For HIV-infected pregnant women who have not received prior antiretroviral therapy and for whom the diagnosis is made, the three-part zidovudine regimen is recommended and their therapy is to be as though they were not pregnant. So, for many of these women, they are obviously being treated in accord with the other adult guidelines and receiving more than zidovudine therapy.

All of the usual cautions about discussing the use of these drugs in pregnancy with women and at the bottom, where you probably can't see it, if a woman has never had any antiretroviral therapy, she may elect not to initiate her treatment until after the first trimester is over. That is, indeed, a discussion which should take place between the woman and her care provider.

For women who are already receiving antiretroviral therapy during their pregnancy, if it's

after the first trimester when they come to attention with their pregnancy, continuing treatment seems very reasonable.

If their pregnancy is identified during the first trimester, then they may wish to stop all their therapy and reinitiate their therapy at the end of the first trimester, and it is recommended that zidovudine be part of the therapeutic regimen.

Now, clearly these recommendations are made prior to some of other perinatal trials, in particular the Ugandan trial, which we're going to discuss in detail. Also, these recommendations were compiled prior to the results of the shorter-term AZT therapy in Thailand and in Africa.

If I go on to the rest of the recommendations, which are really very straightforward. If a woman arrived in labor and had had no prior therapy, it was recommended that she receive intravenous zidovudine and her baby receive zidovudine treatment. This recommendation is made obviously because the only experimental regimen involved treatment of women antepartum, intrapartum, and the baby postpartum, not because we had specific data that said that any specific part of the regimen contributed to diminishing transmission in the infant but because we had to assume that each component part of the regimen was relevant to

protection of the baby.

And the same thing is true for the recommendation that if an infant is born and the mother's diagnosis wasn't made and the infant is identified, hopefully in the first few days after birth, but if not, the recommendation is made to administer zidovudine as rapidly as possible, whether it's in the first few days or thereafter, not expecting that there would be great effects on transmission.

Subsequent to the publication of these guidelines, most of you have received in your packet I believe the paper by Nancy Wade from New York that is looking retrospectively at transmission in infants in New York with the suggestion that the administration of therapy intrapartum and postpartum to the infants may diminish transmission. But this is after these recommendations were made and based upon what was occurring in real life.

So, at the present time it is, to put it in a nutshell, recommended in the United States that zidovudine be administered whenever possible to pregnant women. Whenever possible, it's part of a regimen that begins as early as possible in pregnancy, potentially excluding the first trimester. It is administered intravenously during labor, although we have subsequent information to digest about the oral administration of drug.

We've achieved a remarkable decrease in perinatal transmission in the United States. We have residual areas where women either don't receive antenatal care or they come into the hospital for delivery and have their diagnosis made at the time of delivery.

I think I'll just stop right there.

DR. HAMMER: Thank you.

Are there any questions for Dr. Wilfert? Dr. Hamilton.

DR. HAMILTON: Are there any side effects of these drug regimens that have been identified that are of great significance, Cathy?

DR. WILFERT: The short answer is no, but the long answer is we have some hints of potential problems and we have not the ability to follow the thousands of infants who are exposed. And that's a critical part of our responsibility these days.

For 5-year follow-up in infants that were started on therapy in the 076 trial, there is nothing discernably different about that population developmentally, and there are no harmful effects in the mom. That's the good news.

The recent reports in Lancet, as you're probably aware, noting several children in the French studies that had mitochondrial toxicity and they were

infants exposed to zidovudine in utero have not been confirmed by a retrospective review of very large cohorts in the United States. That is not to say that it doesn't happen. It is to say that it's an observation that we've all paid attention to, have tried to establish that it's a risk that would change our recommendations, and we certainly have not been able to do that. But that would be part of the group getting together considering the guidelines as we bring them up-to-date.

DR. POMERANTZ: We may talk about this later today, but where do you put cesarean section in your use in the United States?

DR. WILFERT: Well, I think that's an important question. You know that there's one prospective study from Europe and there's a meta-analysis, and I believe that's included in your packet. The meta-analysis indicated that cesarean section decreased transmission even for the women who were receiving zidovudine. The prospective European trial showed a decrease in transmission but not a significant decrease in the women who were receiving zidovudine treatment. The transmission rates were 3.3 and 2.2 percent. So, each of these studies were done looking at women who received zidovudine therapy, not women who were receiving combination antiretroviral treatment. So, I think at the moment there is an ongoing study trying to

ask, for example, if nevirapine adds anything to existing combination antiretroviral therapy.

Where I put it probably doesn't make much difference because the appropriate groups have made recommendations. I would say that in North Carolina cesarean section rates have increased from something like 15 percent to 40 percent in the HIV-infected women, so there are people who are using cesarean sections. I think there are no data that convince me that that's an adjunct which further decreases transmission in the face of combination therapy, and I'm not sure it does when you're receiving zidovudine therapy. That's a personal opinion.

DR. KUMAR: Could I ask you a question? What do you make of the American College of Obstetrics recommendations that an elective C-section be offered to all these women irrespective of their viral load?

DR. WILFERT: I'll do the easiest part first. The irrespective of virus burden is because transmission has occurred at unmeasurable quantities of virus, so that part of the recommendation I certainly wouldn't argue with.

I think I've already said this is an area which I think exemplifies how rapidly information is acquired in the HIV arena. That is, if we had had information about cesarean sections before zidovudine was available, there would be no question. We would do cesarean section to

interrupt transmission.

Now we've acquired information about zidovudine, but we're past the primary use of zidovudine alone for the interruption of transmission, but we have a recommendation based upon studies related only to zidovudine use. So, while I personally think that people worked hard to make that recommendation, I'm not sure it fits present day practices with regard to preventing acquisition of infection. I think there's a little time lag here. That's again a personal opinion.

DR. HAMMER: Trip?

DR. GULICK: You said that more than 90 percent of women who are offered zidovudine actually accept that therapy. Is there a lot of geographic variation over that statistic also?

DR. WILFERT: Well, I think that there has been. Actually the Centers for Disease Control did several studies about offering counseling and testing, acceptance of counseling and testing, and acceptance of zidovudine treatment. I don't have the data in front of me, but in the beginning at least, in the early days of when they were trying to assess this, the northeast had greater problems with acceptance of zidovudine. The drug was not well perceived by some populations of pregnant women.

I hope if somebody is here who has the actual

data, they'll correct me if I'm misstating this. There's a greater variation in the acceptance of counseling and testing, and it relates very directly to what the care provider is transmitting to the woman. So, for example, in the northeast and in Florida, the acceptance rate was very high, as well as we have done in North Carolina, particularly in the private sector. The actual offering of counseling and testing was somewhat less than might be optimal. Therefore, its acceptance was less than optimal because it wasn't being offered.

DR. HAMMER: Dr. D'Agostino?

DR. D'AGOSTINO: You may have said it along the way. Excuse me if I missed it. You are reporting a fair amount of data. Are there ongoing concerted efforts to collect data prospectively on the different states, or is this mainly retrospective reporting?

DR. WILFERT: Well, there are a number of different studies, and as I said, I'm a stand-in. I'm not the person who is responsible for trying to set up these studies and acquire the data.

From the standpoint of infants and their mothers, it's a combination of prospective/retrospective. The pediatric spectrum of disease project, which is not in all states, but represents a substantial proportion of all infected infants, tries to ascertain, at the time of

recognition of the baby's birth, whether the mom was counseled, tested, accepted, refused. That's a longitudinal, ongoing study, and the charts are reviewed every 6 months on those babies trying to get those data. And the data are available by year of birth cohort.

There are also ongoing studies in women that include pregnant women by the Centers for Disease Control. They are surveillance data and they are trying to learn about the acceptance and rejection of counseling and testing. There are four states where the data have been published extensively already.

Lynne, do you have anything else that I might add? But there are several ongoing studies.

DR. D'AGOSTINO: Just to add to that, you mentioned -- and I saw also in the material -- that there's 15 percent, up to 35 percent, possibly up to 50 percent of the people with HIV who aren't, in fact, being given appropriate care and what have you. Are there efforts within the NIH, within the FDA to get at those individuals? Again, I missed if there were concerted efforts to actually improve that situation.

DR. WILFERT: The Institute of Medicine issued their report reducing the odds, as I'm sure you're aware. In conjunction with that and as a result of that, there has been approximately $10 million as Ryan White appropriated

funds which the Centers for Disease Control is trying specifically to target the weaknesses in the system with the administration of those funds in grants by grantees. So, that's one very targeted effort. There have been several meetings to ask how can the funds be best used to reach the populations that aren't being reached. $10 million doesn't go a long way in the entire United States the way that the problem is spread out, but there are clearly efforts in that regard.

DR. HAMMER: Dr. Lipsky.

DR. LIPSKY: Could you please clarify where combination therapy is fitting into this and what is happening? In other words, even if you saw someone within hours before delivery, would it still be just one entity or would it be multiple?

DR. WILFERT: Well, there's no guidance here. So, it's probably left up to the discretion of the care providers. The strong guidance is that zidovudine be administered no matter when the woman appears, both intrapartum and to the baby. That's clear. What happens in addition to that, there aren't any guidelines that tell people what to do.

