participate in those trials.

DR. POMERANTZ: All right, so now your 48-week study takes two-and-a-half years or so to complete, because they can't get any patients to enroll in it. Now we've really got no data in the labels for this great length of time.

CHAIRMAN GULICK: The flip side of this issue is safety. And while your patients are asking for low-dose Ritonavir, and we're all assuming it's reasonable to do, we really don't have the data to back that up. I'm uncomfortable with that.

DR. FLEXNER: I guess we do have data with Saquinavir-Ritonavir and Indinavir-Ritonavir now in the literature. There are, I think, at least three papers in the peer-reviewed literature of clinical outcomes in patients on Ritonavir-Saquinavir, and two with Ritonavir-Indinavir. And so if there's something major going on out there, it hasn't reared its ugly head yet. And so I think we can be fairly confident that if there is an increase in toxicity with those regimens, it must be happening fairly rarely, or it must be ignored in the published clinical trials.

CHAIRMAN GULICK: Just to pursue that, one question that must come up every other day in clinic is: Well, which regimen, Indinavir by itself, or Ritonavir and Indinavir at one of the several doses that are suggested, is associated with a higher incidence of kidney stones? Which of those? And I don't think there's an answer to that, but boy, we'd sure like to know it.

DR. FLEXNER: I don't think the study's been done. There's separate studies that suggest that there's a lower incidence of nephrolithiasis with some regimens than with others, but there's not the head-to-head comparison you'd want to see.

CHAIRMAN GULICK: Dr. Yogev, and then Dr. Schapiro.

DR. YOGEV: I wish the agency would listen to the pediatrician in the group, because we said before, again, yes, that for safety we need the numbers. But for efficacy, probably can go on a smaller number and expand it so you can get faster into the field. But you have to follow.

And I just wonder if this compassionate

use that are in the new molecular, as you call it, available earlier than they are really approved. Can some sort of that for the safety can built in, into the process of new formulation and so forth, or combination.

So I agree with you 100 percent on the safety. I would not give up, because we might be unpleasantly surprised. But after you are sure at least there is a trend of efficacy, and reduce the ten percent reduction to a bigger one, I have no problem with going with smaller number of patient, doing the viral load, you see that it is right direction, you got what you were expecting to, check on bigger number of safety. And I thought that's what you said before. And especially for the experienced patient.

CHAIRMAN GULICK: Dr. Schapiro?

DR. SCHAPIRO: Yes, I would continue that thought of Dr. Yogev. And I do agree also with Trip that the issue of, for example, nephrolithiasis is unresolved. I think there's actually some data which is conflicting. There's data from Australia at one dose, and then there's different data we just saw

recently at a different dose. It gets very difficult to tease out the different regimens and the different types of studies.

But the question, if there is some way of allowing -- as you discussed earlier, demanding extended follow-up and possibly allowing the drug to begin use before that is completely completed, but to mandate that that information continue to be collected. Because even 48 weeks, it's sort of an arbitrary number. I think that protease inhibitors were used for more than a year before we realized some of the complications. I think we missed them flat-out in studies.

These aren't magic numbers. Forty-eight (48) weeks is really not a magic number. I think to try to get long term with a smaller group, but requiring that actively with the company, can be sort of a safeguard. And then we find some sort of creative compromise where we don't have to wait 48 weeks, but we do require that type of follow-up, and maybe even beyond 48 weeks.

CHAIRMAN GULICK: Dr. Jolson?

DR. JOLSON: In reality, even though we've been talking about 48-week trials, routinely we have been reviewing data based on 24-week results, interim results, and that isn't even with all patients being at 24 weeks, it's with some agreed-up cohort of patients at 24 weeks. But then a post-approval of Phase 4 commitment that the 48 week or whatever longer term results are submitted.

Am I hearing you all suggest that we could even look at an earlier time point than 24 weeks, remembering that this is combination therapy and -- because we are already looking at 24 weeks?

DR. YOGEV: We burned our finger in the past with AZT. It's an excellent example, that even a year the data for the United States were not in comparison to Europe. And I think 16 showed us that we didn't get the maximum effect. So I think 24 would be my minimum.

But if there is a built-in mechanism that you put in there that -- as we understand today the compassionate use, it's not approved but it's allowed. And you wait till you get the 48, then you approve it

with the data you're compiling for more patient, where the clinical can be on a smaller one.

CHAIRMAN GULICK: Let's consider the next part of the question, which is: How should several dosing possibilities be addressed?

