reproductive toxicology studies where it was actually looked for because of the significance of the effect in the general toxicology studies and that was seen in the dog.

So, as I indicated before, all of the currently approved product labels contain information which is extracted from the nonclinical safety assessments for these various agents and is not based on the human safety data for the effects of any of these agents in maternal-fetal pairs. Right at the moment, the information from maternal-fetal pairs has not been deemed extensive enough to make clear assessments of the safety to be included in the product labels. For the antiretroviral pregnancy registry, there are approximately 800 pregnancies that have been enrolled. The follow-up is relatively short-term in this study, basically to about the time of birth. It's a voluntary enrollment and it addresses very distinctive toxic and teratogenic responses because the follow-up is so short.

The PACTG 219 is the rollover for ACTG 076 and other PACTG trials. Again, it's a very limited sample size with several hundred maternal-fetal pairs enrolled to date. It's controlled but limited scope of follow-up again, as is the antiretroviral pregnancy registry.

Then there are cohort and chart review databases which again, for the most part, address

distinctive toxic and teratogenic responses that are seen in the offspring at the time of birth. Follow-up is generally incomplete. The samples are non-randomized to the various treatment allocations and frequently the exact treatment and the exact time of exposure of the fetus to the various interventions is not known.

So, in conclusion then, all of the currently approved antiretroviral therapies belong to pregnancy categories B or C. All of the currently approved product labels are based in their safety assessment on data obtained from animal studies. The general and reproductive toxicity studies are used to estimate safety for use by maternal-fetal pairs, and the current human safety database for maternal-fetal exposure to antiretroviral therapies is considered limited in size and scope and for follow-up and have not been included in the approved product labels at this time.

So, with that, I'll end and ask for any questions.

DR. HAMMER: Thank you very much.

Are there questions? Dr. Wong.

DR. WONG: Just a couple. One is that you dealt with the animal safety data mostly in groups of drugs or classes of drugs.

DR. MORSE: Right.

DR. WONG: There are a few that, I guess, are of particular interest to our discussion today, AZT, 3TC, and nevirapine. Is there anything special that we should know that you know about these as opposed to any of the others? That's my first question.

The second is, has anything been done in animal toxicology for combinations of these drugs, particularly in the reproductive arena?

DR. MORSE: Well, I think I'll actually answer it in the reverse order from which you asked it. The general toxicology and the reproductive toxicology studies are not done in infected animals, nor are they ever done, to my knowledge, in combination studies. The regulations under which we operate do not specify that a sponsor would need to conduct a trial in that way, combinations of drugs or in infected animals. Of course, for HIV, the infection models are extremely limited, to say the least.

In terms of specific drug products, you're right. I've summarized the classes in order to try and boil it down into a fairly brief presentation. Right at the moment, there are about 15 products out there. Each one of them has 4 to about 10 reproductive toxicology studies that have been performed with that age and at a variety of different doses, different exposures during the fertility, fetal development, or fetal growth stages.

Given that fact, just the sheer volume of the data, I'd rather not comment on any individual agent at this point because there are so many data points in my head that I'm afraid that I'd get them a little bit confused.

DR. HAMMER: Dr. Masur.

DR. MASUR: Can you speculate on why the monkey is not as good a screen as the rodent? And if that's the case, it would seem that in many cases sponsors are encouraged to do studies in monkeys. Is that necessary if the mouse is, quote, a more sensitive model?

DR. MORSE: Well, most of the concerns or considerations I believe, when it comes to the predictive ability of the monkey for the human condition, really relates to the sample size that you're dealing with. The feasibility of doing large enough studies in primates to be able to obtain any kind of statistical significance, the animals are so expensive, and for the most part they only deliver a single offspring, that the ability to conduct those studies is basically prohibitively expensive.

In the area of reproductive toxicology, we do occasionally ask sponsors to conduct studies in primates, although that usually is more focused mechanistic assays as opposed to general screening assays, frequently relating to things like changes in hormonal regulation effects associated that might deal with the induction of abortions

and so forth, as opposed to directly with teratogenic responses.

DR. MASUR: Can you just follow up on one issue? Can you make some comment as to how specific or reliable the findings in rodent models are, how often those turn out, or do you get the opportunity to find out whether or not those are relevant to the human condition?

DR. MORSE: The slide that I showed that dealt with the predictive ability of the various species was based on compounds that are recognized as being teratogenic in humans and then working backwards into the animal data set to try and define whether or not the animals showed a corresponding effect to the human response.

Now, if you want to flip the question around and look at whether or not the animal studies predict to the human for a compound that's not known, you can't answer that question for the most part. An agent that tests positive, a significant positive response in an animal study, would never under normal ethical considerations be taken into the human to define whether or not it was going to produce a similar type of effect.

DR. HAMMER: Would you comment on the dose issues, because often in animal studies, obviously, the doses are pushed to whether there's a lethal effect or some serious effect, and how you interpret that for the human

circumstance?

DR. MORSE: Right. Well, for most of the reproduction studies and the general toxicology studies, there's a range of doses that are used. The normal top dose in any of those studies is designed or intended to develop frank toxicity. You're looking for what organ systems will be adversely impacted by the agent.

When it comes to the reproductive endpoints, though, normally the assessment of adverse effects and prediction to the human condition is not derived solely from the high dose. You're looking for agents that produce adverse effects at the lower doses when maternal toxicity has not been demonstrated at that same dose, so that you can't essentially predict or associate the adverse effect in the fetuses as being an effect that was demonstrated by, let's say, changes in nutrient intake in the mom.

I think that probably pretty much --

DR. HAMMER: Another question. You were hesitant to talk about the specific drugs, but how has the data about efavirenz in primates affected the agency's thoughts? And are primate models required of all antiretroviral agents now?

DR. MORSE: No, primate models not required of all of the agents. The normal spectrum of studies that are done in terms of the reproduction area deal with rodents

and one non-rodent species. It's really up to the sponsor to select what species they want to use specifically. We would comment if we felt that there was some significant difference in the metabolism within one species, that that species did not represent an adequate model to predict to the human condition, but normally that really is up to the sponsor and rarely do they voluntarily go out and conduct their reproduction studies in primates.

As for current thought on the efavirenz, I'd leave that up to Sandy Kweder to answer that question as to whether it's had a significant impact on our clinical thinking at this point.

DR. HAMMER: Dr. Pomerantz.

Do you want to respond to that now or should we open discussion time?

DR. KWEDER: Open it up to discussion.

DR. HAMMER: Dr. Pomerantz.

DR. POMERANTZ: Since you took my main question, which was a good one, if I might say --

(Laughter.)

DR. POMERANTZ: I want to follow up, though, a little bit on Brian's question. I know you have a lot of information in your head, but getting back to specific antiretrovirals, rather than broad groups, are there some that are falling out as worrisome? We read case reports in

the literature, but what's your feeling about individual risk in pregnant females? The reproductive studies.

DR. MORSE: Right. Well, for the reproductive sections of the product labels for all the currently approved agents, they fall out into two categories, B and C. There's a spectrum or a range of effects that have been seen within each one of the classes, some being far more active in terms of adverse effects on the offspring, whether it be a teratogenic effect or a growth retardation effect, and others showing extremely limited effects or effects only at clearly maternally toxic doses. Those that demonstrated adverse effects only at clearly maternally toxic doses are the more likely to have category B designation in the product label. Those that demonstrated adverse effects at doses which could not clearly be associated with toxic endpoints in the dams would be more likely to receive a C categorization.

Now, for rare occurring events which have been reported in the literature recently, the evaluation of rare events is an extremely difficult one in toxicology. As I said several times during the course of my talk, most of these studies are powered to define adverse events that occur somewhere in the range of about 1 percent incidence. Rare events, you have to look at the exact timing of the exposure to the nature of the adverse effect that you're

seeing, the rate of that effect in an exposed population versus a background incidence of that same effect in an unexposed population. For many of these kinds of events, whether they be seen in the animal studies or whether they be seen in humans, the background incidence may be 1 in 10,000, 1 in 100,000, and that becomes extremely difficult to tease out then as to whether or not it clearly is drug associated. It becomes an issue of plausibility of underlying mechanism and timing and incidence.

DR. HAMMER: Dr. Lipsky.

DR. LIPSKY: You had on a slide a potentially intriguing observation. You said decrease in reproductive performance in the F1 generation were the NNRTs. Perhaps could you elaborate a bit on that?

Can you tell us what the state of the art is in following out long-term effects in humans to the subsequent generation? I know obviously there was the very famous case with steroids, but can you tell us what's currently being done and, therefore, what is the standard?

DR. MORSE: Well, actually in terms of the clinical follow-up and the state of the art, I would hope that probably the advisory committee would be providing us with better insight of that as opposed to the opposite way around.

DR. LIPSKY: No, but does the agency currently

receive information on that?

DR. MORSE: I think I'll actually turn that over to one of my clinical colleagues, Sandy or Debbie or Heidi.

DR. BIRNKRANT: I think at this point what we'd like to see with regard to follow-up is something similar to the 076 and other PACTG trials where participants are then rolled over into a long-term follow-up study to assess long-term safety.

DR. LIPSKY: Perhaps not what you'd like, but what currently. Are there any drugs right now that you're worried about teratogenicity or beyond that effects to humans at the time of reproduction after potential in utero exposure? Are there any drugs being looked at? I realize that may be a horrendous undertaking. You're asking us, but I'd like to know in what context currently what is being done.

DR. JOLSON: I guess there are a couple questions. One, are there drugs that we're particularly concerned about versus the rest of the antiretrovirals? I think there were some questions about efavirenz earlier that Dave was asked to comment on, and I think that would be a drug that we have a particular concern based on the animal findings, that there appeared to be a cluster of neurologically related abnormalities in a small number of

efavirenz exposed monkeys. That concerns us. It says that there's a potential signal there.

It's very difficult, though, to follow up on that. If the drug were needed to be used in a pregnant woman, that would be up to the physician to decide. We would hope that that exposure would be reported to the Collaborative Antiretroviral Pregnancy Registry or some other mechanism like that.

Short of that, we have very limited ways of following up other than spontaneous reports that we would receive through Med Watch. As Debbie was mentioning, if there is a controlled trial that goes on, we would encourage sponsors to follow up on those children as long as possible, but out in practice it's very difficult for us. I think we have to recognize that there's a gap in what our knowledge is about the safety of the products that are currently being used.

DR. LIPSKY: But throughout the agency, not necessarily antiretrovirals, do you know of situations where there are any drugs -- that the request is out there to follow them, potentially 20 years out?

DR. JOLSON: There are several drugs where there have been phase IV commitments of sponsors to somehow track the safety of their exposure, usually through pregnancy registries. That's something that the agency is

actively encouraging sponsors to do. Is that the sort of thing ghat you --

DR. LIPSKY: Exactly.

DR. JOLSON: And that's on a wide variety of products.

Another product in this division that this committee discussed about a year and a half ago was the combination of ribavirin with interferon. That was a phase IV commitment of the sponsor to do an active pregnancy registry. So, I think products where there is some particular concern or a very high use anticipated in reproductive age women, we would ask the sponsor to do a post-marketing pregnancy registry.

Sandy, I don't know if you want to comment any more about the agency perspective on that.