If you do a survey and break down the other parts of the treatment, you'll find out that for the first years, AZT and 3TC were used together. You'll find that by

now there is a substantial proportion of people who are trying to think about the administration of nevirapine, and this is clearly for women who haven't received any antiretroviral therapy who are walking in the door.

We get questions all the time. What do I do? This mom stopped and started her therapy 13 times in the past. Now she has come in. Maybe she has resistant virus. What do I do? And the answers are that you always give zidovudine, and you think about giving 3TC. And now you clearly think about giving nevirapine because we know it works.

DR. LIPSKY: And that is together?

DR. WILFERT: Well, it depends. There are no recommendations and we don't know if it's additive. So, we know nevirapine works. We could guess. But we didn't know it before the results of the Ugandan trial. So, again, this is a personal opinion because there aren't any guidelines.

I now know two regimens that work if started intrapartum based upon studies done outside this country, AZT, 3TC, and nevirapine. And I think if a woman has had zero antiretroviral therapy, she deserves one of the regimens that we know works when it's started that late. Now, what else you do I'll let other people decide.

DR. LIPSKY: But do you know what others are

doing? Is there a developing standard of practice with combination therapy, or do we simply not know?

DR. WILFERT: I don't think we know. We can dissect it from the information the CDC receives because they are recording the drugs that women have gotten, but I don't know.

DR. HAMMER: Please.

DR. HANDELSMAN: Would you consider cesarean section as part of the regimen for someone who presents intrapartum?

DR. WILFERT: Yes, which is to say that I think it should be discussed with the woman if her diagnosis is clear. The woman who has had no prior antiretroviral therapy, those are the data that I think are the strongest about cesarean section. So, would I consider it? Yes.

DR. HAMMER: Thank you. I think we need to move on. Thank you, Dr. Wilfert.

Dr. Mofenson will now present an overview of the clinical trials in this area.

DR. MOFENSON: Just a comment, Ed, that if a woman is already in labor, cesarean section is not going to do anything. So, if a woman is presenting intrapartum in labor, I don't think that it's going to be very beneficial to her based on the data we have.

I'm going to take you through a very whirlwind

tour of clinical trials both in the U.S. and internationally. To facilitate your understanding of my rapidly going through this, I have two handouts that you all have. One is a schematic handout that basically lists all the different trials, and the second one, which is the bigger one, has more detail on each of the trials. You don't need to refer to them now, but I think as time goes on in your discussion, you may want to look at these later.

I'm going to first talk about trials in the United States, and then I'm going to move to the trials that are being done internationally. I'm not going to be discussing any issues regarding long-term toxicity, but as has already been brought up, that is really a critical issue, particularly in the United States where women are increasingly using multiple drugs during pregnancy and infants are being exposed in utero to multiple drugs. We can talk about it if you have questions.

This just shows you the scheme for the 076 trial that produced the remarkable results that Cathy has already talked about. At the time this trial was designed, we did not have a good idea as to the proportion of transmission that occurs in utero versus intrapartum. This trial was designed in 1989. Therefore, the trial was designed to target multiple potential time points of transmission.

It was started at 14 weeks gestation to target transmission occurring in utero, but after the first trimester. It was given intravenously during labor with an initial bolus dose to get the mother's level up to virucidal levels and then in a continuous infusion so that the baby would be born with levels that were virucidal regardless of whether it was 1 hours of 4 hours or 24 hours after she presented in delivery.

The purpose of the intrapartum administration has nothing to do with the viral load in the mother. The purpose was to provide drug to the infant during passage through the birth canal.

Then finally, the baby was given drug for 6 weeks. This was to provide post-exposure prophylaxis against potential maternal cells that might have entered the fetal circulation during labor.

This should be pretty familiar to anyone in pediatrics or infectious disease or obstetrics. This is the results of the trial. Transmission was 8 percent with zidovudine, 26 percent with placebo, almost a 70 percent reduction in transmission.

This trial was conducted among healthy women. This was a placebo controlled trial, and therefore entry was restricted to women who did not require antiretroviral therapy. So, the women had to have CD4 counts over 200,

receive no antiretroviral therapy during pregnancy, and not require antiretroviral therapy. So, it was a very specific, healthy population of women.

So, the next question was is this treatment going to be effective in women with advanced disease or who have prior antiretroviral therapy.

A second trial was actually begun while 076 was ongoing and this is trial 185. This was designed for women with advanced disease, all of whom were receiving zidovudine. Everyone, the mothers and the infants, got the 076 regimen. It asked what about if you had zidovudine and you combined it with passive immunization with an HIV hyperimmune immunoglobulin, compared to regular immune globulin without HIV antibody. So, that was zidovudine plus HIVIG versus zidovudine plus IVIG.

The sample size for this study was estimated to be 800 and that was based on the following. We knew that women with advanced disease had much higher rates of transmission than healthy women, like the women that were in 076. Therefore, it was hypothesized that even though these women were receiving zidovudine, that the transmission rate would likely be higher than we saw in 076, and it was estimated it would be between 11 to 15 percent.

There was an interim analysis allowed in this

protocol to be able to see whether our estimated sample size of 800 was correct, and we knew that if the observed combined transmission rate was above 7.5 percent, that we would have adequate power to address the issue.

This is just to provide you a comparison of the 076 versus the 185 patients. 22 percent of the patients in 185 had CD4 counts under 200 compared to none of the women in 076. Almost a quarter of the women in 185 had received zidovudine prior to pregnancy, many for prolonged periods, several years, whereas only 5 percent in 076, and in these women it was only a few weeks. And almost 19 percent of women in 185 had RNAs over 50,000 compared to 7 percent in 076.

These are the results at the interim analysis. Despite the advanced disease stage in these women, the overall transmission rate was only 5 percent. We were very surprised at this. The transmission rate in the HIVIG arm was 4.1, in the IVIG arm was 6.1. This was not statistically significantly different. The p value was .34. Then based on the fact that in order to adequately address this question, we would have had to increase the sample size to a very large number of women, and this product, which was purchased by NHLBI, was a very expensive product. Therefore, the data safety monitoring board recommended stopping enrollment into the trial, and that's

what we did.

Although we were initially surprised at this low rate of transmission, this is just to give you a feel for four different epidemiologic studies, all of which have looked at women getting no zidovudine compared to women getting zidovudine. You can see that the transmission rate in women who received all three parts of zidovudine is 3 to 5 percent in all of these studies. So, the 185 results likely reflect the effect of zidovudine.

What about the mode of delivery? We now know that most transmission occurs intrapartum, or at least near to or during delivery. There was a randomized trial conducted in Europe, the European Mode of Delivery Collaboration. This took HIV-infected women who did not have an obstetric indication for cesarean delivery, enrolled them at 36 weeks, and randomized them to elective cesarean prior to labor, prior to rupture of membranes, performed at 38 weeks compared to vaginal delivery. 408 women were enrolled.

This shows you the results of the study. This is an intent-to-treat analysis. If you look at the randomized assignment, the transmission rate was 11 percent in women randomized to vaginal compared to 2 percent in women randomized to elective cesarean delivery. This was statistically significant.

A number of women randomized to cesarean had vaginal delivery. A number of women randomized to vaginal delivery had an urgent cesarean section. So, they looked then at it as actually delivered, as treated. And the transmission rate in the vaginal delivery and the urgent cesarean -- this is cesarean after labor, after rupture of membranes -- was not significantly different. So, the only benefit was seen with elective delivery, 2 percent.

This breaks it down by zidovudine, and I believe that this is by the as-treated analysis. They presented in that paper two analyses of with zidovudine.

Anyway, this is the women who did not receive zidovudine. Transmission was about 20 percent with vaginal delivery, decreased to 4 percent with elective cesarean. And with zidovudine -- Cathy is correct -- even this is not statistically significant, but those women who had vaginal delivery, 4.3 percent, and with zidovudine it was about 1 percent in those women who actually had elective cesarean delivery.

There are a number of very critical questions about cesarean delivery. First of all, we don't know the morbidity in HIV-infected women, and there are a number of studies indicating that cesarean delivery may be associated with higher morbidity in infected women than in uninfected women. And a very critical question is whether cesarean

delivery is going to be beneficial regardless of viral load or potent antiretroviral therapy. One would imagine that if a woman has a risk of transmission of only 1 to 2 percent, that the risk of cesarean delivery to the woman is going to probably far outweigh the benefits to the baby.

So, what about using a regimen targeted intrapartum that's not cesarean delivery? Although this is from a slide from actually a trial I'm going to discuss in a few minutes, I think it's relevant here because we're doing a study with nevirapine in the United States.

Nevirapine is an ideal intrapartum/postpartum intervention. It's a very potent antiretroviral. It's rapidly absorbed, crosses the placenta very rapidly, so levels in the baby are almost exactly the same as levels in the mother, has a long half-life, short-term safety, and is inexpensive.

We're currently doing a trial in the United States that's looking at standard of care antiretroviral therapy. So, that was initially zidovudine. Now as Cathy talked about, it's combination therapy. And it is looking at whether the addition of an intrapartum/postpartum intervention, giving nevirapine once to the mother at the onset of labor and once to the baby at 48 hours, compared to placebo plus standard therapy, will further reduce the risk of perinatal transmission.

This study is ongoing in the U.S., in many sites in Europe, in the Bahamas, and soon in Brazil, and will enroll -- I think the sample size is now about 1,900 patients -- right, John -- to pick up a 40 percent decrease. We should have this trial enrolled probably by the fall of 2000.