We saw a number of slides today with multiple ways to co-dose protease inhibitors with Ritonavir and presumably other PK enhancers. How should those be addressed in the label? That's an easy one.

(Laughter)

Dr. Acosta?

DR. ACOSTA: Well, in the absence of any 24-, 48-week clinical data, I mean, all we can really put in are the pharmacokinetic parameters, whether it's AUC, C_{max}, C_{min}. Personally, I'd like to still see clearance in there, but that's okay.

UNIDENTIFIED: You can put it in there, it's just that (inaudible).

(Laughter)

DR. ACOSTA: Yes, exactly. But, I mean, it may at least just be helpful to have a small table

showing like this combination regimen, here are the parameters, or the change in the parameters versus this regimen.

CHAIRMAN GULICK: Dr. Mathews?

DR. MATHEWS: The problem for me is not putting that kind of information in or requiring it, it's the sample sizes and how confident you are in what those estimates are.

And to get back to Jeff's point about are we willing to recommend a less strict standard for some of these equivalency comparisons I think a lot of it depends on the population that's being studied and if the confidence interval overlaps some measure of susceptibility.

If it's the situation where there are three to tenfold above the IC_{50} or IC anything, doesn't really matter. You could tolerate a smaller sample size. But if the point estimate is -- I mean, if the confidence intervals are going to substantially overlap some threshold for efficacy, then there's an obvious problem. And if you consider the situation, let's just say if you had -- say 200 milligrams of

Ritonavir would give you the biggest margin of efficacy, but then that's overlapping with the toxicity spectrum, so you want to drop it back. It seems like a small point upping the dose by 200 milligrams a day, but it may have substantial implications for both toxicity and efficacy.

So I think the sample size issues are very important in sorting out which kind of a dosing regimen you would recommend.

DR. YOGEV: Let me raise it in a different context. I think what we are missing in this discussion is how much toxicity we're willing to take compared to the stage of the disease. To me it's fascinating how much more my colleagues in cancer are willing to take toxicity. And maybe the issue is because they have a cure with a higher toxicity, which we don't have. But I think I'll go much further with toxicity on a patient who, in a "salvage portion" that there's nothing else, than in a naive patient.

So I would like to see both, whatever level it is, both how much higher it is, because we already said that if C_{min} at "X" is okay, if I get five

times over it I'm doing okay; but it's under, I can go 25 and I pay with more toxicity. That should be maybe available for me or my colleagues to negotiate with our patient, because he is in a different setup of disease. And I, for one, will take much more toxicity in a patient when I'm running out of options, more severely sick, and on. So I would like to see all of them, both the PK and hopefully toxicity, all those.

CHAIRMAN GULICK: Dr. Fletcher?

DR. FLETCHER: I want to just raise the other side of the criteria to place recommendations in the labels regarding drug-drug interactions, which is the adverse drug-drug interaction. It seems that the usual standard used is: The area under the curve or clearance is affected by less than 25 to 30 percent, it's not clinically significant. But the basis for that statement, to my knowledge, almost never exists. There are no clinical data to say those interactions are not clinically significant.

Couple of examples. Nevirapine lowers Zidovudine concentrations; Ritonavir lowers Zidovudine concentrations. The labels I'm pretty sure for both

say that it's not clinically significant, and we don't know that.

Dr. Gerber I think correctly mentioned that the concentration response relationships for many of these drugs, the PIs in particular, appear to be quite steep. So a 25 percent reduction, a drop, let's say, of a Nelfinavir concentration from 1000 to 750 nanograms per mL, could be very clinically significant.

So, as we think about these recommendations for the PK enhancement side, I also think we really need to come back and reevaluate the recommendations for saying a drug-drug interaction is not clinically significant when there are no data to support that.

CHAIRMAN GULICK: Dr. Flexner?

DR. FLEXNER: Courtney, again, in theory I completely agree with you. Even a one percent decrease in my antiretroviral concentrations might be something I don't want to have happen to me.

However, there's two issues around this. One is if you see in a package insert that combining

Drug A and Drug B resulted in a 25 percent or a 20 percent decrease in the AUC of Drug A, the confidence interval around that 20 percent often overlaps, with no change in AUC. So those studies are often not powered to be able to say with great precision that the change was, in fact, 20 percent rather than 15 percent or 50 percent.