DR. KWEDER: Yes. There are a number of pregnancy registries for various products out there. The vast majority of them don't meet the standard of the follow-up to the PACTG studies where you have patients enrolled in a controlled trial. This is something that we grapple with all the time. I think it's fair to say that in the HIV area, we are rich with information about pregnancy exposures and outcomes compared to the vast majority of products that are widely used by pregnant women.

From an agency perspective, we've put forward a draft guidance document to begin to outline a basic standard for the situations under which we may require sponsors to establish these kinds of studies post-marketing and a baseline standard for what those data ought to look like. But they can be very ambitious undertakings. We recognize that. It's extremely difficult.

I think that the collaborative relationship that some of the sponsors for antiretrovirals have developed to try and put together a registry and the difficulties they've encountered in doing that are quite illustrative of that. I think it was pointed out earlier that there are about 800 women for whom information is available, and we know that far more pregnant women have taken antiretrovirals than that since that registry was established.

DR. HAMMER: Thank you.

Dr. Wilfert.

DR. WILFERT: You're learning about the problems which a lot of people, including the PACTG and a lot of other agencies, have been extremely concerned with. Several thousand women a year receive one or more antiretroviral agents. The vast majority of the children born to those women are uninfected children as a result of having been exposed to antiretroviral agents. The problem

that confronts us is trying to see those children not when they're 2 years old, but when they're 20 years old or 30 years old.

So, when you take in your hands the concept that the long-range follow-up involves knowing who those children are and matching them to the existing registries which are named-based, social security number-based registries, we are confronted with the problems attendant upon privacy at the same time that we have an enormous obligation to try and determine in the long term if these drugs do anything or have adverse effects on the children who are spared HIV infection. And believe me, there have been at least four meetings I've been to trying to deal with the logistics and the ethics of this problem. We are very concerned. We are very interested. We have not solved this yet.

DR. HAMMER: Thank you.

On that note, I think we'll take a 20-minute break. Please return at 10 after 11:00.

(Recess.)

DR. HAMMER: Let's reconvene.

Our next speaker is Debra Birnkrant who will speak on regulatory considerations in the development of drugs to prevent perinatal transmission of HIV.

DR. BIRNKRANT: Good morning.

Previous speakers have highlighted the great strides made in the prevention of perinatal transmission in the United States, western Europe, and in developing countries, and they have set the stage for a discussion of regulatory considerations in the development of drugs for the prevention of perinatal transmission of HIV.

In the next 10 minutes or so, I'll set the stage for the question period that will follow my presentation. We've already heard from speakers and from the discussion this morning, and it's been very informative to the division. We look forward to an equally informative discussion with regard to the questions so that we can provide advice to sponsors seeking to develop drugs for prevention of perinatal transmission.

This slide shows some of the published trials, including PACTG 076, the CDC Thai study, and others. I use this slide just to highlight the point that only the PACTG trial 076 had U.S. sites.

Before looking at some of the published trials in more detail, however, I wanted to focus on the 076 regimen, as others have this morning. The 076 regimen consists of a three-part regimen where zidovudine is administered antepartum, intrapartum, and to the neonate. As was said in introductory remarks this morning, it's really the only antiretroviral approved for this indication

of the 14 antiretrovirals approved for treatment of HIV.

The antepartum part of the regimen is begun after the first trimester, after 14 weeks gestation. Intrapartum it's delivered intravenously, and it's delivered to the neonate for 6 weeks.

This chart illustrates some of the details and differences among the various published trials compared to the PACTG 076 regimen, which you see at the top. Some of the obvious differences are the control arms, presence or absence of neonatal therapy, and whether or not breast feeding was allowed.

So, if we look at the CDC Thai study, they looked at an antepartum regimen of ZDV beginning at 36 weeks, consisting of a dose of 300 milligrams b.i.d. and then intrapartum 300 milligrams every 3 hours. This was placebo controlled, neonatal therapy was not given, and this was not conducted in the breast feeding population.

Compared to the ANRS 049 trial where they looked at a different zidovudine regimen beginning about 36 to 38 weeks antepartum, looking at a dose of 300 b.i.d. but only a single intrapartum dose, this was also placebo controlled and actually there was a week of antepartum therapy in there, which is not depicted on this slide. This was conducted in a breast feeding population.

Then as another example to highlight the

differences among the various zidovudine regimens used in these trials displayed here, we have the HIVNET 012 study which looked at nevirapine, a non-nucleoside reverse transcriptase inhibitor, compared to zidovudine. This was originally a placebo controlled study, but when the results of the CDC Thai trial were made available, the placebo arm was discontinued. So, we then have a two-dose nevirapine regimen consisting of one dose intrapartum and one dose to the neonate compared to an ultra-short regimen of zidovudine not previously studied.

This is another way of looking at the differences among the clinical trials with regard to timing of administration of antiretroviral therapy. This is a schematic. It's not really drawn to scale because the intrapartum duration looks as long as the antepartum duration just looking at it.

So, we have the PACTG trial 076 beginning after 14 weeks with the neonatal component. You can see the various differences among the trials with regard to timing. How do you apply this data to clinical practice?

Individual physicians and other health care providers obviously must use their judgment. As I said before, only one antiretroviral is labeled for prevention of mother-to-child transmission. So, therefore, they have to seek other information when they make their decision to

treat. We know that many antiretroviral regimens are being used in clinical practice, and this is to provide a balance between preventing perinatal HIV transmission and optimizing maternal health. Well, we seek that balance as well between optimizing maternal health and preventing perinatal HIV transmission. Therefore, we encourage sponsors to update their drug labels to include safety and efficacy data where appropriate data exists.

How feasible then is it to conduct trials solely in the United States for prevention of mother-to-child transmission of HIV? Well, based on the broad acceptance of the 076 trial, either alone or in combination with other antiretroviral therapies, with the use of highly active antiretroviral therapies, with improved prenatal care -- we talked a little bit about voluntary testing and counseling, and we mentioned the American College of Ob-Gyn recommendations for elective C-section based on a woman's choice. Well, all of these taken together have led to low rates of HIV transmission.

This is depicted in this slide which comes from an article by Lindegren that appeared in the August issue of JAMA looking at trends in perinatal HIV transmission. It's a complicated slide, but I use it to illustrate a point. Here we have estimates of perinatally acquired AIDS and HIV births. They looked at observed births of infants

with AIDS, adjusted births of HIV-infected infants, and predicted AIDS incidence. But I use it to point out, as others have, that pediatric AIDS cases are decreasing, as is the estimated incidence of perinatally acquired HIV infection.

This is the accompanying editorial to the Lindegren article that appeared in JAMA in August. Dr. Mofenson raises the question, can perinatal HIV infection be eliminated in the United States? I think the answer to that -- that is, her answer to that, as well as others that we may have heard today -- is that it may be possible. And if that's the case, then we may have reached the conclusion that we can't solely study this indication in the United States, that we have to look outside the U.S. to obtain some of our answers.

This is the Code of Federal Regulations as it applies to foreign clinical trial data in support of a marketing application. We've looked at this before for other drugs, not necessarily related to HIV. I'll begin at the bottom.

The third point on this slide is that for an application to be based on foreign clinical data, the data must be considered valid without the need for an on-site inspection by FDA, or if FDA considers such an inspection to be necessary and they are able to validate the data

through an on-site inspection or other appropriate means. This becomes a review issue.

The second point is the studies have been performed by investigators of recognized competence. Again, this is something that we decide at the divisional level as well. It becomes a review issue.

But the first point on the slide, which is the subject of the question period that follows, is, are the foreign data applicable to the U.S. population and to U.S. medical practice?

Are they applicable with regard to the dosage that's used, the timing of the dosage, and the route of administration?

As we've seen, not all of the trials that have been presented have had a neonatal component, and how relevant or applicable is this to the U.S. population?

What about control arms?

How does breast feeding apply to the U.S. population where recommendations exist for women who are HIV-infected not to breast feed their children?

And we touched on the issue of how long should follow-up be.

So, as I present the issues for discussion that will follow, we'd like to have an informative discussion again so that we can provide sponsors with appropriate

advice on how to evaluate new regimens in the setting of the 076 trial which is approved and implemented in the United States. Again, we wanted to ask our committee and guests applicability issues; that is, how do we apply the data to different patient scenarios, whether or not a woman is currently on antiretrovirals, whether she presents in labor not on any therapy. How do we interpret data using different comparator regimens? How do we interpret data from a breast feeding population? How long should the follow-up be again to assess long-term safety, and how long should it be for efficacy? And we'll be asking the committee and guests for suggestions for alternate study designs.

I'd be happy to answer any questions you may have at this point although, as we're running a little bit late, if possible, I'd like to move it along so we could get to the questions, which is the focus of this morning's discussion. Thank you very much.

DR. HAMMER: Thank you.

Any immediate questions?

(No response.)

DR. HAMMER: If not, we will move to the discussion. I would just mention that we are running late, but we'll have time to return to some of these immediately after lunch I think if we don't complete these in time. We

do need to give these full discussion, but I think we can catch up after the lunch break.

I will read the first question. We'll do them question by question. We won't necessarily go around to hear everyone. I'll leave it somewhat open. I would specifically, however, like to urge our special consultants with expertise in the area to comment on each question because I think the agency would like to hear those views as well as any of our other recommendations.

The first question is, given the broad acceptance of PACTG 076, please provide advice regarding how new regimens should be evaluated. It's a rather easy and narrow question.

(Laughter.)

DR. HAMMER: Who would like to start?

(No response.)

DR. HAMMER: All right. We'll move to the second question.

(Laughter.)

DR. HAMMER: Yes, Dr. Wilfert. I was hoping you would start. I was glancing over.

DR. WILFERT: Well, the traditional method is by randomized, controlled clinical trials. Within the framework of the developed world, there are probably some questions which can be addressed by collaboration at many

sites, but the n's for these studies, depending upon the question which is being asked, are several thousand on up. So, there will be a limited number of those kinds of studies that can actually be done.

Method number two is obviously to take the opportunity to utilize data that are gathered in settings where the trials are done well and they, in fact, have been randomized trials and to look at those data for applicability, which is what we're about to do.

But the third and final means is take advantage through another mechanism of observation of those women receiving therapy that are not randomized prospective trials. There are thousands of women receiving various regimens in the United States with an outcome of an infant who is infected or is not infected, and we ought to think about innovative ways to capture those data.

DR. HAMMER: Thank you.

Ms. Dennison.

MS. DENNISON: If the system isn't already set up this way -- and I don't think it is -- it would be very nice if patients who believe that they may be seeing an adverse outcome would have a mechanism for reporting directly and then follow-up being done with the provider because often women have concerns that the providers don't report.

DR. HAMMER: Thank you. That gets to a safety and follow-up issue which is part of a later question, so we should come back to that. That's an important point.

Dr. D'Agostino.

DR. D'AGOSTINO: I think if you're talking about new regimens as meaning new drugs, the controlled clinical trial is quite important. If you talk about new regimens as variations of existing drugs, different scenarios, then the randomized, controlled clinical trial is obviously ideal now with a positive control.