This is just to let you know that there are a large number of other trials going on in the PACTG phase I studies that are looking at some of the nucleoside analog combinations, that are looking at all of the currently available protease inhibitors in combination with ZDV with the exception of amprenavir, because amprenavir had some concerning animal study data. And there are plans to look at abacavir and PMPA as well.

Finally, the last in the U.S., there are plans to do a study targeted specifically at those women who have no prenatal care and who come in labor. That is to look at whether we are going to be able to offer rapid testing to women in labor and then offer to those women an intrapartum/postpartum or potentially a postpartum only intervention to the infant. Clearly with the 012 data, this means that the standard of care would be nevirapine. So, nevirapine would be offered and compared to some combination with nevirapine. This is in the concept sheet stage and hopefully we'll be able to have this in a

protocol next year.

I just wanted to move on to global perinatal infection. Our transmission in the U.S. was and still is a drop in the bucket compared to the global situation. Globally over a million children are living with HIV infection, and about 1,600 newly infected babies are born every day.

Breast feeding is a major component in risk factor for transmission in the developing world. This just is to show you the risk of early breast milk transmission. This is from a paper recently published in JAMA. This shows you that the major risk of breast milk transmission is likely very early, in the first 6 months of life, and then decreases with further breast feeding, but there is continued risk.

To give you another view of this, this is a study of late breast milk transmission that appeared in Lancet last year. This is looking at transmission occurring after about 2 months of age. So, there is probably a large bulk of transmission occurring here that we're not seeing. But you see that there's a continued risk of transmission through breast feeding as long as the infant is breast feeding.

So, the next question is, are there simpler antiretroviral interventions more applicable to the

developing world that might reduce transmission? The strategies that have been employed are we know that most transmission occurs intrapartum, and therefore interventions have been focused to late gestation and intrapartum. The regimen needs to be relevant to the developing world, and therefore we need to minimize the amount of drug being given and hopefully eliminate the postpartum component and try to make it simple. Drug is generally given orally intrapartum instead of intravenously, and then we need to look at whether breast feeding would diminish the efficacy of the regimen. And there have been a number of different tactics taken for breast milk transmission.

This slide schematically shows you the design of the different short-course antiretroviral trials that have been completed internationally. This line shows you the 076 regimen started at 14 weeks, prophylaxis to the baby for 6 weeks. The zidovudine regimens are shown in orange. The strategy here has been to start the drug at 36 weeks and give it orally during labor with or without a postnatal component, and the postnatal component has been very short, 1 week, given to the mother.

Additionally, zidovudine and 3TC combination has been evaluated in a study called PETRA sponsored by the UNAIDS, conducted in several countries in Africa. This has

looked at a short antepartum, intrapartum, and 1-week postpartum to the mother and the baby and compared that to an intrapartum/postpartum and an intrapartum only intervention compared to placebo.

And finally, the HIVNET 012 study that has looked at nevirapine given during labor and then once to the baby.

This is the first of the short-course trials that results became available. This was from a study in Thailand conducted in a non-breast feeding population. This was the short antepartum/intrapartum regimen starting at 36 weeks, given orally intrapartum. The zidovudine group had a 50 percent reduction in the risk of transmission, and this reduction was obvious by age 2 months. You can see that after 2 months there's no further infection. So, this tells us that shorter zidovudine regimens work, although they may not work quite as well as the full three-part regimen.

Now, that trial was conducted among non-breast feeding women. We talked about the importance of breast feeding. In the developing world, safe milk alternatives are not really available.

These are new data since the publication on long-term follow-up from the short-course antiretroviral zidovudine trials. This is actually Stefan's trial. This

is the exact, same regimen as used in the Thai regimen, but studied in breast feeding women in the Ivory Coast.

What you see here is that the zidovudine group at all time points after birth has a lower transmission rate than does the placebo group, but there does appear to be some diminution of efficacy with continued breast feeding. Also in contrast to the Thai trial, you see that after 2 months of age, there is a continued risk of transmission among both groups. At 1 month of age, the efficacy was 44 percent and at 24 months, this had decreased to 24 percent.

This is a second regimen that was studied by the French in the Ivory Coast and Burkina Faso. The difference with this regimen is that antepartum was started at 36 to 38 weeks. Only a single oral dose was given intrapartum, and then postpartum for 1 week to the mother was given. The results of this trial are basically superimposable on the previous trial that you saw that had no postpartum component. Again, transmission continues to occur after 2 months of age. One comment I'd make is that most breast milk transmission has occurred by 6 months, and efficacy which was 49 percent at 3 days decreased to 30 percent at 15 months, but this was still statistically significant.

This is an unpublished trial in Thailand again

in non-breast feeding women that compared four arms with differing duration of zidovudine. It compared a long regimen, an 076-like regimen. This started at 28 weeks, was given orally intrapartum and then the baby got 6 weeks of oral drug. This was compared to a short regimen starting at 36 weeks, orally intrapartum, and only 3 days to the baby. Then you can see that it was compared short-long and long-short.

In the late summer this year, the data safety monitoring board did a first interim review and recommended that the short-short arm be stopped because the transmission rate in this arm was statistically significantly higher than in this arm. This was a safety review. The transmission rate in the short-short arm was 10.6 percent, and if you think back to the Thai trial, that's about the rate they saw in their short zidovudine arm compared to placebo.

The remainder of these arms are still being enrolled to, and hopefully data from the trial will be available by the middle of the year 2000. It just confirms I think what we already knew which is that longer is probably more effective than shorter. Shorter is still effective.

These are results, very short interim results, from the PETRA study that we talked about. Remember we

were comparing an antepartum/intrapartum/postpartum, intrapartum/postpartum, and intrapartum regimen. Data are only available through age 6 weeks. Transmission at age 6 weeks was 9 percent with three parts, 11 percent in the two-part, and 18 percent in the one-part arm. And this was 17 percent here, which gives us an efficacy of 50 percent with the three arms, 37 percent with the two arms, but unfortunately no efficacy with the intrapartum arm.

These are the results from the HIVNET 012 trial which I think finally bring us to the possibility of being able to globally impact on HIV transmission in the developing world. This was looked at in Ugandan pregnant women who enrolled at 36 weeks gestation who were breast feeding, and it compared intrapartum/postpartum nevirapine, a single dose to the mother given orally at the onset of labor, a single dose to the baby given at 48 hours, and it compared this to an intrapartum/postpartum zidovudine regimen where zidovudine was given every 3 hours during labor and then for 1 week postpartum to the baby. Remember, this is a breast feeding population.

These are the data that show you the results over time. The transmission rate at basically birth was not statistically significantly different between the two arms as one would expect since you weren't giving anything antepartum, but by week 6 to 8, there was a statistically

significant difference with the transmission rate in the nevirapine arm being 12 percent compared to 21 percent in the zidovudine arm. And at 4 months of age, there was really not a whole lot of increase in the transmission in the nevirapine arm. It was now 13 percent and 25 percent in the zidovudine arm, and you can see this is highly statistically significant, which is why the trial was stopped. I think Brooks Jackson produced a publication in the most rapid time that anyone in the world has ever gotten anything published after a trial has been done, 4 weeks.

This just gives you a summary of those data, which was that nevirapine was 47 percent more effective than zidovudine in this population, and if one makes the assumption that zidovudine had some effect, then likely nevirapine has even more of an effect if it were being compared to placebo.

So, what can we learn from the antiretroviral trials?

Well, first both antepartum/intrapartum and intrapartum/postpartum interventions significantly reduce transmission. That's been shown by a number of these trials.

Data I haven't shown you are that the antepartum interventions probably work by lowering maternal

viral load.

Unfortunately, intrapartum strategies alone -- that is, providing the baby only with pre-exposure prophylaxis -- does not appear to work with the exception of elective cesarean delivery that we talked about. At least, it doesn't appear to work in breast feeding populations. Therefore, the neonatal prophylaxis piece is likely a critical important component based on the results of HIVNET 012 and the PETRA trial, and that there is continued transmission while breast feeding. So, we still need to be able to develop an intervention capable of further reducing transmission in women who require to breast feed.

I'm going to give you a very brief run through the non-antiretroviral trials. There were two vaginal cleansing trials done in Malawi and Tanzania with low levels of chlorhexidine. This is where women come in in labor and they have their vaginal area and cervix swabbed with chlorhexidine, and then the baby has a wash. Unfortunately, there was no significant difference in transmission in either of these studies, although there was in one study a trend, a significant difference in women with prolonged duration of labor. However, there was a significant decrease in maternal and infant morbidity and mortality in the chlorhexidine arm.

There have been three vitamin A or multi-nutrient studies done in Africa. In each of these studies, there has been no impact on perinatal transmission unfortunately, but again a very significant decrease in maternal and infant morbidity and mortality.

Finally, there was a breast versus formula trial performed in Kenya. I'm going to show you that result. This trial showed that with formula, a 43 percent reduction in transmission was seen. The formula arm is shcwn in orange here, and I just want to point out that there was only 70 percent adherence to the formula arm. So, this efficacy was seen despite the fact that some of the women randomized to formula also breast fed.