The second issue is: Where's the evidence that decreasing the dose of one of these drugs by 25 percent is associated with a significant bad outcome? And actually there is some evidence out there. A 25 percent decrease in the Indinavir dose, when you give Indinavir as a sole PI with nucleosides, was associated with a significant change in viral load responses. So there is some evidence out there for Indinavir. I don't know that we have that much data for other drugs, at least as currently used. But that's something that would need to be factored in, obviously.

DR. FLETCHER: What I thought you were going to say, Charles, was that, "But we can't do these type of clinical studies for all drug-drug

interactions." And I was going to agree with you on that. But where two drugs or three drugs are going to be used frequently in combinations, such as, perhaps, Cyovinine-Nevirapine for maternal-fetal transmission, perhaps that interaction really does need to be studied to see whether it's clinically significant or not.

So I'm not saying we have to tie ourselves in knots and everything has to be studied. But where the frequency of use is high enough, and the consequences of the adverse drug-drug interaction severe enough, as I would think maternal-fetal transmission would be, I think we ought to know whether some of these interactions that we call clinically insignificant, are truly that.

UNIDENTIFIED: How would you do that?

DR. MASUR: The question is: How would you do that? I mean, some of these studies I think are great to propose, but the question is, you know: How do you actually perform them in some cost-effective way?

DR. FLETCHER: Well, I don't know, design-

wise, that it's a whole lot different than the enhancement side. You know, Jeff and Kim talked about, you know, a study to look at virologic effect when you're boosting a regimen. Well, you could look at virologic effect when you're -- if you will -- kind of un-boosting a regimen, you know, so to assess the effect of that drug-drug interaction. And if it's adverse, I don't know why you couldn't detect that in the same time period that you could detect the benefit of a beneficial drug-drug interaction in that same, you know, 24-week period of time; probably sooner, I would think.

CHAIRMAN GULICK: Dr. Pomerantz?

DR. POMERANTZ: Yes, I want to go back to what Charlie said, which I think is a good point that brings up what you want in a package label. Now, you can't make the print any smaller.

(Laughter)

So you have to decide how you're going to do this. As an example, you used a 25 percent change in Indinavir as a sole PI in a triple drug regimen, which was shown to be significant virologically.

DR. FLEXNER: Actually, I think that was only from Indinavir monotherapy studies, and there may be some people here from Merck who can back that up. But I know that I think decreasing the dose from 800 to 600 TID was associated with a difference in at least short-term antiviral effect.

DR. POMERANTZ: Well, let me give a case where that might be important. And it's hard to put these things in clinical labels. We know now, from many studies both in the United States and Europe, that the height of the initial RNA level when you're therapeutically naive does determine your chance for becoming undetectable, and the strength of maintaining undetectability.

If you start out with 750,000 copies, it's a lot different than if you're being treated at 10,000 copies if you're naive. That may be a real difference where you can get away with one group of drugs with the 10,000 group of people, but you can't get away with trying to make them undetectable if you're treating the greater-than-750,000.

Now you get to what Dr. Masur talked

about: How many studies do you want to do for a particular drug? Are you going to take that drug, when you've changed it by 25 percent, and then say, "Well, you're going to have to get a group of 10,000, a group of 50,000, and a group above 500-, 750,000"?

Now, there's data suggests that you would get good information from that, and that they will differ. But are you going to require it, rather than just let the physician know -- who sort of knows about these things -- yes, that person at 750,000 you should edge on having a stronger drug combination, rather than how you might treat someone who comes to you with 10,000.

CHAIRMAN GULICK: We need to draw some closure here and move on to tackle the last couple of questions. I guess you could say drug interaction issues have been very complicated, to say the least.

(Laughter)

The agreement that we heard was that providing some data is better than providing no data at all, which is what most clinicians are using right now; no data at all. We heard suggestions that having

the PK parameters alone at least would provide some indication. There were concerns about safety, variability, patient populations, et cetera.

Let's move to pediatrics. Once an alternate regimen has been identified in adults so successfully, should we expect identical PK profiles in children, or only equivalent critical parameters? And does this apply to all drugs and all sub-populations, or are there different situations?

Dr. Yogev?

DR. YOGEV: And the answer is definitely different. First of all, it's probably the formulation we'll be taking with pediatrics will be completely different than adult. So you have an issue of the formulation. Either interaction in the gut, because of the liquid, effects of PH and so forth, what you're really getting, absorption is different.

I think it's wrong to say pediatric without defining that they are so different in different ages. We burn our finger again and again and again. And the interaction might be even more. The foods that pediatric are taking in different ages

are different, it might affect differently.