But going beyond, there are other ways, just to follow up on the first response to this. There are epidemiological studies you can do where you can have very careful recording of individuals as if it were a controlled trial, but recording of individuals and their background characteristics and extensive follow-up on them. You can even include, if it's feasible, what we call a simple trial where you basically do actual use, actual livelihood, but you introduce a random component, and if that's feasible, then you get an actual randomization if there's enough variation in the regimen, a new regimen against a previously existing regimen, with a little randomization. These things are possible to do, and they have been done in other settings.

Aspirin for children and so forth, for example,

was done with an epidemiologic study where there was a randomization. It turned out to be very effective and very clear cut.

There's even the case control modality where you take an individual with the particular method that's given, the new regimen, and get some controls possibly who are using some other method, and again follow them.

So, you don't necessarily have to impose a randomized, controlled trial. There are variations which can be very productive. What you don't want to do is you sort of leave it to whatever happens, collect whatever is there, and sort of move on. You really need to have it as if you're running a very careful study with very careful instruments and very careful follow-up being done and this sort of imposition of the new regimen. I think there are a lot of possibilities.

DR. HAMMER: Dr. Pomerantz.

DR. POMERANTZ: Just two points. I think one of the things that keeps being brought up is the difference between these studies in the developed world or in the United States and in the developing world. Sometimes, as we've seen with nevirapine, it probably can be used to give us information in both areas. But if you're going to talk to companies, I think that there are going to be studies that will only be useful or primarily be useful because of

the problems in the developing world, and they may not all be interpretable to the changes that we're seeing here with HAART therapy, with different access of care.

So, I think when you talk to companies, you will have those studies that probably should be done helping only the developing world that cannot be used with the changing face or will have minimal impact here in the United States. We'd like it to be both, but I don't think it will always be the case, especially as the therapies in the United States continue to evolve, as we know on this committee.

The other thing, the second point, is this has sort of come of age a little bit with the HIVNET study and 076 so that now we can ask more specific questions -- and I think that would be the most important -- clinical questions of what do you do specifically for women who present in labor. And those will be hard to bring in large numbers of patients, but I think that's where you have to get to now is specific questions. What do you do with people on HAART who have come into therapy? What do you do for people who are presenting early in pregnancy but have never been on anything? And then the question of resistance, which I've said recently will continue to evolve, will be something that you'll have to look at. Not a problem now. I would imagine it may become one in the

future.

DR. HAMMER: Dr. Gulick.

DR. GULICK: It's interesting to observe a parallelism with the situation with antiretrovirals in pregnancy and what's happening in the field in general. With the advent of so-called HAART, the field turned a corner, and we now have a lot of different regimens that can all work the same way. Rather than evaluating them so much on the primary endpoint, which typically would be a reduction in viral load, we're continually now addressing other issues about the regimens. And I see a parallel in pregnancy here. With 076 we literally turned a corner with reducing the primary endpoint, the percentage of transmission.

But now it strikes me that it's time to look at some of the secondary issues that have been mentioned, complexity of the regimen, how that impacts on adherence to the regimen. I asked about tolerability before because I'm still amazed with how well tolerated these doses, particularly with zidovudine, drugs are in pregnancy. Feasibility has been mentioned, using intravenous formulations or not. Resistance has also been mentioned. So, now that, it occurs to me, the primary endpoint is sort of taken care of in a way, it's time to look at secondary issues to evaluate similar regimens.

DR. HAMMER: Although the primary endpoint is taken care of for the United States -- not completely taken care of for the United States because I think, as Dr. Wilfert mentioned, there are women presenting without prenatal care, but there is responsibility, obviously, to the rest of the world even if this committee and this agency deals with drug approvals in the United States. That's why we're having, I think, this meeting today.

I might just say something and then continue to maybe stimulate some additional discussion. I think the charge, of course, for this committee is to see new drugs maybe used in new combinations and also to look at expanded indications of already approved agents. So, what that means, in order for data to be developed, although there are different levels of studies that are accepted by the agency, is that for the most part you want prospective, randomized, controlled trials. To some extent, you accept other types of controls, but trials are going to be the key issue for expanding indications or for new drugs. Given the diminution in the rate of transmission in the United States, it automatically means, as is obvious from the presentations this morning, that those studies have to be international because you won't ever see the numbers. That raises a lot of ethical issues.

But I think one other thing it brings up is

that we talked this morning about the developed and the developing world. The developing world is not one entity, and as we have seen, there are different regimens that are applied. In fact, the 076 regimen is being studied in Thailand. So, there are ranges in the developing world where, in fact, one can think about areas where we still might be able to do studies that have controls or that are close to the 076-like regimen as opposed to totally having to extrapolate from control regimens which give rates of transmission that are unacceptable in this country at the time and were really not standard control arms by U.S. standards. So, I think we have to look across the international framework to say where these studies can be done and put appropriate control arms in place that are ethically acceptable and regionally specific.

We will then still be left with, I think, extrapolating from that because if A versus B comes up with some result, we'll have to then say, well, B versus C was such and such in another study. I think in this field we're going to be left with comparisons across studies and what those implications are for drug approvals in the United States. I think that's going to be part of the problem, as well as extrapolating those results, because many of those control arms would not be what we would accept as standard, but again I'd say there's the potential

still to put relatively standard regimens in place.

And also, as was already mentioned, there's the opportunity and the need to study different lengths of regimen, whether it's short course, prenatal, and intrapartum regimens or at delivery and postpartum regimens. Those need to continue. They need to be done in some kind of rational framework as we develop new agents and combinations. It's going to get increasingly complicated with the permutations, but that's why we have organizations such as the PACTG and European and other international clinical trials organizations to try to organize these to work together.

Dr. D'Agostino?

DR. D'AGOSTINO: Just to follow up on that, the baseline characteristics or the characteristics that make the non-U.S. studies so hard to extrapolate seem to be fairly well known. They were listed. There are probably some surprises, but they were listed. While one doesn't want to get involved in lots of subset analyses and so forth, there are ways of extracting information about the spectrum on a particular variable. There are a lot computer simulation techniques of clinical trials now which in fact can be used to sort out and to try to get at that information. I think the call is for very careful design of these studies and the realization that the non-U.S.

population is quite different, and what kind of sensitivity analysis is needed to try to make those extrapolations so that you can do it in a sensible way.

Before I give up the mike, in the comments I made before, I gave sort of the positive. I think what would be a dangerous thing to suggest is some sort of retrospective registry as a way of sort of justifying claims. It's a way of getting a sense of what studies you might want to look at, but I think it would be a dangerous way of actually getting at satisfying new claims.

DR. HAMMER: Dr. Wilfert.

DR. WILFERT: I think that there are two issues which need to be addressed and could be addressed. One is, as has been said, zidovudine is currently the drug with the indication during pregnancy. Zidovudine and 3TC in controlled clinical trials have been shown to be effective and now nevirapine. So, the first issue would be the demonstration that other antiretroviral agents do effectively diminish perinatal transmission. I'm not proposing randomized, comparative clinical trials, but an attempt through controlled use of the information to derive that information and encouragement of the sponsors to seek that kind of approval.

The second area, I think, is that of virus burden which has clearly been shown to be related to the

frequency of transmission. It has to be possible, from the existing population of women receiving antiretroviral therapy, to derive some very relevant information about virus burden and the impact in the antepartum setting which is clearly related to the United States and the developed world.

DR. HAMMER: Dr. Masur.

DR. MASUR: A number of our comments seem to focus on the fact that maternal transmission appears to be at a very low level and our presumption is it's going to. I guess one of the concerns I'm sure we all share is that in the near future, as acquisition of drug-resistant HIV becomes more and more common, we may well be faced with a situation in which many women are likely to have nevirapine and AZT-resistant strains whether because of acquiring that type of strain or because of exposure at intermittent times prior to delivery.

I guess my concern is just how we're going to mind this observational database so that if we're in an era where we have difficulty relying on AZT and nevirapine, there may well be reasons to add them to the regimen. We clearly need information, at least some idea, about the efficacy and safety of all the other drugs that we're using.

So, as Trip said, we have turned the corner,

but clearly with patients we've turned another corner in which we're looking for more and more alternative regimens. I would presume the same is going to be true here.

DR. HAMMER: Dr. Mathews.

DR. MATHEWS: I was going to make a similar point. Besides the issue of breast feeding, the whole issue of prior antiretroviral experience is a major difference between studies in the developed world and the developing world. There really is a niche for the kinds of strategy trials which are being done to look at the impact of resistance testing in non-pregnant populations during pregnancy. Unlike the situation of post-exposure prophylaxis during pregnancy, there is time to get these kinds of results back and to fashion regimens with that kind of information in mind. I don't know. We'd have to look at what the numbers are. As people are improving their health, gaining more and more antiretroviral experience, a study which shows that a very vulnerable drug like nevirapine is effective may mean absolutely nothing in many of the populations that are going to be under treatment in the near future.

DR. HAMMER: Dr. Lipsky and then Dr. Handelsman.

DR. LIPSKY: Well, I think if you look at the first question, in view of 076, provide advice how new

regimens should be evaluated, I presume new regimens for the indication of preventing maternal-fetal transmission. Well, okay. You have a complex situation here. You have two patients and you have several outcomes, and you have to divide that. You have to break that up. So, for instance, you have the example -- and in different circumstances. So, it's very complex.

So, if you have a situation where you're aware early on in pregnancy the mother is HIV positive, are you then saying or wish to state that the approved therapy is monotherapy for the prevention of transmission? You're saying no. Okay. But isn't that the question you're asking? Be very clear.

Are you saying, okay, the approved therapy that you have with an FDA indication is monotherapy, albeit there are guidelines that say there should be a discussion of whatever that would be. But if you're designing new clinical trials, are you stating that you'd want to put a new regimen up against what is the standard? I mean, that is the issue. People are shaking their heads no.

Well, let's look at what people are doing and do epidemiologic, et cetera. Well, that can be good, I guess, sometimes. It can be a little muddled sometimes.

But I think that one is going to have to be clear. What is it going to be for the situation where you

know that someone is pregnant? What would be the study that you'd want to design? What is ethical? What is appropriate? What is going to scientifically work? I don't know if in the next 45 minutes this committee can answer that question.

The same way on the other end. For the short course for a child in the United States, for the neonate, we have a recommendation of 6 weeks. We're aware of other studies where, as you pointed out, there are shorter courses. What are you going to do on that end? Is it the gold standard and should it be a comparison always against initially against the 6 weeks that you have out as the official treatment, official protocol? But what if you know early on the child is positive? What does that do? And certainly wouldn't there be testing?

It seems like there has to be detailed analysis of all the scenarios. That's just talking about this country and about the fact that you have knowledge early on. But there also questions about what if you don't have -- what is the situation where the mother shows up at the time of delivery without any and you're aware that the mother is HIV positive? What do you do at that situation? That's different. You don't have to worry about the first part and what is going to be the gold standard there and then go on. Well, where is that? In United States. Then

you will have further follow-up and further information. That again will apply a bit to what I was saying about the short course for the baby. Obviously for the mother after delivery, there are standards of care which obviously this is not the indication and you don't worry about.

So, I think that one has to do a detailed analysis of what the scenarios are, what are the circumstances that are currently appropriate, and what are the ethics of what you're doing, even for this country. Because I think we have a situation. It would be interesting to poll the people around there. You have a mother at 12, 16 weeks gestation. What is the best therapy for that mother at the time? We have this discussion, but it might be interesting just to find out what people say. What is the best? I can ask the Chair since you're the expert. What is the best therapy for the mother?