The breast feeding arm here is shown in yellow. Transmission was 37 percent at 24 months in the breast fed versus 21 percent in the formula fed, and mortality did not appear to be significantly different. I do want to point out that this was done in an urban area in Africa where clean water is available, and this is probably not applicable to more rural ares where clean water is not available and a sustainable source of formula is not available.

This is just a summary of the prevention studies. I don't have a slide but would just briefly like to describe to you some of the trials that are currently

ongoing internationally.

In terms of perinatal treatment of STDs and chorioamnionitis, I haven't presented you the data, but a number of studies have shown that chorioamnionitis appears to be related to the risk of perinatal transmission, and there's one trial that is going to look at antibiotic prophylaxis given during late pregnancy and labor to see whether that can reduce the risk of transmission.

A number of other antiretroviral regimens are being looked at, including PMPA. There's a phase I study to look at that, another long-lived drug for which there's good animal data in terms of prevention of transmission with a similar regimen as given for nevirapine.

I'll talk about the breast feeding ones in a moment.

In terms of immunotherapy, the concept is that one could provide a regimen such as the nevirapine regimen and then give something additional to prevent breast milk transmission, and a number of different approaches are being used, including the use of passive immunization with HIVIG being studied in Africa, potentially the use of a vaccine. There's a phase I study of the canarypox ALVAC vaccine that's going to be done in Africa. And then the idea of giving antiretroviral drugs to the baby for a certain period of time followed by early weaning, and that

is being studied in India and Ethiopia and South Africa.

There is an additional trial, which I think will be very interesting, that's comparing the intrapartum/postpartum nevirapine to the intrapartum/postpartum ZDV/3TC.

There is one more antiretroviral trial that's being conducted in South Africa. It's a phase II and it's comparing short-course ddI alone versus d4T alone versus combination ddI and d4T versus zidovudine, the short-course zidovudine.

I think that's the end of this rapid tour.

DR. HAMMER: Thank you very much.

DR. MOFENSON: Does anyone have any questions?

DR. HAMMER: Questions? Dr. D'Agostino.

DR. D'AGOSTINO: Thank you very much for that presentation.

The studies where you have the long-term, short-term and so forth, I think the data is quite impressive that the more, the better.

Are there follow-ups in terms of other potential safety problems to the child and the mother?

DR. MOFENSON: In Thailand you mean?

DR. D'AGOSTINO: Well, even in the U.S., all of these studies where there are different regimens, and the more complete regimen seems to be better.

DR. MOFENSON: Right.

DR. D'AGOSTINO: But is there an implication of potential safety factors later on?

DR. MOFENSON: Yes, there is a study called 219 in the PACTG that was designed to provide long-term follow-up to infants whose mothers were enrolled in perinatal trials. That follows the children through age 21 years and includes periodic evaluation of a variety of different laboratory tests looking for organ toxicity as well as echocardiograms, et cetera. Initial results of that were presented in a publication in JAMA last year that Cathy was talking about, and with follow-up through 6 years, there didn't appear to be any difference in immune development, growth, or neurodevelopment in the children.

There is not currently a very good way to provide consistent follow-up for the large number of babies who are receiving in utero exposure outside of perinatal trials. The CDC does collect information about antiretroviral exposure on their HIV reporting forms, and when we began to look at the potential for mitochondrial toxicity after the French data, we were able to take data from the PACTG, from our natural history studies, funded by the NIH and the CDC, as well as surveillance, and pool all of that data together. Based on that, we looked at records of over 15,000 uninfected children and we looked

specifically at deaths, and in that group of children -- I think there were about 40-something deaths -- we did not see anything that was related to mitochondrial disease.

But we're currently in the process of doing a retrospective evaluation looking at the living children to see whether any of them have mitochondrial symptoms. This is not easy and it needs to be done prospectively. We don't have a good mechanism for that yet.

In the developing world, I think that kind of follow-up is going to be extremely difficult and maybe Stefan can talk a little bit about what has been done in the Ivory Coast and maybe he knows a little bit about what has been done with the CDC study in Thailand.

DR. HAMMER: Dr. Pomerantz.

DR. POMERANTZ: I've seen some small cases about levels of antiretrovirals in breast milk. Is there good data comparing and contrasting the different new antiretrovirals, not only levels but antiviral activity from breast milk in women?

DR. MOFENSON: My understanding with zidovudine is that although it gets into the breast milk, it's in really tiny amounts and was not felt to be sufficient to be protective. Nevirapine does pass into the breast milk, but I don't know that we have any real good studies about the association between the levels and viral load of the breast

milk. I'm pretty sure we haven't looked at that yet.

I don't believe we have much data on any of the other drugs. I'll just comment that the protease inhibitors do not appear to, at least, cross the placenta very well. Whether they're going to get into breast milk I don't know. But I think it's the assumption of most researchers that having the drug present in the breast milk is not going to be the way to really interrupt, but rather to provide the infant with some protection for some critical period followed by early weaning.

DR. HAMMER: Dr. Masur?

DR. MASUR: You mentioned that cesarean section doesn't appear to work after labor is induced. Could you expand on that a little bit about why you think that doesn't happen if delivery has not, in fact, yet occurred?

DR. MOFENSON: I think that there are probably two different mechanisms for intrapartum transmission. One is when maternal blood is transfused into the fetus during uterine contractions, and there actually have been studies that looked at that and found an average of 3 cc's of maternal blood pass into the fetus during labor. So, clearly if labor has already started, it's not going to prevent transmission that way.

The other mode of transmission is when the infant is exposed to the secretions directly, it swallows

maternal genital fluids and blood, and that's the place where one might think that cesarean section might have some additional efficacy. What this might be telling us is that maybe the intrauterine transfusion is a more important piece than the intrapartum exposure, direct exposure, but I don't know that we have any real data to address that.

DR. HAMMER: Dr. Handelsman?

DR. HANDELSMAN: Lynne, all of these short-term studies that are being done seem to involve the reverse transcriptase inhibitors and not the protease inhibitors. Is there a particular pharmacologic or safety reason for that?

DR. MOFENSON: In the U.S. you're talking about or in the developing world?

In the developing world, I think it's completely unfeasible to look at protease inhibitors. They're just not going to be available. They're too costly. I think we need to have there as short a regimen as possible. Ideally it would have been a single dose at labor if it worked. That's what you need there.

In the U.S., I think it's going to be very difficult to try to assess. If we get transmission to below 2 percent, which I think is the hope that we would get with the nevirapine, it's going to be very difficult to assess any additive effect other than through epidemiologic

studies.

DR. HAMMER: Dr. Hamilton.

DR. HAMILTON: Since some of these trials, particularly those in the States and in Europe are utilizing multi-drug combinations in therapy, have there been any efforts to systematically assess the frequency with which genotypic resistance is passed on, and is there some selectivity of transmissibility based on presence of resistance mutations?

DR. MOFENSON: Yes, it's a very good question, and I have a whole series of slides that I don't have with me on that. But the data I think from 076 and a number of other studies indicate that resistance at least today does not account for the majority of zidovudine failures.

There was an interesting study presented by Paul Palumbo three weeks ago at a global strategies meeting on perinatal transmission where he looked at the prevalence of RT mutations both against the nucleosides in total and against ZDV in particular. 24 percent of the population of over 200 women had one or more resistance mutations to a nucleoside. 17 percent had resistance to zidovudine, but the transmission rate in those who had and did not have the resistance mutations was the same. So, there is data from one study that suggests that potentially resistant virus may be less fit in terms of transmission. It looked at

women who had mixed viral populations and then looked at what their infected babies had. So, women who had a mixture of wild type and mutant virus in general had the wild type virus present, not the mutant virus.

I don't know what we're going to have happen as things go on in the future, and clearly that's going to need to be monitored.

DR. HAMMER: Can I ask a corollary question, different but important? Have any of the isolates from the babies who were infected on the nevirapine arm in 012 been looked at for NNRTI associated mutations?

DR. MOFENSON: Brooks, I don't think we've done it yet. Right? No, not yet.

DR. HAMMER: Dr. Gulick.

DR. GULICK: One thing that strikes me, looking at some of the studies, is how well tolerated zidovudine appears to be in pregnant women. It's in contrast to naive non-pregnant patients taking zidovudine where there's a relatively high incidence of GI intolerance, for instance. Is that seen pretty much across all the studies that it's well tolerated?

DR. MOFENSON: Yes. My impression is that adherence has been very good. Actually in the 076 study, there was absolutely no difference in terms of anemia or liver functions between zidovudine and placebo women.

DR. HAMMER: Thank you. I think we need to move on. Thanks, Dr. Mofenson.

DR. DIAZ: Scott?

DR. HAMMER: I'm sorry. Dr. Diaz.

DR. DIAZ: I just had a quick question. With the post-exposure infant prophylaxis trial, could you just go back and review that briefly?

DR. MOFENSON: It would start with a pilot that's going to be able to look at can we do rapid testing during labor, and that's a question I think that still needs to be answered, although I will say that a number of sites in the U.S. -- Toulane, for example -- have already set up rapid testing during labor programs. New York I believe is also setting up a rapid testing during pregnancy program. So, you'd offer a rapid test to the woman and if she has an initial positive on a rapid test, she would be offered nevirapine. The initial positive would then be confirmed postpartum. It was confirmed postpartum, the baby would get nevirapine. That would be the concept, and then they would be compared to two drugs or three drugs. It hasn't been decided yet.