So saying the pediatric unfortunately present to you with so many different factors, it has to be done in pediatric separately, and at least because of the numbers issue, whatever, at least a pharmacokinetic for sure.

But I have a lot of problem also with side effect. I'm amazed how many of my patients ask for Ritonavir instead of ice cream and when they're adult, they don't want even to look at Ritonavir. So there is a major difference in side effect that, because of the constraint United States we must maybe limit the number. But you cannot interpret the adult side effect and pharmacology to pediatric. It's a different planet.

CHAIRMAN GULICK: Dr. Hansen?

DR. HANSEN: Just going to remind us of something else, and that is that I think not only obviously is our transmission rate down in terms of perinatal infection, but also I think the likelihood in the future that we'll see, quote-unquote, "naive infected children" will become a much less likely

option. Because, unfortunately, with extended and more use of Zidovudine and Nevirapine and other kinds of drugs, I fear that we will see children who will have resistance at the beginning of their infection.

So the first thing just to acknowledge, is that the naive population in children will probably be in our teenagers, and not in our babies. And so, just as you start talking about what you develop for naive and experienced children, I think you should just think about will they really be babies that are naive. I don't know. The data on Nevirapine is a little worrisome, and so just that heads-up.

Our numbers are small, and that's the bottom line, and they always will be small. So you just can't hold us to a sample size with a delta change that comes up to 500 to 700. It's never going to happen. So I think smaller numbers for whatever you're looking at is going to be important.

We've already been burned on two drugs, one a PI and one an NNRTI, and had to do dose-ranging studies effectively, even though we thought we were not doing them, by using adult parameters. That begs

the question someone brought to my attention, that maybe the C_{min} we used in the adult parameters was not correct in the first place. I don't know. But either way, maybe we need to be very careful in the pediatric population and assume that we're going to have to do those studies.

And then I think Ram also addressed the issue of differences in age groups. Not only in the younger age group, but I would also challenge us to think about the young teenager, even though most of us from a legal perspective, think of somebody's who's 13 to 19 as an adult, and that we can do that. It is a time of significant changes, and I don't know how those changes impact, in fact, PK; and I don't know how those hormonal changes or other changes and other things that are going on in that group of youngsters will impact their responses virologically.

CHAIRMAN GULICK: Dr. Fletcher?

DR. FLETCHER: One of the issues that's important, I think in this question, is the definition of "equivalence." Would we say that if the mean PK parameters in a child and adult are the same, that's

equivalent; or would we go to the more strict bioequivalence definition of the confidence intervals?

In the first example, I really worry about just comparing, let's say, a mean area under the curve in a group of children with that that's produced by the alternative regimen in adults, because it's that tail of the distribution that you're not seeing. What proportion of children are less than some worrisome value?

I would feel better about a more bioequivalence type definition of equivalence, in terms of then saying, okay if that alternative dosing regimen in children could meet that type of definition, then perhaps we can feel better about just PK parameters forming the basis for an alternative dosing regimen in children, and then not having to do the larger, longer-term safety antiviral-effect evaluation.

CHAIRMAN GULICK: Dr. Bertino?

DR. BERTINO: If I can put my pharmacist hat on here and not talk about the antiretrovirals, talk about the vehicles that are used for the

antiretrovirals, and I think that that's an important consideration. And we just reviewed this with FDA about Amprenavir and the large amounts of, I think, propylene glycol it is in that preparation. And so you need to also factor that in, to make sure that children are not getting large doses of these things to soluble-ize or stabilize or emulsify the antiretrovirals, also.

CHAIRMAN GULICK: Dr. Yogev?

DR. YOGEV: You probably could help me on that. When you say bioequivalence, I hope you're not mean to the adult. I think one of the major problem we have in the adult, showing so beautifully, that the response depends on the viral load. And in pediatric we are one load or more, especially in the young one, above. So if you take a bioequivalence to adult to compare, you already doom the pediatric to be less effective.

And if we say to prove bioequivalence, for example, take a drug like Ritonavir that we now find out that we need almost a third more in less-than-two-years, and for sure less-than-a-year or six months, is

that the bioequivalent we're talking about if there is a new formulation that you're looking for? Or would we accept adult bioequivalence, whatever C_{min} or area under the curve?

DR. FLETCHER: I think I understand what you're asking. But let me maybe try to expand my example a little bit better.