DR. HAMMER: I'm going to defer that for now because, although we have to think about the care of the mother, we're actually talking about a specific issue of mother-to-child transmission. We have to take into account the best care for the mother, but I don't think we should go into specific recommendations at the moment. I'll defer that.

Dr. Handelsman.

DR. HANDELSMAN: I think in response to the

prior commentor, a lot of those analyses are being done in many different places by maternal and pediatric HIV specialists.

In terms of what studies are applicable to providing advice regarding preventing perinatal transmission here, I think international studies are definitely applicable because just as the developing countries are not a uniform population, neither is our population. I think we have certain subsets of our population for which studies, such as HIVNET, such as the PETRA studies, are certainly applicable.

I think we also need to recognize that we do have a very large portion of our population that is on HAART, and I think prospective enrollment studies looking at these are certainly doable in terms of the population, in terms of the numbers. It takes a lot of funding to do those, but in terms of comparing different HAART regimens, I think we should be attempting that.

DR. WILFERT: I want to be sure that what I said about the guidelines is clear, and that is that the guidelines say on the first line that a woman should receive therapy for her infection according to the same recommendations as people who are not pregnant.

Second, as a consideration, if she is pregnant, then the regimen that would best affect transmission needs

to be considered. Those are written as two separate parts of the guidelines with the baseline recommendation being that women receive therapy according to their own disease.

DR. HAMMER: Thank you.

Last comment on this question. Then we'll move on. Dr. D'Agostino.

DR. D'AGOSTINO: Just to elaborate a bit on the term "epidemiological" in this sense, it means exactly what you said, that you have a priori a prospective protocol identifying the different types of subjects, pregnant women who may come at different stages, and that there's a careful follow-up on them, but also a clear, not a retrospective trying to sort out what they had, but a prospective anticipating what situations you're going to have so then when you follow them, you in fact do have the right condition identified. There's also this imposition that once you identify them and put them in the right category, the idea of a large, simple, randomized, controlled trial where "simple" means that at this point you might be able to do some randomization into one of the different regimens and then you follow from that point as opposed to a detailed clinical trial. So, there's a lot of thought that has gone into these things, and they have been successful in other arenas. I think this is one that might work well also.

DR. HAMMER: I think it's worth mentioning the pediatric 316 trial which is trying to look at the nevirapine question in this setting where other antiretroviral regimens and combinations are used. That's a situation in which it's a good design to try to tease out that one question about adding something intrapartum and intermediately postpartum. That's a design that we need to think about, but I think as one gets into very complex regimens in the United States, the multiplicity of regimens -- you'll be able to answer the question antiretroviral therapy, virus load, outcome. You will, I think, have a lot of difficulty answering the question of specific regimens or certainly any agent unless you do a very, very large epidemiologic study, and the outcomes in this country are going to be so small that it's still going to be impossible to sort that out.

I think what we're dealing with here is the question of new agents and extended indications that will come before this committee or the agency, and that's part of the study design issue. The epidemiologic questions are critical as to what's happening with antiretroviral therapy and prophylaxis for maternal-fetal transmission, but I think for the committee's discussion, we should also try to keep a focus on what the questions that will come drug-specific and potentially regimen-specific before the

committee and the agency because that's what they're asking us to comment on.

DR. D'AGOSTINO: As I said at the very beginning, the new agents I think do need controlled clinical trials. It's the variations on existing agents that you can do something else, but for a new agent I think you do need the controlled clinical trial.

DR. HAMMER: Let me move on to the second question. We've already touched upon these and many of these are interrelated. So, I'll read the second question, some of which we've begun to answer, but let's be specific.

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

Do you want to start?

DR. WILFERT: I'm not an obstetrician, so I think I should decline from answering in my experience about the presentation of women.

I will say that 2 percent of women in the State of North Carolina who are HIV positive have had no

antenatal care. So, that's not more than 2 or 3 women because the whole population is probably 150 per year who deliver.

The second question is about what to do when you know a woman is positive who comes in at delivery. I think I said this when I was speaking and that is that there are two regimens which have been proven to reduce transmission in that setting: AZT, 3TC started intrapartum and continued in the infant; and nevirapine given as soon as possible and a dose to the woman. So, whatever else transpires as far as the antiretroviral part of this regimen, I would think that one of those two things ought to occur in women who present with the diagnosis and have received nothing.

DR. HAMMER: Can I just ask you a question? In translating these results, specifically to this question of no previous treatment, you have the proven results. Again, we're missing the obstetrician expertise here. But wouldn't it be often a combination of these entities, given the fact that we extrapolate and often use two, three drugs at least in this situation to try to maximize the chance of success even if we don't have the data to support it?

DR. WILFERT: I know. Because we don't have the data, what I was trying to say is that I think that that's the minimum, and what other drugs people might

choose to add would be interesting. Remember that if it's a reduction in virus burden, it is unlikely that administration of one dose of drug is going to accomplish that prior to delivery, just as a problem, but it doesn't remove considerations of adding regimens together, AZT, 3TC, and nevirapine, for example.

DR. HAMMER: Let me ask you to be somewhat provocative, but in the United States population, for example, the nevirapine regimen for a woman who presents without prior treatment and the baby gets exposed to a week or more of nevirapine because of its half-life but subsequently is infected, in this country, when we now are thinking about treatment of the baby and there are drugs available and the issue of resistance emergence -- we don't have the data because I've already asked that question. But isn't that one circumstance where at least in a broad fashion the use of the nevirapine-alone regimen would be a concern in the developed world?

DR. WILFERT: Well, remember that the nevirapine regimen is two doses, one to the mother and one to the infant, with a half-life that allows it to persist for as long as a week. I guess I would be balancing something which I know has a beneficial effect in terms of interruption of transmission at the time of delivery versus the subsequent choice of therapy if an infant is infected

despite that regimen.

DR. HAMMER: I guess what I'm saying is wouldn't that push one toward combination therapy if one was going to use the nevirapine therapy in the United States.

DR. WILFERT: Yes, but I mean, no data.

DR. HANDELSMAN: Scott?

DR. HAMMER: Dr. Handelsman.

DR. HANDELSMAN: As a pediatrician, I do get consulted when a woman presents in labor, and in Brooklyn in our hospitals I would say we do have between 10 and 20 women presenting as such per year.

I think also with the advent of rapid testing, as Dr. Mofenson said earlier, New York State has just regulated that all women who present in labor without a known HIV result from this pregnancy be offered rapid testing. And by Dr. Wade's statistics, that will be about 500 women who may be HIV-infected per year that we will detect in New York State.

Given that, I think that we do have this large population, and I think our recommendations would, again without data, clearly be a combination of IV AZT and oral nevirapine. I think also depending on the stage of labor, depending on whether membranes are ruptured, and depending on whether the woman is progressing rapidly or not, it

would affect the obstetrician's decision whether to perform a cesarean section or not.

DR. HAMMER: Thank you.

Dr. Pomerantz.

DR. POMERANTZ: Yes, in the same light. I agree with Cathy that obviously there's no data for the combination, and yet we do many things that have some teleological reasoning.

As someone at least in Philadelphia who unfortunately gets these phone side consults a lot, we've had to think about that. AZT, 3TC, and nevirapine is a quite adequate HAART regimen regardless of pregnancy. So, we would suggest just what I heard at the end of the table, AZT, 3TC with IV AZT, whether that means anything or not, intrapartum, continued with the dose afterwards of at least the nevirapine, and again, more likely than not, get a C-section at least in our area. But again, looking at the data, it's not that clear if they present already in anything other than very early labor.

DR. HAMMER: Dr. Kumar.

DR. KUMAR: I wanted to offer some perspectives on what we see in the Washington, D.C. area. The number of pregnant women that present at the time of labor without being tested is less than 5 percent, but we continue to see patients that are tested but offered antiretroviral therapy

but for several reasons are unable to take them. I would put that number in our experience to be anywhere closer to 10 percent, who are for several reasons are unable to take the prescribed antiretroviral therapy. It is for those women that we think short-term courses of antiretroviral therapy during labor and immediately after labor would be of great importance.

DR. HAMMER: Thank you.

Dr. Masur.

DR. MASUR: One of the issues I'd be interested in some of the pediatricians' comments on or perhaps one of the obstetricians who's not here --

(Laughter.)

DR. MASUR: -- is that for a regimen like Roger suggested, AZT, 3TC, and nevirapine, that has a lot to recommend in a patient who's compliant, but given our experience for how quickly nevirapine resistance can occur, if we're going to recommend this and we're thinking about what the standard of care is for a patient population that is going to have difficulty adhering for one reason or another, is this really going to be a practical regimen that is preferable to treating the patient at the time of delivery such that at least we have a good shot at having drugs that are active? That's just a question I pose. What kind of resources do we have to try to maximize

adherence?

DR. HAMMER: Ms. Dennison, did you have a comment?

MS. DENNISON: You can respond to him and then I can go ahead.

DR. HANDELSMAN: In response to that, at least nevirapine as one dose would be given in the hospital. So, we can virtually assure compliance with that, presuming we trust our hospital staffs.

In terms of the 076 6-week regimen, we've had extraordinary compliance with the pediatric portion, and what we've seen is that even though a lot of women may not take the medication for themselves or even intrapartum, they're usually extremely consistent postpartum. Although 6 weeks sounds like a lot, it's a limited duration regimen. So, I don't expect difficulty with compliance in that regard.

DR. MASUR: Actually, though, what I was referring to more is if the mother is taking these drugs intermittently and then presents for delivery, are you going to have a situation where the mother and the child then have a resistant isolate that you may or may not get some benefit from your drugs, but you're certainly at least logically compromising that chance.

DR. HANDELSMAN: Well, I think that to some

degree we've had that situation for the past 5 years. We know that maternal compliance with HAART regimens and with the 076 regimen has been good, not great. In the studies of compliance, they'll see anywhere from about 50 to 70 percent compliance. Nevertheless, we still do see the reductions over that period of time and we still do see very substantial reductions despite that. And the limited data about resistance has not shown many resistant isolates in the babies.

MS. DENNISON: To the best of my knowledge, I'm the only consumer on the panel. I'm an HIV positive mom that was in the ACTG 250 study, and I do a lot of counseling with HIV positive women who are pregnant. One of the barriers I see is the IV AZT during delivery is a real concern for a lot of the women that I talk to because relatives may be planning on attending or even partners who are often abusive who haven't been told of their status, especially when the woman tests positive during pregnancy and she's dependent on that partner and hasn't gotten around to telling that person yet. People are very concerned about nurses coming in saying, here's your IV AZT, and in fact that happens a lot.

Another thing that I see a lot is the hospitals not actually having the IV AZT in stock, and so we've seen cases, even in the Bay area, where prisoners whose status

was known who were on triple combo therapy go to deliver in a local hospital and the hospital doesn't have the IV AZT and they don't get that. And others, women who are in rural areas but wanting to go to specialty clinics or areas where they think they'll get more compassionate care, but where the time of the distance traveled to get there means they're going to be very far along in their labor by the time they arrive. Those are all situations where women have expressed a lot of interest in knowing more about this nevirapine regimen.