DR. HAMMER: Dr. Jolson.

DR. JOLSON: Lynne, first, thank you very much for that excellent overview.

I just wanted to get your thinking on something

that I've wondered about since seeing the Lancet publication of the HIVNET study. You pointed out the observation that rates of transmission shortly after birth were very similar between the nevirapine and placebo group and then the curves diverged I think at the 6-week time point. You also made the comment that your interpretation was that that showed that the dose that was given to the child after delivery was important.

My question for you is your opinion about whether or not that effect is related to prophylaxing the child against subsequent exposure to the virus through breast feeding or somehow it's providing prophylaxis from the inoculum that was received during delivery.

DR. MOFENSON: Well, the only trial we have that looked at an intrapartum intervention and showed it didn't work was the PETRA trial which was in a breast feeding population. So, I can't tell you that.

My guess is that it's both. My own personal feeling is I think it's both, that you need both. My own feeling in the U.S. is that the population for which 012 is ideal for is the women who are coming in without anything who present at labor, that that is a very important target group for the use of nevirapine instead of using AZT which in my view is and was an unproven regimen, what we were previously recommending.

DR. HAMMER: Dr. Lipsky.

DR. LIPSKY: A very quick question. What's known about the rate of spontaneously clearing in a neonate of HIV? I got to feel that it does occur, but is there any handle on that?

DR. MOFENSON: Well, there was a paper by Lisa Frenkel. She looked at, I think, 30-some cases -- is that right, Cathy -- of supposedly cleared virus and found out in most cases the positive tests on the babies had been lab errors. So, whether it actually occurs or not I don't think has been proven.

Thanks.

DR. HAMMER: Thank you very much.

The next speaker is Stefan Wiktor who will talk about the conduct of trials in developing nations.

DR. WIKTOR: Good morning. I appreciate this opportunity to share some of my experiences and thoughts regarding the planning and conduct of research to prevent mother-to-child transmission of HIV-1 in developing countries.

A brief introduction. I work at the Division of HIV/AIDS Prevention at CDC. Up until recently I was stationed in Abidjan, Ivory Coast, where I was the Director of Projet RETRO-CI, which is a large AIDS research project. It's a collaboration between CDC and the Cote d'Ivoire

Ministry of Health. While there, I was the principal investigator in one of the short-course AZT regimens that were just presented. Before that, I was here in the Washington area working at the National Cancer Institute at the Viral Epidemiology Branch focusing on HTLV-1 perinatal transmission.

In covering today's topic, I just wanted to cover a few points. First, try to set the scene and contrast some of the differences that are in the health-related and HIV-related situation in developing countries. For the developing countries, I'll be focusing primarily on Africa since that's where the contrast is perhaps most stark with the situation in the United States, and also that's the area where I have the most experience.

Then I'll cover some of those logistical challenges to conducting perinatal interventional research trials in Africa, give some of our own data, giving you some of the background of how one study was conducted, and then discuss a little bit of what are the things that should be kept in mind in interpreting data from international studies.

In trying to compare the situations in the U.S., Europe, and developing countries, especially Africa, there are so many differences, it is hard to know where to start. However, this table tries to summarize at least

some of the major differences in the health status and the level of health care in the two, as it relates to antenatal and obstetrical care.

First of all, the burden of HIV disease, as you obviously know, is very different. In the United States, the prevalence of HIV among antenatal patients is less than 1 percent. In Africa, the range is large. However, in many urban settings, the prevalence is between 10 and 30 percent; in some settings, for example, in southeastern Africa, even greater than 40 percent, for example, in Botswana.

The baseline differences of pregnant women coming in for antenatal care is very different. This can affect the rates of transmission and also affect perhaps the magnitude of the effect seen from interventions. Some of these differences are a higher prevalence of anemia and vitamin A deficiency, as well as other micronutrients due to nutritional deficiencies and due to chronic malaria causing anemia. There's a much higher rate of sexually transmitted diseases, including chorioamnionitis. All of these are risk factors for transmission and are part of the explanation for the higher rates of transmission seen in developing countries.

Access to prenatal care is also very different. In the U.S., it is generally good, although as you've

heard, there is some proportion of women that do not access prenatal care. In Africa, that proportion is much greater and the level of antenatal care is very variable. In some urban settings, it's available. In many rural settings, it is totally unavailable. Even in the settings where it's available, the level of care is not always the best in the sense that there are many barriers to good access to care. Women come for perhaps one or two visits and don't return because of financial barriers or because of the poor quality of care that they receive and the amount of time that they spend at the prenatal clinic.

We heard earlier some of the HIV-specific obstetrical practices that are recommended or at least common in the United States. The best example is cesarean sections. In most African settings, that is unavailable and is not practiced.

Turning now to some of the more specific differences regarding HIV prevention in the perinatal setting, in the U.S. HIV antenatal counseling and testing is widely available and seems to be well accepted, with most women accepting the testing and getting appropriate post-test counseling. That is unfortunately not the case in Africa and in other developing countries. Outside of research settings, HIV counseling and testing is largely unavailable. There are perhaps some notable exceptions,

for example, Botswana in South Africa. But even in settings where it is available, it is poorly accepted, and the rates of acceptance of testing vary but the rates of refusal are between 10 and 30 percent of women who refuse, and a significant proportion of women don't come back for their results. Part of that failure to return for results is what I mentioned earlier, the difficulties to access health care, and part of it is sort of a delayed refusal perhaps for the HIV test. This will present a significant barrier to any implementation of perinatal interventions on a wide scale in Africa.

The standard of care for the prevention of transmission in the U.S. is, of course, the ACTG 076 regimen. In Africa, the standard of care remains no prenatal or intrapartum care for the specific interventions for the prevention. That is changing now with some pilot programs in some countries sponsored by UNICEF and a French initiative to try to at least make available counseling and testing and prenatal AZT.

A major difference is the feeding practices recommended. In the U.S. as in other developed countries, women are counseled to formula feed, and in Africa, although the recommendations are changing, the reality is, though, the vast majority of HIV-infected women breast feed their infants.

The therapy for the mother's HIV disease is also different. Here many women receive antiretroviral therapy for their own disease, and due to the unavailability of antiretrovirals, that is very, very uncommon in Africa.

In view of these differences, what can we say about the directions for future research in Africa and in the U.S.? Although globally the objectives are the same -- that is, to maximally reduce mother-to-child transmission of HIV-1 -- the way in which that should be approached is obviously very different.

In the United States, currently the goal would be to develop strategies that will identify all HIV-infected pregnant women and to treat them with the most effective regimen. The current challenge is to provide treatment to the women who do not access prenatal care and who don't have an HIV test result prior to going into labor.

In Africa, due to the differences I just mentioned, the priority remains to identify simple, practical, and effective regimens to prevent mother-to-child transmission and, secondly, to try to do operational research to try to identify ways to implement these in a practical manner.

Therefore, for a researcher from a sponsoring

country, one who sponsors the research in a host country, the real challenge is to identify research objectives that meet the host country needs and priorities, in other words, try to face the problems of lack of access to care and try to identify interventions that will be at a future time, hopefully, implemented in that country, but also that will meet the ethical review standards in both the host and the sponsoring countries.

Secondly, the challenge to conduct high quality research is to have in place appropriate research infrastructure to properly conduct these studies, and I'll go into that later in my talk.

I won't spend a lot of time on ethics, but just wanted to highlight how difficult it is to meet some of the challenges I just mentioned on the previous slide. These are two quotations from two documents that are some of the guiding principles for the design of ethically sound research studies. The first is the CIOMS document which, as you can read there, "Studies should be designed to obtain knowledge that benefits the class of persons from which the subjects are representative." And the second from the Declaration of Helsinki, "In any medical study, every patient should be assured of the best proven diagnostic and therapeutic method."

I hope, from the information I've just

presented to you on the socio-economic and health-related differences in the two countries, you can see how sort of balancing these two principles can be quite a challenge and has been, as you all know, the topic of very heated controversy over the short-course AZT regimens.

Turning now to some of the more logistical aspects regarding the challenges to conducting perinatal interventional research, this slide just covers some of the elements of what needs to be in place for high quality research to be done.

These include development and having in place appropriate human resources. That means the research staff to do the study.

It requires the technical infrastructure. That means the laboratory and the data management infrastructure to monitor the patients in the study and to assess the outcome of the study.

Also, something that's not often discussed, an institutional review which is something that is a novelty to many countries in Africa and is one of the responsibilities of sponsoring researchers, to help develop this process to have appropriate institutional review of research protocols.

There are a number of logistical challenges. These are true of any studies, but there are some specific

elements in conducting studies in Africa which need to be faced. That's challenges to enrollment, ensuring informed consent, avoiding stigma regarding HIV, and a proper follow-up.

Researchers from sponsoring countries who come to developing countries to do studies -- oftentimes it will be the first clinical trial that's conducted in that country, if it's a sub-Saharan African country. Therefore, there is very little infrastructure in place, few trained people in the conduct of clinical research. It's the challenge and the obligation of the researchers coming from developed countries to try to nurture along and develop that infrastructure. This involves the training of the clinical staff, the design and the conduct of the study, epidemiologists who will assure that the protocols are culturally appropriate, other clinical staff that will do the enrollment, the follow-up, the monitoring of patients to assure that the protocols are being well adhered to. Obviously, in a clinical trial, study pharmacists must be available and well trained for the proper labeling and dispensing of drugs, for monitoring the distribution of the study drugs.