Let's say we have two -- a standard regimen and an alternative regimen in adults -- and they were shown to be virologically equivalent. What point I was trying to raise, then, if we're going to look at that alternative regimen now in a child, what definition of equivalence -- and now I want to make this pharmacokinetic equivalence -- do we look for? Do we look just for a comparison of the mean value between the alternative regimen in a child and the alternative regimen in the adult, or do we look for the more rigorous bioequivalence type of definition of equivalence?

And I would argue we need to move at least more towards the more bioequivalence type of definition, because it's going to protect I think what

you're worried about, Ram, which is children being under dosed --

DR. YOGEV: Exactly.

DR. FLETCHER: -- because we simply compared mean values between adults and child.

DR. YOGEV: What I'm trying to suggest is, the agency -- and correct me if I'm wrong -- usually is accepting to start a dose which will give the same area under the curve as an adult. And we found out in the pediatric more often than we'd like to, like Ritonavir-Nelfinavir, that you need more of the drug than the adult. So when a new combination come or a new formulation, I'm encouraging to look into what is the new one and not what was there as a definition to start comparing the drug and saying the same in the opposite way.

CHAIRMAN GULICK: Dr. Hansen?

DR. HANSEN: I just wanted to second what Dr. Bertino said about additives. Because during that first year and second year of life you're having a tremendous amount of antigenic challenge. It's stimulated by the medical community, which in itself

has raised concerns from the FDA, and made us all go back and just look at childhood immunization. So it will be important for us to take a look at that.

I'm not worried about mercury. Don't misunderstand me. But I do think that we need to be really cognizant of what is in that, how much alcohol is really there, what's going to create problems for us such that, first of all, it tastes so nasty that it's horrible, unless you can do something with barbecue sauce, from a Texan, of course, or --

(Laughter)

-- or you're not placing them at some risk and meeting some other -- or maxing out on some other FDA requirement.

CHAIRMAN GULICK: Dr. Murray?

DR. MURRAY: Well, I just wanted to say I think when we pick out the initial dosing regimens for children we are never really equivalent, from a bioequivalence standard, to the adults. I mean, we're lucky if we get six to eight children for each childhood age group like two to six, six months to two. I mean, we're just ecstatic if you have eight to

ten patients. And so, I mean, it gets whether it's mean or -- really, we just kind of look at all the data, and a mean on such a little number of patients, I mean, you're basically looking at all the data points, essentially.

I think the question was, as the age gets younger a lot of times, the drug appears to clear faster and you can't match all the parameters. So that in order to get the same AUC -- and if you think C_{min} is important, to get a good C_{min} -- you might also have to increase C_{max}.

And so I guess it's back to the -- we've been going around and around what's the important parameter. I think the question, what we're trying to ask, if you had to match parameters for children and adult, which ones would you try to match on, knowing that they're not going to be all the same? Which are the critical ones that you would think are important?

DR. HANSEN: I think Dr. Fletcher actually gave a good idea about that, and I would agree with his comments.

DR. FLETCHER: Yes, well, if I really had

to, I'd really look for AUC for the antiretrovirals. Based on what we know, I'd really try to match on AUC and C_{min} first, and then go from there.

And I understand the point about the small numbers of children, just having any data at all. And I guess I'm just suggesting I think we need to look closer at what those actual pharmacokinetic parameters are, what is the range; and distribution-wise, what proportion go below certain values.

DR. HANSEN: Just as suggested in the adult population, if you're going to compare, then I would just say make sure that for pediatrics you also feel real comfortable with the C_{min} that you picked in the adult studies, because if later that's flawed, then we're flawed by definition.

CHAIRMAN GULICK: Okay, Dr. Bertino.

DR. BERTINO: It's another question for people who I'm sure know a lot more about this than I do. What about using the metabolic weight calculation to come up with your initial dosing regimens for kids? Courtney, you may be able to comment on that.

DR. FLETCHER: Well deriving that first

starting dose the first time you go into children, it's not a straight-forward thing, whether you do it on body weight, milligrams per kilogram, or per meters squared, or you go to the more allometrically scaled type of formulas.

Our experience with at least the PI and the NNRTIs says we get a better starting dose when we tend to go with body surface area or we go with -- you call it a metabolic weight, or it's also the same as some of these allometric formulas. It doesn't mean that's where we end up, but we begin to approximate adult exposures better when we start there.

The difficulty becomes if you use the allometric formulas. For people that haven't seen them, they're weights and heights, and they're raised to exponents, and they're not something that you can easily calculate or dose from. Then how do you translate that back into dosing guidelines that can be easily understood and interpreted and calculated? So you'll end up still having to make cut points with weights and ages and things like that. So that's the challenge.