DR. HAMMER: It's also a situation where the international trials that have used oral AZT intrapartum is helpful in translating it to this population.

Dr. Lipsky.

DR. LIPSKY: Though it may be complex what goes on if you know in week 16, but I'd be interested just around the table here for the pediatricians or neonatologists or infectious disease people what they consider the standard of care for the situation where you have a mother who shows up at the time of delivery without prior therapy. What would be the regimen that they would give, that they would feel would be the standard of care to prevent transmission to the child? Is it monotherapy with AZT? Is it a combination? Because I think that's what we're wrestling with. And would you participate in a trial

that potentially had monotherapy?

DR. HAMMER: I'll just speak for the group and disagree with me if you will. I think it's pretty clear that if antiretroviral therapy were started at that stage of pregnancy, you're also thinking about treatment of the mother, and so AZT monotherapy would not be any standard in the United States starting in the midpoint of pregnancy.

So, I think if the woman were at a very early stage and you could defer treatment till later, then one would think about perhaps starting a regimen in the 076 variety in some areas, but most would start a combination. If you were thinking about treatment of the mother, it would be a standard of care regimen for the mother with the only exclusion that I'm currently aware of being efavirenz.

DR. LIPSKY: I'm sorry, Scott. You misunderstood. The first you know about it is the time of delivery during labor.

DR. HAMMER: There is no standard of care for that, and I think Dr. Wilfert outlined it as to what those issues would be.

DR. LIPSKY: But maybe we can get a sense around the table because one question comes up if you're designing a trial, are you going to design a monotherapy trial in the United States. Currently to prevent maternal transfer, if I understand, the only approved package

insert, labeling is for monotherapy with AZT in the United States. Is that correct?

DR. HAMMER: It is correct.

DR. LIPSKY: But who does that now? Because that not may be a practical gold standard --

DR. HAMMER: You're mixing up two things. There's the approved regimen which is the full 076 regimen. If you're asking mothers who present at delivery, what the standard of care is and what control arm you could use in that delimited setting for maternal exposure and to prevent child transmission, that's different than treatment of the mother because then you can have a very delimited exposure with even a single drug like nevirapine to the mother or AZT and then think about what the treatment of the mother should be thereafter. I think it's very complex and maybe one more comment.

What you're getting at I think I agree with. What control arms can you put together? But I think I would not confuse that with the full 076 monotherapy regimen because we're not talking about monotherapy extended exposure to the mother.

DR. LIPSKY: No, and I was trying to state my initial comment. What is the situation? Who are you treating? Right now we're talking about the situation where the first time you see the mom it's during labor,

you're treating to prevent the child from getting therapy. What is the standard of care right now?

DR. HAMMER: I think Drs. Wilfert and Handelsman are best able to answer this question here, and I think they've approached it already.

DR. WILFERT: I need to repeat again that you're honing in on the weaknesses of the existing guidelines, and we need to have a consensus opinion about the way to approach that. It's in the works. We're going to try to do that. At the moment, the consensus opinion based on the guidelines would be that a minimum of zidovudine according to whatever part of the regimen you could administer would have to be given to the woman, and I think on the basis of the existing data, I've already said that I think we're not up to date with what the optimal recommendations would be and that would include an effective regimen.

DR. HANDELSMAN: I guess I would just reiterate what Dr. Wilfert said. I think the guidelines say the 076 regimen, AZT as early as possible, but I think we obviously have some new, recent data which has changed clinical practice.

I think also a point that was made is that in labor at the time of delivery is not the optimal time for a mother to choose her antiretroviral regimen for herself,

and I think that decision would be and should be delayed.

DR. HAMMER: Dr. Masur and then we'll move on to question 3.

DR. MASUR: One thing that wasn't clear in what Dr. Birnkrant or the other regulatory officials said is in order for a sponsor to get approved for a regimen, would it have to be compared to the one regimen that's currently approved or to placebo? What would the comparator have to be?

DR. BIRNKRANT: I think the bottom line is we have to be able to interpret the data, and then we're also looking to a discussion here today to help us with that situation, given that the trials that were presented this morning for the most part used a variety of comparator arms, the most consistent one, though, being placebo.

DR. MASUR: That's a somewhat different standard than we use in other circumstances if we're simply looking for interpretable data, but not putting it in the context of other regimens?

DR. JOLSON: It's a little different, but it's not that unusual. Remembering, let's say, the circumstance of a woman presenting in labor, well, in reality there's no antiretroviral that has an approval for that specific niche. So, the ZDV regimen that we keep saying is the only approved regimen, that's a regimen that starts earlier in

pregnancy. I think as has been pointed out --

DR. HAMMER: That's what I was trying to say earlier.

DR. JOLSON: -- we don't know the efficacy of the individual components. That's a hard question. So, in your mind, if you're trying to wonder how you would establish efficacy for a product for women presenting in labor, there is no approved regimen for that.

The question comes to mind can you interpret the results of the study, as Debbie was mentioning. If for example it's a superiority design trial and you have a superior result, well then, it's the credibility of that finding and in terms of whether or not you can extrapolate it to maybe the U.S. population. It's a little bit of a problem then if it's an equivalence design. But again, we would just have to make certain that based on historical data, we could interpret the information.

DR. HAMMER: I want to move on to question 3, but maybe I'll try to provide a summary of question 2 for the agency. Question 1 was not really possible to summarize. But you're really asking whether essentially there is a situation in the United States of substance where the full 076 regimen cannot be given, and I think the consensus of this committee is certainly yes, and that although the numbers may be argued, there are substantial

numbers of women who present for the first time in labor infected and without previous treatment and are deserving of prophylactic treatment for the infant.

As far as the issue of the optimal regimen, I think the summaries by Drs. Wilfert and Handelsman should stand as to what the minimum issues would be in consideration of obstetricians and pediatricians now, but that probably in practice that gets improved or added to by individual practice, and that there is no standard, and that the studies need to be done. But at least there's a basis to move forward with current data from AZT and specifically the nevirapine trial.

Does that summarize things? Okay.

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

I think Dr. Masur should probably answer this question.

(Laughter.)

DR. HAMMER: Because he just asked it. Not to put you on the spot. Does anyone want to take this? Go ahead.

DR. MASUR: I don't know. Perhaps I'm missing

something here, but it seems to me there are so many situations in the United States where patients can't take the regimens that are "standard," that as long as the data is interpretable, then the results are applicable to the unique patients that we see that either are drug exposed or drug intolerant or unwilling or unable to take various regimens. So, I think there's a lot of applicability even if they're not standard regimens.

DR. HAMMER: Dr. Mathews.

DR. MATHEWS: I think the key feature is that they directly apply to antiretroviral naive populations who present for care at the similar stage as those that were enrolled in those trials. Beyond that, I think it becomes much more complex to make extrapolations.

DR. HAMMER: I would just comment. It's a point I tried to make earlier. They are applicable and one has to take those data. If these are adequate and well-controlled trials and, for example, you see a substantial reduction from a comparator arm, even if it's not a "standard" 076 regimen, I think if all GCP and other issues are in place, one has to take those data for what they are.

I think the difficulty becomes in extrapolating it to use and practice in the United States, not in believing the data, in part because the comparator arms are again giving us transmission rates that we know are by

history lower than would be without treatment but are higher than any standard regimen would be. So, what we don't know is taking those isolated regimens, they would not be immediately placed into care here except perhaps for the immediate intrapartum and immediate postpartum nevirapine-type regimen, but certainly any other regimen, if we're talking more broadly about maternal-fetal transmission interruption when there is treatment given prior to delivery, it's an extrapolation.

I think we're going to be left with again cross-study comparisons and comparing A to B to B to C to C to D. That's not ideal, but I think what we're going to have to say is incrementally what is going on with these treatments. Are they better than the drug, and in what situations were they given? Antepartum and intrapartum or intrapartum and postpartum?

I think one thing we've learned is that intrapartum alone doesn't work, that, however, two components are clearly necessary or helpful reducing maternal viral load and prophylaxing the baby. So, I think what we'll see are comparisons of, where we can, a more full 076-like length regimen, but mostly prepartum/intrapartum with a short postpartum or intrapartum for women who present at delivery and postpartum.

I think that it's hard to make a generalization personally of what data to accept. The comparator arms again in most developing countries are going to be not what were used here, but if there are substantial and believable reductions with drugs or regimens that have not been used previously, those data need to be taken quite seriously.

Dr. Wilfert.

DR. WILFERT: I want to just tighten up something you said. You said what we've learned is that intrapartum only doesn't work. What we have learned is that the one intrapartum only regimen that was tested which was AZT/3TC administered intrapartum doesn't work. Those drugs might not be optimal for that timing. So, rather than casting out the concept -- it's absolutely correct. It didn't work, but maybe it's not been fully tested.

DR. HAMMER: Thank you for the clarification.

Dr. Lipsky and then Dr. Fletcher.

DR. LIPSKY: Just one comment on using data from another country. In this country when a clinical study is done, certainly with support from the NIH and FDA, there's always concerns of the makeup of the population. I think those concerns at least should be taken into account for foreign studies.

I don't know if you should use the word would there be a double standard being held with the nature of

the study or not, but studies are being done in certain place and there are certain populations that are used and that's the nature of it. Sometimes in the United States there are locations where there can be similar considerations. But anyway, obviously the mix of the population has to be taken into account. I think there was an example here with sulfonamides or sulfamethoxazole where there were differences. But anyway, I think one has to be very clear what is required in the United States, what is required elsewhere, and what is the generalizability of the results.

DR. FLETCHER: Scott, I agree with your summary that if a trial is well done, the results should be believable, but it is the extrapolation of those results where there are difficulties. I'm struck by the fact, unless I've missed something, I don't see that any of these trials have compared to the exact 076 regimen. So, we don't know is oral AZT intrapartum as good as intravenous, is 4 milligrams per kilogram twice daily for 1 week as good as 2 four times daily for 6. How you then try to communicate that information to the health care providers, to the consumers about these differences in the regimen and what we don't know in terms of the efficacy that they may contribute to the regimen I believe is where we have a real challenge ahead of us.

DR. HAMMER: Let me just illustrate the difficulties here if you just consider the broad developing world. We've seen transmission rates that are considered successful in the 10 to 13 percent range in some of the African studies. Well, as Dr. Mofenson showed, the Thai study, the Mark Lollimon study that looked at 076 and three other comparative regimens, the short-short arm was prematurely discontinued because the transmission rate was 10 percent, which was considered good and the best result in some of the African studies. So, it highlights I think what you're saying.

I think we can't give a general answer to this question because it's going to be the individual study, the individual results, and then what specific patient population could be targeted and that regimen adapted to in the U.S. population.

In the studies we've seen this morning and are likely to see in the immediate future, there's probably no directly applicable regimen to a U.S. population except perhaps for the nevirapine issue. However, I think still many physicians would still not just use that alone, to be honest. But I could be wrong about that because one still sees a lot of variability in clinical practice.