One of the real challenges in setting up a clinical trials infrastructure in developing countries is the ability to monitor for adverse events since that

requires a laboratory and a data management infrastructure that allows for the rapid turnaround of laboratory results so that clinicians on site can decide whether a study drug should be stopped or not. This includes laboratory diagnostic capability which needs to be on site for the monitoring of hematologic and other outcomes, as well as for the monitoring of the primary outcome of the study, whether that's detected by HIV serology or HIV DNA PCR.

Data management also, as I mentioned, primarily for adverse events monitoring needs to be on line and a system needs to be in place to able to return the results rapidly to clinicians so that they can decide on how to proceed with the study subjects.

Much of this infrastructure development can be accomplished, thanks to the links that are created by the sponsoring organizations and the host countries. These involve technical assistance in all of the fields that I just mentioned, also in providing access to expert data safety monitoring boards, since that sort of expertise, the statistical and clinical trials expertise, is usually lacking in developing countries. Also, the sponsoring researcher can provide a link with pharmaceutical companies, since that data is often difficult to access by host country researchers, and that's access to pharmacokinetic and safety data, getting the study drug and

placebo and also getting these protocols through regulatory issues. These are best done by the sponsoring researchers.

I mentioned earlier one of the challenges is institutional review in the host country since all research protocols need to be reviewed and approved by the IRBs in the host country, as well as the sponsoring country. Many of these countries do not have a long tradition of IRBs, and there's a lack of personnel who have the experience in properly reviewing this. Our own experience has been that this is a gradual process that continues, and as time goes on, the level of expertise is increasing. I think it's one area where sponsoring countries could do more to provide formal training to in-country researchers as to the proper conduct of institutional review.

I've labeled on the same slide the second difficulty is obtaining appropriate informed consent. In trying to explain complex study designs and trying to pass the message of placebo and trying to explain the issue of probability of transmission, those are difficult concepts for anyone to understand. I think it's particularly difficult in the settings where the subject is often someone who has no education, who is illiterate. There is such a big gap between the health care professional providing information and the potential clinical subject that it can be a real challenge. I think there again some

work needs to be done to try to develop methods to try to better get the message across regarding these studies.

Also, one of the issues that are specific to perinatal research is if sponsoring organizations require the approval of the father of the fetus or the child, that is almost impossible to obtain, at least in west Africa where fathers are entirely absent from the prenatal health care process and oftentimes where women do not reveal their HIV status to their husband because of fear of reprisals.

Enrollment is difficult in these studies. In most of the studies, it's between 20 and 30 percent of HIV-1-infected women are actually enrolled in the studies. There are many reasons for this.

The first I mentioned already which is the poor access to prenatal care. By that I mean that women often will come for one visit to get a health card which will allow them to deliver there and then don't plan on coming back because of the cost involved, because of the time involved.

However, there are also, in addition, specific barriers to the acceptance of HIV testing, and that's fear of stigmatization which is something that also requires considerable more study since it, at least in our experience in the short-course zidovudine trial, was something we really underestimated, the level of fear of

learning of one's HIV result and the fear of rejection and the fear of stigmatization.

Also in the absence of any antiretroviral therapy or other therapies for the mother, at least prior to the perinatal intervention trials, there was really little benefit for a woman to know her HIV status. Perhaps now with short-course AZT and nevirapine, that will change, although our experience in the last year or so, when we were doing open-label AZT in Abidjan, the acceptance of the regimen has not really improved dramatically.

Finally, the time at which one identifies an HIV positive woman, does the voluntary counseling and testing is usually at the first prenatal visit which occurs generally in the second trimester, and the intervention actually doesn't start till 36 weeks or in labor. So, there's a considerable period of time between there during which women can move, change their mind, and not be available to be participating in the study.

To highlight this, I just wanted to review some of our own data from the enrollment into the short-course AZT study that we conducted. This is enrollment over about a 2-year period of time, during which 1,600 HIV-1 women were identified through voluntary counseling and testing. Yet, only 280 were enrolled. What were the reasons for non-enrollment?

The biggest slice was non-return for post-test counseling for the reasons I already mentioned. Almost 40 percent of these women did not come back for the result and did not learn of their HIV positive result.

Of the women who did come back for their HIV result, 18 percent were lost, and that's lost between the time of post-test counseling and 36 weeks when the study enrollment began.

12 percent of women refused. So, although I mentioned that there are challenges in doing proper informed consent, at least this would indicate that some proportion of women understood and made a decision not to participate in the study.

And then the other, ineligibility, 11 percent, and other reasons.

And the result, only 18 percent of women who could have benefitted from this regimen actually were enrolled in the study.

Another important thing to consider is the difficulties in doing proper follow-up. Most of these studies have a short-term outcome, which is an HIV-1 PCR at 3-6 months. That certainly is easy to do. Even doing follow-up for 18-24 months, the duration of breast feeding, is also feasible. One of the advantages of this sort of winnowing process that I just described is that the women

who end up being enrolled are those who adhere well to the protocol and adhere well to the follow-up.

But particularly for assessing safety, there's a number of barriers that make this a difficult reality.

First, long-term follow-up is difficult to assure. These are highly mobile populations, people moving back and forth. In Cote d'Ivoire, a high proportion of women are immigrants or their partners are immigrants, and they're coming in and they move back to the village or move back to their country.

Other women come specifically to the city for obstetrical care and then return to the village. So, obviously that will make follow-up difficult.

There's a high background rate of mortality. That's a high background rate in the absence of HIV, which is often 100 per 1,000 infant mortality rate. If you add HIV to it, then it becomes a significant mortality. So, at the end of 1 or 2 years, a significant proportion of the children have already died.

Finally, in assessing the cause of morbidity or the cause of mortality, one is faced with the barriers of the poor quality of health care in general. So, if a child or a mother in a study dies or has a serious adverse event, it's often difficult to assess what was the real reason for that because of the lack of hospital care. The children

either will die at home with no information or even when they come to a hospital, there's not much infrastructure in place to really be able to assess the cause of the death.

Just briefly an example of Projet RETRO-CI. Projet RETRO-CI is in Abidjan, Ivory Coast, which is a west African country, population of about 15 million people. HIV prevalence in Abidjan, the principal city, is 15 percent. In the interior of the country, it's 9 percent. So, it's not as significant an epidemic as in southeastern Africa, but still by far the most severely impacted country in west Africa. AIDS is the leading cause of adult death, and the per capita health expenditure is $22 per year U.S.

Projet RETRO-CI was established in 1988, and it's, as I mentioned, a collaboration between the CDC and Ivorian government. A broad range of HIV-related research has been conducted there, with recently a particular focus on interventional research.

The study that we conducted was conducted in a large public antenatal clinic, set up voluntary counseling and testing there. The obstetrical care was provided in the labor and delivery ward of the clinic.

The population was primarily west African. By west African, I mean that about 40 percent of the population were foreign born from the surrounding countries, and 60 percent of women were without any

schooling. Therefore, as I mentioned earlier, some of the difficulties in explaining difficult concepts regarding the study.

Obstetrical care was provided by midwives with very limited equipment and very limited ability to provide any sort of high level medical care for women in labor or else to the babies if they had any distress.

The regimen was mentioned briefly by Lynne, and our result was again a 3-month, 37 percent reduction in transmission.

Some of the specifics regarding safety monitoring. I mentioned some of the necessary elements for proper review of safety. We had an on-site laboratory and data management. The monitoring for laboratory and clinical adverse events was using the ACTG guidelines, and the data and safety review was done with the help of the NIAID DSMB with an Ivorian representative. The laboratory also was on site, including HIV DNA and RNA PCR.

So, it's at least our experience, I think certainly the experience from the other studies you heard about, HIVNET, the PETRA studies, that it is possible to conduct quality research in developing countries, but the things that have to be nurtured and developed is human resources development, as I mentioned, all the different types of people necessary for doing appropriate studies.

That's best done through a long-term commitment and long-term partnership with the host country, providing training, short- and long-term training, development of laboratory and data management infrastructure.

These sorts of studies go through lots of ups and downs. I think certainly for us all the controversy around the ethics of these studies was a real test of our relationship with the Ivorian ministry, and luckily we had a long-term commitment and a long-term history of collaboration, so we were able to weather the storm. But the sort of trust that's needed to properly get through these studies shouldn't be underestimated.

Finally, the contacts, as I mentioned, the pharmaceutical companies and the DSMB and statistical technical assistance provided by the sponsoring organization.

What are some of the factors that need to be taken into consideration in interpreting data from international studies of mother-to-child transmission? I've mentioned some of these, so it's a review.

Some of the differences in baseline characteristics. The prevalence of risk factors for transmission are very different in the two settings. So, the background transmission rate can be different in U.S. studies and studies from Africa and other developing

countries.

There are racial differences. This was perhaps best exemplified in a different study. We did a co-trimoxazole prophylaxis trial where the safety profile was much better than was experienced in studies from the U.S. primarily done among caucasians. So, that has to be taken into consideration.

There's a different distribution of HIV-1 subtypes. In Abidjan it's primarily subtype A. To date there's no convincing evidence that subtypes are related to risk of transmission, but again that's something that should be taken into consideration.