But from a drug development point of view, to just finish, we will under dose fewer children if we at least start the dosing, I think, with those type of formulas.

DR. BERTINO: So if you were to say you wanted to study a new agent and use those formulas for your studies and then convert it back, in the PI, into milligrams per square meter or whatever, would that be reasonable to do?

DR. FLETCHER: Yes, I think it would. Like to ask the pediatricians, get their point.

Because there's some question, then, that comes is: What error do you introduce? And so, if you're going to dose a drug on a body surface area basis, what error might you introduce in the calculation of that dose based upon the calculation of body surface area? I'd like to hear what Celine or Ram have to say about that, but I think most pediatricians are probably pretty good at being able to calculate BSA and so I tend to think that's not a major problem.

But yes, Joe, in principle that's how I

would think. You're going to have to translate it back to something that's easier to use.

DR. YOGEV: You're correct, maybe, on pediatricians don't have some problems. But family physicians may have some issues about the surface. And that's why it would be nice if we could convert it later. But in the real situation, I think you should go with meters squared. But, for example, many people in herpes simplex left the meter squared and used milligram per kilo just because it's easier to perform, not to mention the measurement of length is quite inaccurate in many situations, the younger you are.

So I agree with what you're saying wholeheartedly, but we need to keep in mind that the agency might consider what milligram per kilo, at least for the older kid, would be better.

CHAIRMAN GULICK: Dr. Hansen?

DR. HANSEN: I agree that translate better outside of academic areas where you're talking to somebody in a very small town who's trying to pull out their old Harriet Lane saying body surface area. Did

he get a burn? I don't remember that.

The other issue I was going to bring up, related to weight, actually, was the teenager. And we have a lot of our perinatally infected kids are teens now, and they're small, they're really runted, and they're not a 50-kilo adult. And those are the guidelines that we have for them. And I think in the public hearing we heard some requests that we think about gender differences as related to weight.

And I would just have you remember age differences as related to weight, not only for my teenagers, but also because I have older people that I care about they seem to get a little bit skinny, too. So we just need to think about weight in the adult population, if you want to call adolescents adults.

CHAIRMAN GULICK: So, just to sum up, it sounds like certainly you cannot just extrapolate from adult pharmacokinetic parameters to children. We're reminded, of course, even within children, that there are different subgroups; not to forget about incipients; and that data may be hard to get, simply

because of numbers of patients. Let's move to the final --

DR. GERBER: Just one quick question. I'm not a pediatrician so I -- is there any difference in protein binding in the pediatric population of these drugs, especially PIs or NNRTIs, than adults?

DR. FLETCHER: I'm not aware, John, that anybody's looked.

DR. YOGEV: The few which we look in antibiotic, there was not. But in those, I don't know.

Before you go to the last one, I just unfortunate thought on the question. I just want to put a clear request, demand, whatever. Pregnant women. I think it's a major problem. We have women taken off medication because supposedly there is no data. Teratogenic is carried over even that you cannot give a Nevirapine delivery because it teratogenic.

And I would appreciate if the agency would change criteria, that, for example, my own IRB is giving me a hell of time every time when we exclude

every women. We're just saying it's totally unfair not to test this population, which is unique and need to have the data, and would help us to the pediatric, is less resistant of what you mentioned before. But things which are now done are even less known than in pediatric, how to deal with those drug in this population.

CHAIRMAN GULICK: Thanks for that. Let's turn to the last question.

In the last couple of minutes, what kinds of studies are needed to better define PK/PD relationships for antiretroviral drugs? Something we've come back to pretty much all day.

Dr. Mathews?

DR. MATHEWS: I just want to talk about the perspective of the treating physician again, because you can't spend a whole day talking about this without the issue of therapeutic drug monitoring coming up.

And given the variability in pharmacokinetics, I think that this issue can't be avoided anymore. And the problem is, we can't bring

everybody into a CRC to measure AUCs in the acute and chronic dosing setting. And I think that there needs to be studies which correlate with the more established pharmacokinetic measures, with simply-measured time, post-dosing levels, and so on, that correlate reasonably with the more established parameters, so that these kinds of measures can be used in the practice setting.

And if you think about it, the denominator of the C_{min}/IC_{50} ratio is now available in clinical practice, and we don't have the numerator at least routinely available yet. And this kind of data could be generated.