One other thing to remember is that this issue is not static internationally as antiretroviral therapy is

not static here. Once we have issues of short-course AZT and nevirapine each individually looking good and potentially somewhat affordable, if we want to start studies to make that better, that means combinations or additional drugs or newer drugs which, in order to show efficacy, are going to have to be done internationally. Then we're going to face ethical issues, important ethical issues, about availability of those drugs in the target populations in which they're studied internationally. Those things should not be avoided. They should be taken head on.

But the natural thing is to study these AZT or two nucleosides with nevirapine or protease inhibitors, although I think the point has been made how expensive they are, but these international trials are going to go forward to better and better comparator arms. At least they need to. We can't just look at each single drug and be satisfied with a 10 to 13 percent transmission rate.

There are realities in the developing world, but I think the nature of clinical trials is going to push this envelope forward and some of that may edge a little bit closer to the standard of care in the United States, but it still will be somewhat separate I think.

Dr. Fletcher.

DR. FLETCHER: Scott, if I could just follow up

on that. So, if you take the nevirapine results and then extrapolate them to the United States where, as you said, it may not be given alone, but given in the setting with other antiretroviral drugs, are both the efficacy results and the safety results going to be the same? And we don't know. Certainly one potentially concerning issue still remains, this possible drug interaction between nevirapine and zidovudine with zidovudine concentrations being lower. So, what happens then if you add nevirapine on top of an AZT-containing regimen?

DR. HAMMER: Dr. Gulick.

DR. GULICK: Just to put a positive spin on this same issue, it's somewhat of a relief to me that across all these studies, at least there's very consistent findings that antiretroviral therapy is certainly better than placebo. Also, taking a global view, it almost looks like -- of course, you don't like to compare across many different studies -- but that there's a dose effect here, that higher, persistent doses of the antiretrovirals lead to lower rates of transmission, which also seems to be somewhat reassuring.

The other thing that reassures me is that we do have all kinds of international data here. There are so many instances in HIV where we have no data at all. At least we have something to look at and try to apply to our

situation.

DR. HAMMER: I'll try to quickly summarize this question about the comparator arms and applicability to the U.S. Although I think Dr. Fletcher raises important issues of interpretation, I don't think there's disagreement that those are interpretable if the studies are done well and that inferences will be made to incorporate those into practice in the United States. I think we've already probably seen some of that and will continue to see that. That's no different I think than any antiretroviral therapy and the extrapolations and implications that are made to quickly evolve standard of care and actually treatment of infected individuals.

So, unless someone wants to disagree that some of the comparator arms we've seen should be disregarded, I think they shouldn't be disregarded. They need to be interpreted and it's a study-by-study, drug-by-drug, regimen-by-regimen, patient population-by-patient population interpretation. Disagreement?

(No response.)

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

Dr. Wilfert.

DR. WILFERT: Well, I think, first of all, our knowledge about perinatal transmission and our ability to longitudinally assess infants helps us address this question. All of the studies that have been done have a residual amount of transmission which presumably occurred intrauterine, for lack of a better term, a residual infection rate of somewhere between 2 and 10 percent.

When you look at the comparison arms in the breast feeding populations in the first month to 6 weeks of life, there is substantially less difference between those arms because the transmission by breast milk is occurring across a longer spectrum of time. So, yes, there's breast milk transmission in the first weeks of life, but if you look at the first 6 months of life, as the study that Dr. Mofenson quoted by Dr. Miotti, it's spread out over that period of time where the breast feeding occurs. So, my response to this is for the developed world looking at those studies, when efficacy is demonstrated, maybe we might underestimate efficacy, but we're not going to over-estimate efficacy.

DR. HAMMER: Can I ask you a question? It's an opportunity to be educated about a study that was published recently in the Lancet that confused me about breast feeding and non-breast feeding and the three arms of the

study, one -- or however it was interpreted that the women who intermittently breast fed versus those that breast fed all the time had a higher rate of transmission. Was that something we should think about or is that an aberration?

DR. WILFERT: It's not an aberration. It's something we should think about. This is the study from South Africa where retrospectively with small numbers of women who were enrolled in a vitamin A trial, the women were separated by whether they exclusively breast fed, meaning breast milk only, no water, tea, or anything else by mouth, and a group of women who did breast feeding but also supplemented with little bits of whatever else and a group of women who formula fed. Now, remember, they weren't randomized up front. This is going back and asking the feeding history. The conclusion of the study was that the women who exclusively breast fed had transmission rates which were comparable to those of breast feeding implying that the feeding of additional substances does something bad, like create inflation in the GI tract and enhance transmission of virus.

I think that's a tantalizing suggestion that needs to be substantiated by a good clinical trial because there are clearly important regions in the world where breast feeding is the norm. So, the confusion is that exclusive breast feeding looked like formula feeding and we

need to learn quickly whether that's correct or not.

There are folks in the audience who may want to comment about this.

DR. HAMMER: Other comments about the breast feeding issue?

I think Dr. Wilfert summarized it nicely. Actually one of the issues, even women coming and appearing at labor are advised not to breast feed. It's a cleaner population here in that regard, but in interpretation of the studies, if anything, the differences are blurred, and in a non-breast feeding population, results might be expected to better than in a breast feeding population. Is that what you were saying?

Question 5. I think what we'll do, since we're moving, is go through all the questions here rather than break in the middle. What duration of follow-up is needed to adequately assess the safety of MTCT prevention strategies? Do you have any suggestions regarding follow-up approaches?

Since Dr. Lipsky suggested that we go through the next two generations, I think I'll ask him whether he has additional comments on this.

DR. LIPSKY: No. What's adequate and what's practical and what's reasonable? The ideal situation, just like the toxicology we heard presented, they take what

happened in the F1 generation. So, what does that mean? You'd probably want to set up a registry and have someone a generation after us looking at that. That's the ideal. Whether that's practical, that's a different question.

DR. HAMMER: It's a scary thought to think about this committee in the next generation.

But, Dr. Wong?

DR. WONG: I think this is an important point. As was pointed out this morning, almost all of these efficacy studies that are being done around the world cannot incorporate a long-term follow-up safety study. As we all know, there's been a lot of discussion over the past couple of years about the ethical burden that we have in the United States to ensure that people in other parts of the world are not exploited exclusively for our benefit in drug trials. This is an opportunity where the FDA I think can really play a role in ensuring that people all over the world have the benefit of the experience in the United States in that the long-term safety of these regimens in the children is really carefully followed. I would recommend that that really be a mandate on the companies, that they do more than is usual to follow safety of usage of these drugs in this country because it's not able to be done in many other countries.

DR. HAMMER: Thank you.

Ms. Dennison?

MS. DENNISON: I think one of the challenges is how to balance the mother's concerns for confidentiality about her status and for her children with her concern for having her children followed long term. You might want to look at providing mothers, when they give birth, some kind of envelope, file folder, something that helps them organize the child's documents that includes information about how the mother or whoever adopts the child when the mother passes can keep connected to whatever those follow-up studies are.

And the other is using the mass media and the AIDS publications to do outreach. I do the only women's AIDS newsletter that's published monthly in the country, and in all this time, nobody has ever approached us about doing outreach to women who might have been lost to follow-up who have been in these studies, and we would happily do it. So, there are mechanisms out there that haven't been used.

DR. HAMMER: Dr. D'Agostino.

DR. D'AGOSTINO: Just to follow up on the last two individuals. This is something that's bigger than just a drug company. This is a public health problem. There are surveillance projects that the government funds, CDC, and what have you. I don't see why they wouldn't pick this

up and do things more than just the drug companies. You could find out who was enrolled in studies. You could take the confidentiality very much into account, but you could move it into a different arena in terms of follow-up. I certainly think that we should recommend more than just the drug company.

DR. HAMMER: Dr. Jolson?

DR. JOLSON: I just wanted to follow up on Dr. Wong's comment and just sort of clarify what FDA can require and in what settings so that there's no confusion about it. When a sponsor comes to us and makes it clear that they are pursuing an indication, we can certainly make it clear that we would require whatever amount of safety follow-up a committee like this would think is appropriate.

On the other hand, if sponsors are doing studies without necessarily an intention of registering the product or licensing it for this indication and the studies are being done outside of the United States, then the agency doesn't really have any jurisdiction because we only regulate studies that are done within the United States unless we anticipate that they're going to be submitted in a future efficacy supplement for an indication.

So, it may be that many of the studies that we've discussed this morning -- FDA may or may not have seen them before they were done, but FDA would have had

limited authority to say, well, the length of follow-up isn't long enough or isn't intensive enough because they're being conducted outside of U.S. jurisdiction.

DR. WONG: What I'm suggesting is something else, not that the length of follow-up of the clinical studies be assigned at a certain level of scrutiny, but rather that an active program of surveillance of people who received the drug during pregnancy be established and required of the sponsors because this particular safety issue is unlikely to have been addressed in the registration trials themselves.

DR. JOLSON: You mean as a phase IV?

DR. WONG: Yes.

DR. JOLSON: Yes, and that would be the sort of thing that I'm certain we would routinely ask for for just that reason, but with some of the limitations that Sandy had mentioned earlier in terms of what is actually feasible to collect in that setting.

DR. KWEDER: I would just add to that. Philosophically we're generally in agreement. I think the balance that we have to strike is that if we're indeed interested in having sponsors pursue these indications and study them carefully, we don't want to put them in a position of giving them a disincentive to do that and forcing all use to be off label, which would create

probably more confusion and more difficulty. That's what sponsors tell us are some of the big challenges for these sorts of things, and we see them in this population, as well as in pediatrics.

DR. HAMMER: Dr. Handelsman and then Dr. Diaz.

DR. HANDELSMAN: As a pediatrician who takes part in several longitudinal follow-up studies, I can say that the antiviral registries created by the companies are very difficult in that the obstetricians have part of the data, the pediatricians have another part of the data, and there's really no incentive, aside from wanting to do good, for the patients or the providers to be really aggressive in maintaining that data. That's only over a couple of years. If we're trying to extrapolate this over 20 years, that's simply not going to happen.

On the other hand, longitudinal follow-up studies such as the PACTG 219, such as the WITS study, which do provided government funded staffing, is a lot more. There's incentive for the patients to come back. They get data. They get results. There's incentive for the providers because they get staffing to do the studies. So, I think those are much more effective than the antiviral registries.

DR. HAMMER: Dr. Diaz.

DR. DIAZ: I agree, as you pointed out,

Rebecca, that we need some innovative strategies to try and follow prospectively women and, in particular, their children. As Dr. Wilfert pointed out earlier today, most of the children that are receiving these regimens are not going to be infected in the long run, and these are going to be children that are going to be much more difficult to follow over time, especially as they pass perhaps to adoptive parents and other situations. In particular, I do feel the onus is upon us in this country to provide some of that safety data, long-term safety data, because we have children that are being exposed to a large number of antiretroviral drugs and many more combinations than are being exposed to overseas.

So, although I don't know what those innovative strategies may be, certainly funding surveillance projects and other things like that are important, and yet doing that kind of retrospectively looking back is going to be very, very difficult I think in terms of being able to find these children at a later point in time. It needs to be done kind of prospectively and done in some mechanism where there are some incentives for children who are uninfected to remain in some kind of long-term follow-up.