I've already mentioned the background level of antenatal and obstetrical care, the absence of cesarean sections, the absence of any specialized obstetrical care for women with HIV.

The biggest difference has already been discussed and that's breast feeding, which continues to be almost universally practiced, and the considerable risk of HIV transmission through breast milk, with that risk seeming to be highest in the first few weeks of life.

And finally, the background infant mortality rate which will be an impact on any studies conducted in developing countries.

With that as the background, what are the

precautions or things that need to be considered? There are some clear advantages for considering and for including results from international studies, and that's the ability to rapidly answer research questions concerning prevention strategies. That specifically for the U.S. means what to do for women who show up without any antenatal care. So, what sort of regimen can be given to women in labor to prevent transmission?

And also, because of the larger number of HIV positive women in these countries and the ability to enroll large numbers of women, despite the difficulties that I mentioned, there's the ability to assess the efficacy of the antenatal, the intrapartum, and postpartum regimens. Some of the data presented earlier is an example of that.

So, in summary, there are major differences between the economic and health-related differences between developing and developed countries, particularly in Africa. These have to be taken into consideration in reviewing data from international studies.

Sponsoring countries conducting research in host countries need to keep the priorities of the host country in mind in developing it. That's true for deciding what intervention to evaluate and also what comparator arm to use for assessing that intervention.

There are many important logistical challenges

to the conduct of clinical trials.

There are differences in populations and HIV-related factors that can affect the interpretation of the data since it can affect the rates of transmission.

Despite all this, it's my feeling that it is possible to design and conduct rigorously controlled clinical trials that address important scientific questions which would not be carried out in the U.S., and with the high seroprevalence and substantial number of late presenters, there's a possibility to evaluate regimens focusing on intrapartum and the postpartum periods.

It's important to remember that the estimates from these trials were probably conservative because of breast feeding and the prevalence of other risk factors for transmission, as I've earlier mentioned.

And finally, that the applicability of findings to U.S. populations need to be considered on a case-by-case basis given the study drugs, the trial design, and the relevance to U.S. women.

Thank you.

DR. HAMMER: Thank you very much.

Are there questions from the committee? Dr. D'Agostino.

DR. D'AGOSTINO: You just made a comment about the breast feeding producing conservative estimates, but

also you could argue the other way because these individuals may be at such high risk that the estimate you get here may in fact also turn out to be better than what you'd see in the U.S. population because of the care and so forth. So, there's a tricky business in both directions.

DR. WIKTOR: That's correct.

DR. HAMMER: Dr. Mathews.

DR. MATHEWS: Could you comment on to what extent the results of the short-course trials have sort of refocused the debate about placebo controlled trials in developing countries and what you think is the remaining need for placebo controlled trials in this setting?

DR. WIKTOR: That's a very difficult question. Following the release of the Thai AZT results, a statement was made by CDC and NIH that all placebo controlled studies should stop in developing countries. In fact, in all the ongoing studies, that was done.

I think the argument in justifying these studies is that there was no proven regimen that was implementable, that was practical and that could be implemented prior to the development of short-course zidovudine and the combination therapy studies, the PETRA studies. I think with that result, that's certainly no longer true.

I think that the focus of research is shifting

in my opinion to two areas. One is implementation and two is focusing on postnatal transmission.

So, I think at this point a clinical trial looking at transmission would have to include some sort of regimen to the women. It's a rapidly changing picture, but I think one of the benefits of having gone through this difficult phase is that we do have interventions that can be applied, and now with the most recent results even for women just in labor. I think that's the good news coming out of these studies. So, I would say, yes, that it would be difficult to imagine a placebo controlled trial in any setting now.

DR. HAMMER: Dr. Lipsky.

DR. LIPSKY: You mentioned studies on implementation. After the study is done, can you tell us what then happens to the standard of medical care in the country? Is there an impact, or economically is that still difficult?

DR. WIKTOR: Well, obviously another obligation of research is to think about what's going to happen afterwards. That was our concern in developing the protocols. Some of my colleagues were saying, well, nothing is there yet, so if you show that it works, nothing will happen afterwards. Others were saying, well, if you can demonstrate efficacy, then resources will be mobilized.

At least in Ivory Coast, I'm happy to say that that has been the case following the release of these results and there was another study conducted in Abidjan by the French ANRS group. Both research sites were able to continue open-label AZT, and since then there have been several initiatives, one funded by the French government and another now coming in to place through UNICEF, to try to provide the elements necessary, HIV counseling and testing, short-course zidovudine, formula feeding if a woman desires it. So, steps have been initiated to make this available.

Unfortunately, the reality is that, for the reasons I mentioned, there are significant barriers that remain before this will really become a widely implemented intervention. So, the hardest step to get over is the HIV counseling and testing. One can't overstate how difficult it is to get that into place in settings where there are already overburdened clinical staff who are seeing 60, 70, 100 women a day. Providing proper counseling and testing is a significant effort and the cost.

So, there are a lot of barriers. There has been progress made. I think on the research agenda, operational research needs to be done to try to improve the uptake of counseling and testing and try to find ways of delivering these interventions in a manner that can be included in the normal practices of the antenatal clinic.

So, a lot has happened since the release of these results. A lot more has to be done.

I think another point is I've focused on Africa. I think some countries -- Thailand is perhaps the most notable example -- have made a decision to make universal short-course AZT available to all their pregnant women. It has not yet happened, but there are several regions throughout the country where this is the case. So, there are some middle level countries where these results have already made a difference on a wide scale. Botswana is another example where the government has made a commitment to providing throughout the country antenatal testing and some sort of regimen.

DR. HAMMER: Dr. Fletcher.

DR. FLETCHER: I'm wondering if you would care to comment on the results of the HIVNET nevirapine study for HIV-infected women in the United States, as to whether those results should be adopted or could be adopted as a standard of care for HIV-infected women who come with no previous therapy.

DR. WIKTOR: I'm not that familiar with the situation in the United States, but I would say yes. That remains the main challenge for the prevention of transmission in the United States, and it is the regimen that's shortest and it seems to be effective.

I think, as I mentioned, one consideration is assessing safety and that's something that's difficult to do in these international research sites because of the reasons I mentioned, but if it were up to me, I would say yes.

DR. HAMMER: Dr. Handelsman.

DR. HANDELSMAN: Given the results of the HIVNET 012 study, are the studies that contain comparator arms of short-course AZT no longer ethical? Are those no longer the standard of care in foreign trials?

DR. WIKTOR: That's something we're grappling with ourselves in designing follow-up studies to the results of our study and the other studies. I would say no. I think that one could argue the contrary, that not providing the short-course AZT would mean that you would miss a prevention opportunity for women who did come in who, for example, delivered at home and forgot their nevirapine. So, I would say no. I think to the contrary.

It's not that short-course AZT has to be part of any perinatal intervention regimen. The two are potentially complementary in the sense that one works primarily on reducing viral load and the other presumably post-exposure prophylaxis. One of the questions that should be answered, although it's probably not as high on the research agenda as others, is what is the additional

benefit of combining those to regimens.

As I mentioned, the horizon is moving forward rapidly. In places that have implemented short-course AZT, which isn't that many places -- in Africa it's Cote d'Ivoire and I think Botswana and a handful of other countries -- many of the public health ministries are deciding what to do. I think probably many will go directly to nevirapine since it's less expensive and easier to implement.

DR. HAMMER: Dr. Wilfert?

DR. WILFERT: Two just short additions. The question in regard to placebo controlled trials. In practice the HIVNET program, in the process of designing the antibiotic trial to interrupt transmission which will occur, is doing that on top of nevirapine therapy, a dose to the mom and to the baby because of adopting that standard of practice, and I would expect in other trials too. So, it is in place that that available therapy is the baseline.

And two, after the demonstration of the Thai 4-week course of therapy, I believe UNICEF/UNAIDS have established 21 pilot projects which are at various stages of implementation along the way. It has taken a long time, but at least there are attempts to work through the problems in several sites.

DR. HAMMER: Thank you. Thanks very much.

We'll move on. The next speaker is David Morse from the Division of Antiviral Drug Products to speak about safety considerations.

DR. MORSE: Good morning. I'm David Morse. I'm a toxicologist in the Division of Antiviral Drug Products. I'm also the Chairman of the Reproductive Toxicology Committee of the Center for Drugs and the Associate Director for Pharm/Tox in the Office of Drug Evaluation III.

What I've been asked to do today is provide a brief introduction to the testing procedures which contribute to the safety assessment of pharmaceuticals for use by maternal fetal pairs, and perhaps after all the discussion of long-long and short-long and short-short, I should call this an ultra-short course or introduction to nonclinical safety assessments.

Right now there are three classes of drugs which are approved for use in the treatment of HIV infection. All of these products are categorized either into pregnancy categories B or C. The safety evaluations included in the pregnancy and fertility sections of all of the currently approved product labels are based solely on data derived from animal studies.

So, what exactly constitutes pregnancy category

B or category C? Category B can be obtained in two different ways. You can demonstrate no effects in humans with an adverse effect in animals, or no significant adverse effects in animals without or in the absence of human data. In C, you can demonstrate adverse effects in animals without human data or you can achieve a category C with no data available, animal or human. The underlined considerations are the ones that are used right at the moment for the labeling of all of the currently approved antiretroviral agents.