One of the studies, I noticed the abstract on Nelfinavir, where there was data on a two-hour post-dose, which is quite reasonable to get in a clinic setting. Whereas, coming in first thing in the morning for a C_{min} is a bit more difficult.

CHAIRMAN GULICK: Dr. Gallicano?

DR. GALLICANO: Just to further elaborate, I'm aware right now that there are three major therapeutic drug monitoring trials going on in the

world: one in Canada; one in Holland, through Richard Hoetelmans' group; and through David Beck in the UK. And they're specifically designed to look at the clinical utility of therapeutic drug monitoring.

Most of these studies will look at two time points: C_{min} and a pseudo-C_{max}, which is either a two- to a four-hour time point. One thought that has been going into these studies is not to use the observed time points. And that's really what we've been talking about throughout this whole discussion, is when we relate PK/PD measurements, we're looking at observed PK exposure measurements versus pharmacodynamic parameters. The problem with these single time points is, because of non-adherence, as John has pointed out, these patients often come to the clinic a little later than what they should be, through whatever reason.

And what we're trying to do now is to establish population pharmacokinetic models for all the protease inhibitors, such that these observed parameters, whether they're taken at eight hours or 12 hours, can be corrected for body weight and corrected

for the time that the sample was taken, and a predicted value is generated, and then those are plugged into your PK/PD models. And also, they are used to correlate to your virologic parameters.

So I think that's a move right now to get away from observed values because of the problems with variability, and try to minimize those through PK/PD model similar to what Terry's been discussing.

CHAIRMAN GULICK: Dr. Flexner?

DR. FLEXNER: Well, I guess, just as a general response to this question, what I come away with from this session today is that my colleagues and I in clinical pharmacology have failed to move the clinical practice community into thinking that we can substitute pharmacokinetic and pharmacodynamic data for clinical endpoint studies.

And it reminds me quite a bit of the discussions we had eight to ten years ago about using surrogate markers like CD4 and viral load effects to evaluate the potential clinical utility of new antiretroviral drugs. And it took several years and studies, and some persuasive investigators, to

convince the FDA that we could use changes in viral load to substitute for clinical endpoints. And I guess it's going to take several years and larger studies and more persuasive pharmacologists to convince this group that we can use pharmacologic endpoints to substitute for clinical endpoints.

It's interesting, in that, out of necessity, we seem to be paying more attention to pharmacokinetic data in pediatric recommendations than in adult recommendations, because we can't do endpoint studies with different -- clinical endpoint studies with all the different dosing regimens in the pediatric population, because there aren't enough patients. And I wonder if we'll soon be approaching that situation, at least, with eligible subjects in the United States. Maybe that will push us to gain more faith in our pharmacokinetic and pharmacodynamic models.

Anyway, I hope that the therapeutic drug monitoring trials will not only improve our understanding of the treatment of this disease, but also focus attention on the potential value of

pharmacokinetic parameters in clinical practice.

I'm less sanguine that those trials will have an impact on today's discussion regarding use of PK/PD endpoints in regulating approval of new drugs and new regimens, and I fear that applying a standard of clinical endpoints to development of new formulations and new regimens is going to reduce the number of prodrugs and new formulations that are brought to the FDA for approval, and also mean that accommodation regimens involving approved drugs will just simply be used in the community, with collection of data as we see fit, and with no or little regulatory oversight.

With respect to the studies that I would like to see done, I think it would be nice to continue to do prospective trials to define target concentrations for all of these regimens associated with acceptable toxicity and virologic outcome, and I know that a number of those trials are currently in progress.

I'm a little bit worried that the -- if you consider weight of evidence and which study

designs are most likely to provide you with the most convincing results, the best way to evaluate a pharmacokinetic endpoint is to randomize patients to a pharmacokinetic endpoint. And that's not being done in most of the prospective studies that are being conducted, at least in the United States.

And so, for example, concentration-controlled clinical trials or dose-individualized clinical trials, at least prospective randomized ones, as far as I'm aware, there isn't a single one taking place in the U.S. right now. So we may be stuck with decision-making based on less than optimal trial designs.

But, nonetheless, I think we will continue to learn, and we've got a lot of work to do.

CHAIRMAN GULICK: Dr. Bertino?

DR. BERTINO: I think also in terms of some other studies that need to be done, since we're seeing patients with HIV living longer, and we're seeing other concurrent drug therapies that are not antiretroviral -- lipid-lowering agents, things like that -- the patients with hep C and the dilemma about

using Ribavirin and interferon in these people with drugs like Zidovudine and the possible downside to those kind of things, I think we really need to see those studies to try to sort that out.