DR. HAMMER: Can I ask Ms. Dennison a question? The longitudinal studies or certainly prospective ones are the best, and there are challenges to that. But a question

arises in my mind is it might be reasonable to do a cross-sectional study. There are now plenty of women who have been on treatment and who had children years ago and over the last several years with antiretroviral therapy on board who haven't been followed prospectively but might be willing -- and correct me if I'm wrong -- to actually have their children looked at in a one-time cross-sectional fashion for developmental milestones. It might give us some important data about years out from antiretroviral exposure in that regard. What do you think is the feasibility of something like that to at least develop a cross-sectional data set to actually put some hypotheses together?

MS. DENNISON: Well, I'm not a researcher so I can't talk about how valid that data would be or how it would be used. But there are an awful lot of women that I think would be very enthusiastic and actually reassured to be asked to bring their children in to be monitored, partly because they're worried. A lot of them never have ever heard of anybody else who took whatever combination of medications it was that they took. So, to think that the risk that they took was not in vain or not just limited to that family but that that might help somebody else, that's a sentiment I hear expressed all the time, or the hope that maybe if they participate, somebody else might participate

and come up with something that could help their child.

One of the challenges that I see and that I experience personally is that in our enthusiasm to reassure women or to encourage them to do things that would reduce perinatal transmission, we tend to be silent or minimize how little we know about the long-term effects of these medications. After the NCI study came out, I know there were guidelines that said that women should be told about the NCI studies, which haven't even been mentioned here this morning, and then told that the known benefits of taking the AZT outweighed the unknown risks of taking AZT.

But I can tell you in the real world, I have not hardly ever met a positive pregnant woman who has ever heard that information at all and even feeling responsibility to share that with her, I understand why women aren't told that because they are already scared. They're already terrified. You don't want to make people more afraid at a time when you want to really be supporting them to do positive things for their health. But it makes it difficult to do follow-up later on if you haven't kind of let somebody know that this is necessary.

I'm aware of it. I'm aware on a daily basis that I could die of AIDS not knowing if my kids are really in the clear. We think when our children have a negative antibody test, that everything is now okay forever, and

there are very few of us I think that actually realize that the impact of these medications wouldn't necessarily be immediate, that it could be a long ways down the road. Most people think if your kid was born with 10 toes and does okay in preschool and doesn't have HIV, that it's over. Your worries are over. Everything is fine and you just try and live a normal life as long as HIV lets you.

DR. HAMMER: Dr. Wilfert?

DR. WILFERT: I can give one example, and maybe somebody is here from the health department in New Jersey.

I believe that the HIV surveillance system where the seropositive infants are reported, kept confidentially, but it's named reporting, was linked to the tumor registry and the congenital anomalies registry, but linked at one point in time by one person so that the confidentiality of the database -- if that one person violated it, it would be over. But the confidentiality of the state database and the linkage to the other registry occurred and the assessment was made about relatively short-term follow-up, but 5, 6 years' worth of what could you find in the population that was being reported, as mandated by law.

I think mechanisms like that to both ensure confidentiality and to link to existing death registries, tumor registries, congenital anomaly registries would be

one of the few mechanisms by which you could pick out the very infrequent occurrences. And, Tom, I'm about to point my finger at you because you did some calculations about sample sizes that would be necessary to detect toxic effects in populations, and if you're interested, Tom could tell you. But it's literally thousands of infant pairs, just to know what the obstacle is when you start up front to try and capture events that you want to know about.

DR. HAMMER: It would be important information on the record if Tom would like to. If you would just announce yourself for the transcriptionist. It's Tom Quinton. Tom --

DR. FLEMING: Tom Fleming.

DR. HAMMER: Tom Fleming. I'm sorry. Am I embarrassed.

DR. FLEMING: University of Washington, biostatistics.

Well, there's so much to be said. As Cathy Wilfert has indicated, we've had days and days of meetings on this very issue. My own experiences have been on the FDA vaccine advisory committee for CBER over the last 10 years where we have confronted this concept of safety assessment for vaccines. My own philosophy on this is a combination of approaches are necessary. We have to do careful follow-up of randomized trials, as well as active

and passive surveillance systems, and in the vaccine world, we use VAERS as our passive surveillance system.

As Cathy points out, it takes thousands. What we're looking at, of course, are many different levels of safety concerns, and if we're looking at safety concerns on the order of 1 in 1,000 or even 1 in 100, we're looking at sample sizes of 2,000 to 20,000. Those are conceivably doable in clinical trials. When we're looking at mitochondrial dysfunction, as we're looking at right now in the perinatal transmission area, that's 200,000. So, you're clearly in an active and passive surveillance approach.

The problems with active and passive surveillance systems, though, have been pointed out by our colleagues in the FDA earlier and that is that you've got non-randomized settings, you've got a lot of missing data, you've got selectivity. That's why it kind of leads us back into the importance of getting maximal follow-up in the randomized clinical trial setting where you're able to get more complete assessments. But then again, because a lot of safety concerns are latent or rare, you really have to have the combination with the active and passive surveillance.

So, I think that's kind of a long answer, but it's actually in a sense an inadequate answer to something

that we could spend days talking about. We really need a combination, though, of active and passive surveillance systems, together with careful follow-up in randomized trials where we're not just doing an ACTG 219 following 076.

I served on the data safety monitoring board that ended 076, but we really didn't end it. When we made the recommendation that there should be no more randomization in that trial, we urged that there be complete follow-up of all participants long term because there was a lot we didn't know about safety. That was what we said on the DSMB the day we made the recommendation to stop the continued randomization.

We can't just roll people over, though, at voluntary will to go on to another trial. We really need to have informed consent at the time the randomized trial is initiated so that we don't have the selectivity because we're looking at rare events as well as common events, and in a prevention setting, if you allow for the bias of letting people choose to be on a cohort for follow-up or following people that are readily followable, we have a great chance of missing the signal.

DR. HAMMER: Thank you very much.

Dr. D'Agostino.

DR. D'AGOSTINO: I just wanted to reinforce

what was just said. If you pick a strategy like a cross-sectional, I think you have tremendous potential for biases coming up as was just mentioned. So, again, if we do make recommendations, I think the notion of following from the randomized trials, setting up also groups of individuals that we can follow who we know what they actually got is very, very important. I would strongly suggest that we don't just come up with a strategy that we think might have a big pay off and sort of simple to do, but these multiple strategies.

DR. HAMMER: I think that's the point. I wasn't suggesting a cross-sectional study as the only study. It's a way to capture children who otherwise are not seen at all and there's no data.

Just to summarize this question, as far as follow-up, the simple answer is as long as possible. But I think what has been brought up is that studies done in the developing world are truly difficult to have any kind of long-term follow-up. Those should be maximized as much as possible, recognizing the limitations. Any study done in the United States, I think there should be a strong effort to have long-term follow-up.

The other points that I think were mentioned, though, was I think Dr. Fleming's point about active and passive follow-up for large numbers is important, but I

think we also heard from Dr. Handelsman that we need to make the registries easier. I think working with the pharmaceutical firms and the CDC to make the registry database more user friendly is probably one of the most important things to do here because although we may have 800 names in the registry, it's actually remarkably low to me and it should be a lot easier to do that.

Then I think the pros and cons of a cross-sectional analysis have been brought up but maybe could add to this at least to try to find some things out that we may be completely unaware of and may not want to wait 5 years for the prospective data to show us.

The next question is please discuss study design approaches that would provide useful information about prevention of MTCT in your community's clinical practice setting.

Dr. D'Agostino.

DR. D'AGOSTINO: We could go back to some of what we're doing with 1. If we have existing agents that we now want to talk about variations of, the ideal is always going to be the randomized, controlled clinical trials. Then if that turns out, one could say, well, we'd like to get the practice moving in the States and we'd like to learn from these non-USA studies by varying the present practice and present labeling type of claims that are in

the States already, how do you go about doing it?

Well, at least the randomized, controlled clinical trials should be considered, but these other types of large, simple trials where you still might be able to put a random component and assignment of treatment should be looked at. I think that as you start moving further away from that and you're getting into sort of an epidemiological type follow-up, you run into some tremendous bias problems. We should ask ourselves would we as a committee or consultants to a committee recommend that labeling changes should, in fact, be approved on these sort of follow-ups that don't really have a random component to it. I think they run into a lot of problems.

So, I'm back to the randomized, controlled clinical trial, keeping it probably as simple as possible, and then asking what does the committee feel about non-randomized follow-up on these individuals. But I think some sort of very clear research setting is needed as opposed to just hoping for medical records that are going to give us the information.

DR. HAMMER: Dr. Wilfert.

DR. WILFERT: I think there has to be an attempt to utilize the information which is accruing because I do think that there will be very many more women receiving therapies than are enrolled in clinical trials.

The for instance that I would use is one that I'm familiar with, but I do not wish to say that it's the best or the only.

We have data for the entire State of North Carolina almost as an accident because all the testing of the babies is done in a single laboratory. So, we also have the denominator of the now defunct mother seroprevalence study where all newborns were tested anonymously, so the number of infected women delivering babies was known up until 1995. I believe that those data have been extraordinarily useful in documenting the efficacy of whatever regimen the woman was on. Because that information is provided to us when the test is done on the baby, we know what the regimen is. And because there are some really collaborative investigators, we have access to the information from the charts on an ongoing basis.

It seems like a reasonable model because we are meticulously trying to collect the information prospectively and not just sitting back to wait for the reported incidence of AIDS to document that it has in fact decreased in the babies.

So, I think there are some other probably even better mechanisms, but we can capture these data.

DR. HAMMER: Let me ask you a question. Do you think it's an important study design question or study

question to get away from the mythology of AZT as necessarily part of a regimen? Do you think we have enough data on AZT intolerant women who have taken other regimens as far as delivery? Because one of the things we're strapped with is the excellent results of 076 that get, in an applique fashion, put on every other regimen that we, at least in this country, have to design because of those results. And it may be something magical about AZT, but it may just be that it's an antiretroviral agent.

DR. WILFERT: I don't think we have our hands on it, but I think there might be larger numbers than any of us are aware of.

Another mechanism by which it is being gathered and I alluded to is the Pediatric Spectrum of Disease project where at least initially the mothers' regimens and the babies' regimens are now captured so that you can look longitudinally at a large number of exposed infants in the United States. If you ask the question of that study that now has a database between 3,000 and 4,000 infected babies, how many women didn't get zidovudine but got other things, I don't know what the numbers would be, but you could at least ask the question and see what came out of that very study.

DR. HAMMER: Dr. Pomerantz.

DR. POMERANTZ: Just as a corollary to that,

one of the questions that I'm asked a few times, mainly because our laboratories have some interest in residual disease, is what do you do with a patient -- and it goes along with what you're saying in a little different light -- who is on HAART therapy, who has undetectable virus for some amount of time, is pregnant now, and is not on AZT or nevirapine. Are you going to change this thing that has obviously worked virologically because there may be something magical, or are you willing to let her ride through this, knowing that those that have no detectable virus, although you still have some transmission, they're pretty rare?

DR. HAMMER: My response is it depends on the obstetrician that you're working with, and that's one circumstance where not having that expertise hurts the committee because I think that there are many obstetricians, even in that setting, that would want AZT as part of the regimen, either added or substituted. But you raise an important scientific question. We don't have the answer to it.