So, the categories are defined by the availability of animal reproductive toxicity data, whether it be positive or negative, the availability of human effects data, whether that be positive or negative, and if you were to look at all of the categories ranging from A to X, it also includes consideration for the indication of use.

So, what are the underlying nonclinical safety studies that are used in the evaluation of reproductive and developmental considerations? There are two main study types. There are repeat dose general toxicology studies and specialized reproductive and developmental toxicology studies.

Now, it's important to understand that there are a number of characteristics of these studies. The

nonclinical safety assessment for human pharmaceuticals represents a focused screening assay. It is very definitely not an open-ended research project.

Most of the studies are designed to detect effects which occur at approximately the 1 percent incidence rate. And by the use of meta-analysis, the combinations of multiple study data sets, the evaluation of events that occur at significantly below 1 percent is possible.

Now, just to confuse the issue a little bit more, drugs that are going to be used for different durations in the clinic are evaluated for different durations in the nonclinical safety assessments, but seeing as how HIV being a chronic disease, the drugs are all assumed to be for chronic use in these patients, and therefore the toxicologic assessment of these agents for general toxicology would be expected to start with acute dose and range up to 6- or 12-month repeat dose studies typically in one rodent and one non-rodent species.

The 2-year repeat dose carcinogenicity studies for chronic use drugs are normally done in two rodent species, and I'm not really going to be talking about those studies at all today.

Now, the safety study characteristics. What they look at for the most part in the general toxicology

studies, morbidity, mortality, and clinical signs. So, these are in life.

Pharmacokinetics is very important to make an assessment of the relative exposure of the animals to the human condition. There are repeated clinical chemistries, hematologies, urinalysis -- that's not quite as frequent as the chemistries and the hematologies -- again in life, with normally also a terminal assay of these endpoints and extensive histopathology, 30 to 50 tissues or organs per animal with multiple sections per tissue.

One of the things that's very important here is that histopathology, changes in morphology, are frequently extrapolated back to changes in functionality of the organism. This is the kind of data that we can get from the animals which is typically not accessible from the humans.

Now, in the area of reproductive and developmental toxicity, the study characteristics change somewhat. Again, you have morbidity and mortality and clinical signs. Occasionally there's pharmacokinetics. This is a move within the field that this should be added. Based on human pharmacokinetic data, we now know that pregnant females for the most part are not generally like adult male animals, and therefore they need to be taken into consideration in terms of their exposures, and it

needs to be measured.

Reproductive performance and fertility are the primary endpoints of these studies. It's focused primarily on reproduction. Reproductive system histopathology is normally included in these studies, and there's very limited histopathology of the progeny and almost no histopathology of non-reproductive system organs in these studies. That histopathology is assumed to remain constant from the general toxicology studies.

So, what are the underlying studies that go into reproductive and developmental toxicity and the endpoints that are involved? There's a change in this field right at the moment in terms of the way these studies are addressed, what they're termed and the various endpoints. There's an international harmonization which has been going on the last couple of years, and the reproductive endpoints are now referred to as stages A, B, C through F. But traditionally the studies are done as three separate main study categories, segment I, II, and III.

Segment I deals with pre-mating to conception. So, it's male and female reproductive function, gamete maturation, mating behavior, and fertilization. And then in the female, conception to implantation. So, it's female reproductive function, pre-implantation development, and

implantation processes.

In the segment II, it's implantation through closure of the hard palate. So, female reproductive function, embryonic development, and major organ formation. These are the classic teratogenicity assays.

In segment III, it's ICH stages D, E, and F. It's hard palate closure to parturition, parturition to weaning. So, female reproductive function again, neonate adaptation, pre-weaning development and growth, and then weaning to sexual maturation, post-weaning development and growth of the offspring, adaptation to the environment, and attainment of sexual function.

So, the aim of the reproductive toxicology studies are to reveal possible effects of an agent on mammalian reproduction and to allow detection of both immediate and latent effects on reproduction. And that comes primarily from the multi-generational effects seen in segment III studies.

Now, there are a number of constraints on reproductive toxicology studies. First of all, the sampling unit is the litter. It is not the fetus. It is the litter because all of the fetuses within any given litter are genetically related and so they cannot really be treated as independent samples.

Studies are powered generally to detect events

that occur at the 1 percent incidence phenomenon.

And for the most part, reproductive toxicology studies are not repeated, unlike the general toxicology studies which begin at about 2 weeks of repeat dose exposure up to about 1 year or so of repeat dose exposure. Therefore, the data sets can be combined to some extent. The reproductive toxicology study for the most part is a single study.

Measurements of general toxicity are rarely included in the reproductive toxicity studies. Non-uterine or testicular morphology, clinical chemistry, and hematology for the most part is just not done.

So, what is the predictive capacity of these studies for the human condition? Based on approximately 38 recognized or generally recognized human teratogens, if you look backwards then at what went on in animal studies, 37 of those 38 were positive in at least one animal species for teratogenic effects. 29 were positive in more than one laboratory animal species, and 8 of those 38 were positive in every animal species in which adequate studies were done.

Then if you break that down by the species in which the tests were actually conducted now, some compounds were tested in more than one species, but not all compounds were tested in all of these species. To look at the

predictive ability of individual species for the human condition in terms of teratogenic responses, the rodent, the mouse or the rat, is usually positive about 80 to 85 percent of the time for known human teratogens, the rabbit about 60 percent of the time, and the hamster and the monkey, 45-30 percent of the time.

Now, the monkey is kind of a difficult one to evaluate because there are a number of study constraints just based on the sample size and the fact that the monkey normally only delivers individual fetuses as opposed to multiplicity of fetuses with these species.

So, what I'm going to try and do now is run through a very, very brief summary of the general toxicology that was seen with the three classes of antiretrovirals and the reproductive effects that were seen with these same agents, but not talk specifically about any one of the individual agents.

So, for the antiretroviral nucleosides, the species in which the general toxicology studies were conducted, rodents, rat, mouse, also rabbit, dog, monkey. The studies that I've included in this summary range from approximately 1-week to 12-month repeat dose studies. The major effects were hematologic in all the species. Neurologic effects were seen in the rabbit, in the dog, and also in the monkey. Renal effects in rodents and in the

dog. Mitochondrial injury, even looking at the data sets in terms of a meta-analysis, did not seem to pop out, although that may not be surprising if the incidence data for humans is fairly accurate and somewhere along the range of 1 in 10,000 or 1 in 100,000.

In terms of what effects these agents had as a class on reproductive endpoints, all of the studies were evaluated in either a rat or a mouse and the rabbit normally being the second species for the reproductive endpoint studies. There were slight decreases in fetal growth and weight gain for most of these compounds and increases in embryo fetal loss, not surprising for the fact that most of these compounds are very closely related to cytotoxic agents used as antineoplastics, and a decrease in viability of the offspring in almost all of the species.

There were for some of the agents slight decreases in skeletal variance and malformations, primarily seen in the rabbit, and to go along with the decrease in growth and weight gain, there were delays in skeletal ossification, although this is usually considered to be a recoverable event.

There were, interestingly enough, slight decreases in the F1 generation reproductive performance, so that comes from the segment III study where the offspring are allowed to mature and are then bred, the only exposure

these animals had to the pharmaceutical agent being late-term in utero exposure or pre-weaning exposure.

Mitochondrial injury was again not evident in any of these studies.

Now, for the non-nucleoside reverse transcriptase inhibitors, there was a slight variation in the species that were used, the rodent, mouse, and rat, dogs again, monkeys, rabbits. They got kind of confused between the various studies in which some of them were applied. I think that might actually be a mistake there, that the rabbit was also used in some of the general toxicology studies.

But for the general tox results, liver injury and hepatocellular necrosis, and hypertrophy were seen in all the species for basically all these agents. GI erosions, ulcers, hemorrhages, cutaneous effects were seen for the majority of these agents. Vasculitis in the heart, the liver, the lungs, and other tissues which was not necessarily associated with the GI erosions or the ulcerations was seen. And renal tubular injury in the rodent, the dog, and the rabbit. In this case that specifically was seen in the reproduction studies.

For the reproductive toxicology endpoints, there was again an increase in embryo fetal loss, much analogous to the nucleoside reverse transcriptase

inhibitors, and a decrease in viability of the offspring in all the species.

There was an increase in cardiovascular intraventricular septal defects, and increase in skeletal variance, supernumerary ribs, primarily in rabbits, although these appeared to be clearly non-dose related effects which is kind of problematic for ultimate evaluation, and a slight decrease again in the F1 reproductive performance in the rat study that was done.

For the protease inhibitors, these studies were done in rodents, mice and rats again, dog, monkeys, and rabbits. There was again a significant incidence of dose-limiting liver injury in these chronic toxicology studies, hepatocellular hypertrophy, hyperplasia, and increased bilirubin, increases in liver function tests, increases in triglycerides and cholesterol, and decreases in circulating glucose, renal tubular injury in the rodent and GI tract erosions and enteritis with these agents.

For the reproductive toxicology results, there was a slight decrease in fetal weight and growth rate which occurred through lactation. So, this was a late gestational effect and pre-weaning effect that was seen. An increase in skeletal variance with wavy ribs seen in the rodent, and again delayed ossification. Interestingly enough, this increase in bilirubin carried over into the