DR. WILFERT: I don't have the answer, but I suspect that many people would not change the woman's regimen if she is suppressed to undetectable. They might consider whether, in the absence of other information, they were going to be sure they got intravenous zidovudine when

she goes into labor.

DR. LIPSKY: But there's a situation right there. Then she should get intravenous zidovudine when she goes into labor. As we just pointed out, that's not the indication. It's part of a three-part regimen.

DR. HAMMER: Dr. Handelsman.

DR. HANDELSMAN: I think as you said, it varies from obstetrician to obstetrician, and I think a particular issue is when a lot of the obstetricians will add zidovudine to that regimen. Then we run into the problem when someone is on stavudine in which zidovudine is contraindicated. Again, I don't think there is an answer to that right now.

I think one of the other populations that we need to really look at and try to design trials that will benefit are the women who are on HAART or had been on HAART and who now have a high viral load. What do we do around the time of delivery or prior to the time of delivery to try to lessen the viral load to try to prevent transmission? Those are studies which I think my population really needs to have done.

DR. HAMMER: Dr. D'Agostino.

DR. D'AGOSTINO: I think in this discussion with the question that we're looking at right now, the premise I think is that it's not good to just do off label,

that the approaches to study design should try to understand what's going on and should try to in fact move from off label to actual label claims where we can naturally state regimens that we have proof that work.

DR. HAMMER: Dr. Hamilton.

DR. HAMILTON: It seems to me that implicit in this question is that the study designs would be relevant to the community we're considering at the moment, which is United States populations. I would posit that to imagine -- and though this was discussed earlier this morning and by several others along the way -- I would think that accomplishing the design of a study that would reduce perinatal transmission from arguably 8 percent to significantly less than that in a country abroad would be challenging at best. It seems to me that really I would like to think that we, the committee and the FDA at large and the government, would see a major priority arising in the form of studies relevant to those countries in which we're proposing to do these studies.

I was very impressed with the figures that Dr. Wiktor told us in terms of the frequency with which individuals who were asked to participate in studies simply were lost to follow-up, declined, were unwilling to. These are people from whom a huge, huge price has been exacted and will continue to be exacted.

I think it also has implications for the feasibility of doing studies when they see children who are not involved in studies dying right and left. I think there are some huge social, economic problems to overcome. I'd grant you that that's not the mandate for this committee, but I think it's terribly important to keep that in mind.

DR. HAMMER: Ms. Dennison?

MS. DENNISON: In the work that I do, I see two fairly different populations of people in terms of treatment. One is people who are taking treatment for their own medical care and one of the concerns that comes up -- and I don't know how this fits into study design -- is just how difficult it becomes for people to maintain their treatment after they go home with a new baby and they're not getting any sleep and everything is for the baby, the baby, the baby. The other is that group of women who aren't on any medications right now and don't want to be. For their own health, they're not at a place yet that they want to start HAART therapy.

I would think that you would be looking at very different interventions based on whether someone was taking treatment for themselves or not wanting to. If you're not on therapy before you bring home a baby, I don't think that's the time that you want to go home starting some new

regimen. You want to figure out what can you take to reduce the risk of transmission to your baby that's also going to have the least likelihood of damaging your options in the future.

DR. HAMMER: Dr. Mathews.

DR. MATHEWS: In our practice in San Diego, the thing that has most of us worried is the increasing drug exposure. Just to put some numbers out for you, in the last 6 months, 400 new entrants into our clinic. 14 percent of them had already had exposure to all three drug classes, and there was no difference by gender. So, that creates a population of people that international trials are not going to be able to address, as I said before.

It's difficult to conceive of how a label could adequately respond to the issues of prior drug exposure and what the implications are. The scenario you were talking about earlier was the person on HAART who has an undetectable viral load, but what about the person who has been exposed to 10 drugs who has a detectable viral load and has been exposed to all three drug classes? What do you do in that setting?

DR. HAMMER: Dr. Handelsman and Ms. Dennison, whichever.

MS. DENNISON: One of the things I'm seeing a lot is women who are on HAART with undetectable viral load,

but because they're pregnant and their partner is also infected, they've been having unsafe sex throughout the pregnancy. And he has actually been non-adherent and he's got viral load through the roof.

DR. HANDELSMAN: Again, following up, I think there are some ways in which perhaps the studies done outside the U.S. can be applicable. I don't know again how ethical, how well they fit in with the populations in which they're being done, but one of the things that I would be curious to find out is in the short-course regimen, in the prenatal regimens, if they're started at the onset of labor or if they're started a week before labor or 3 weeks before labor, at what time do you see a maximal decrease, a nadir in the viral load? That might play an effect in even the heavily experienced populations. I think those studies might be helpful.

DR. HAMMER: So, I think with regard to number 6, the study design applicable to the U.S. setting, we've been given some suggestions here. Certainly the issue of women who are heavily drug experienced and undetectable are experiencing virologic failure. In the former, one can do intensification like studies, and in the latter, it's an issue of comparative trials perhaps with new agents but fairly standard designs.

Clearly we brought up before that there's a

substantial population of women who haven't seen treatment and appear at the time of delivery. That's something that can be done as part of an international trial.

The 316 trial again, which I don't know if it's considered intensification in this fashion, but adding to existing therapy or placebo a drug that has a long half-life in the baby is an interesting design. Those results are going to be pretty important.

So, I think there have been some suggestions for a design, but again I think for the United States, it's the issue of what our n is as far as outcomes are concerned and how big the study would need to be to really study it. But there are substantial populations that will provide, over probably the course of 3 or 5 years, studies that would be important.

The last question is what are other types of information should be obtained from trials for the prevention of MTCT. So, this is a general question for what else we should learn.

Dr. D'Agostino.

DR. D'AGOSTINO: I have to throw in a comment about the last question. I'm sorry to hold up.

Trials don't have to be superiority trials. You don't have to design a trial to beat some existing regimen. You could design a trial to say it's as good as

some other regimen that exists. Now, those require large samples, but then you start making the inferences, as you were talking, to the foreign studies. I think it should be made clear that it's clear that we're not always thinking that the new regimen is only good if it beats out something else. It could be just as good as an existing regimen.

I'll let somebody else answer the last question.

DR. HAMMER: Dr. Gulick.

DR. GULICK: Two things that I think we haven't spoken a lot about this morning that would be interesting. One is on assessment of adherence on these different regimens. Clearly people are leaning one way or another given how complex they are. Usually complexity impacts directly on adherence.

The other that we really haven't touched on at all this morning is cost. In weighing regimen A versus B in this country, we often don't consider costs, although maybe other people do. Certainly in the rest of the world, cost is critical. It would be interesting to see a cost effectiveness analysis of the new nevirapine regimen, for example, which in the paper they quote is $4 for the regimen. That would be helpful I think certainly to the rest of the world with reduced resources to aim resources towards prevention.

DR. HAMMER: I would say to come up with other agents and regimens that we've discussed before in other circumstances and other types of information are clearly important or some of the viral and immunologic questions that go on here. This was touched on earlier, but certainly in the international side, this subtype issue is important. It does certainly relate to at least one class of drugs, and potentially that's the NNRTIs with group O being an outlier group and a small group but still resistant to some of the NNRTIs. So, I think it's not an all or nothing issue with the subtypes and drug susceptibility perhaps, although it's largely an envelope derived characterization. But that's important.

We talked about viral load. We talked about the issues of resistance, and there are the clear-cut primary resistance mutations, but there's a lot of interest now in what the polymorphisms are that relate to both RT and protease that may not give phenotypic resistance but may be important. I think that has come up in some of the epidemiologic studies of primary resistance to NNRTIs and has given some confusing data, giving some higher rates of resistance in naive subjects that are probably related to polymorphisms. It may be interesting to actually see, particularly as NNRTIs become more common in maternal-fetal interruption, whether they have any impact on outcome.

So, there are a number of virologic characteristics and some of the more fine tuned virologic characteristics such as relative fitness, replicative capacity, et cetera, and then also viral load in general secretions, local immunity. There are a lot of sub-studies, if you will, that can be put into these larger trials, particularly if they're done internationally, which will give very interesting comparative information in different populations that I know are being thought about. At least as far as this forum, we've talked about the larger clinical result issues, but it's the underlying pathogenesis and viral susceptibility to antiretroviral agents on the immune system that ultimately determine the outcome.

Roger?

DR. POMERANTZ: Yes, let me just underline that because a couple of weeks ago there were two papers in JAMA that I was asked to write an editorial on. One of them was from Aaron Diamond and one of them was from San Diego. What was interesting is it looked at primary resistance characteristics. As Scott said, even these two laboratories could not agree on what is resistance phenotypically.

Before you take it to the next level, which is studying it with perinatal transmission, I think you have

to be very careful. There are clearly cases that are very easy to tell that this is high level resistance, both genotypically and phenotypically, but those were only even in these studies about 2 or 3 percent. If you look at most of what we call resistance, they are difficult to diagnose because the definitions vary from laboratory to laboratory.

So, if you're going to look at this -- and I think you should because I believe it's going to increase -- you have to be careful that you know what you're going to look at. At this point, I might keep it at high level multi-drug resistance because, as Scott was saying, the polymorphisms or the genotypic negative, phenotypic low level is very difficult to interpret what that means because there's no clinical correlates. I think it's important to look at, but I'd be careful that you keep the definitions straight.

DR. HAMMER: Dr. Wilfert.

DR. WILFERT: I think some of what I'm going to say is implied in what we've talked about before, but I want to be sure, and that is that there are trials asking questions about non-antiretroviral interventions which might be low cost and helpful, particularly in the developing world. Those ought to continue to be addressed appropriately.

Secondly, on the immediate horizon probably are

attempts to define whether or not an antiretroviral regimen, a very simple one, could further diminish transmission by breast feeding. That's an important, I think, follow-up. We don't know if a postpartum only intervention works. I think we should figure out how to ask that question in a way which is ethical and scientifically sound.

Finally -- and I'm sure that Dr. Sullivan and others will point this out -- but the durability of the nevirapine intervention is not immediately explainable to me on the basis of drug persisting. It suggests to me -- and John can shoot my balloon down -- that something interesting is happening with regard to the infant who is protected under cover of exposure to drug. At least the question ought to be asked, how come this effect is so long? It appears to be out to 3 months. And we need to understand that because maybe it will help us with the other interventions.

DR. HAMMER: Thank you.

Ms. Dennison.

MS. DENNISON: We need to know what motivates or prevents women from getting prenatal care in the first place.

DR. HAMMER: And I would just reiterate we need to look at viral resistance emergence in the neonates who

do, unfortunately, become infected after exposure.

Any other comments?

(No response.)

DR. HAMMER: Before we move to what I think will be a very brief open public session, are there other questions, Dr. Jolson, or clarifications that you need from the seven points we've tried to discuss?

DR. JOLSON: No.

DR. HAMMER: Okay, if not, we will now enter the open public session. There were no individuals who had signed up before, but if there's anyone from the audience who would like to make a public statement, please come forward and identify yourself.

(No response.)

DR. HAMMER: Seeing none, I will declare this session over.

Thank you all very much. I would ask the committee members to reconvene in closed session at 2:15. That is not open to the public. Thank you.

(Whereupon, at 1:10 p.m., the committee was recessed, to reconvene in closed session at 2:15 p.m., this same day.)