So, not just with antiretroviral studies, but with the other therapies of infectious diseases and other chronic diseases or antiretroviral drug-induced iatrogenic diseases, drugs that we use.

CHAIRMAN GULICK: Dr. Yogev?

DR. YOGEV: I disagree with Dr. Flexner that you failed. I think you are at the beginning of a very difficult road, but many of us are convinced that the PK had something in it, we just can't put our finger on it. But you just sound to me like ten years ago people stood up in meetings, says, "It's the virus, stupid," and we said, "It's the CD4, idiot," and we were kicked out. And the CD4 now becomes an important factor.

And it's fascinating to me how people today are still fighting over what these codings mean and still trying to change therapy, when maybe we don't need to because we don't know. So --

DR. FLEXNER: So should I say, "It's the C_{min}, stupid," before you beat me to it?

DR. YOGEV: Yes.

(Laughter)

DR. YOGEV: And I say, "Just check on it, idiot." No.

I would like to help on what you're saying. One of our major problem is really compliance. And I never saw any company or any study which were done PACTG, forcing us to do a PK level at a time we consider failure. And we are just doing it in a population, PK, we are thinking about it.

Another thing, we need a prospective study when a patient declared to be failing, before he's taken off medication, a PK should be taken and we identify the potential important one, which is the C_{min}.

And there is nothing better than a C_{min}, because the if patient lying to you and they say they took it 12 hours ago, and you don't find it there, where you are because you know what the range is. So future studies should impose to look for the PK, and

it's importantance in that environment, how it's doing, and maybe even on those who are supposedly doing well, especially those who came down from the 750,000 to undetectable, which are not many. Are they high on the PK than those who came down from the 10,000 or the 20,000 only to the 5,000?

And we might get, by that, some notion of where is the importance of the PK, the C_{min}, for example, or the C_{max}, or whatever in that different response to the same therapy. Are we really in the travel of the two logs differences, or is it really only one of the factors that we can identify, taking out, let's say, adherence problem, but it might be other metabolic and so forth.

CHAIRMAN GULICK: Dr. Gerber?

DR. GERBER: Yes, I just wanted to say, I mean, measuring levels for adherence is flawed. For example, if somebody is failing and you did a C_{min}, and that C_{min} could be absolutely perfect or great, and it still doesn't tell you how the person was taking the medication for eight weeks prior to that, and that might be the reason he failed.

And I think it's an important concept for people to understand that when you take single levels that gives you only an idea of what's been going on in terms of the last few days, in terms of drug taking. And I worry about that, because I don't want people to walk away thinking that you could use TDM to look at adherence, because you can't. And I think Terry knows it probably better than anybody else. And I just --

DR. YOGEV: I was not mentioning one. I thought once a month you take it in a population, sub-population, and follow them to see those who failed, those who didn't, what happened to their PK along the road.

So, you're right, point in time, it's no good. But we had a patient who claimed he took the medication, and we look at his PK. And we have one patient who was zero all the time until we found out, after his mom unfortunately died, that everything was under the bed. So when we did multiple, it came out something is wrong over here. But when you do one, you're absolutely -- so what I'm suggesting is progressive population, sub-population, PK, do it once

a month as we do viral load.

DR. GERBER: I think if you want to pick up patients who may be hyper-metabolizers, you probably want to pick it up very early. And if you want to do maybe TDM after two weeks or something with an observed dose, that you may be able to pick those patients up. I have a feeling -- and this is a personal feeling -- that those will be in the minority in terms of the ones who eventually fail.

CHAIRMAN GULICK: Dr. Fletcher?

DR. FLETCHER: John's heard me comment on this before, so, I mean, of course I agree with him. In terms of the problem -- and particularly with these short half-life drugs and trying to use them as surrogates for adherence -- but if drug development leads us to compounds that have longer and longer half-lives -- such as, for example, the non-nucleosides -- there they do become, I think, better surrogates for telling you now about dosing for the last week, the last two weeks, and, as half-lives get longer, perhaps even further back than that. So I think there could be some potential utility, depending

on what happens drug-development-wise.

The only comment I want to add is to really agree with Charles in terms of the potential value or the value of concentration-controlled studies in the drug development sense, in that they specifically allow you to test a hypothesis: Is this concentration important or not? And you can randomize between two different concentration exposures, you can compare with standard dosing. So, as a type of trial design to allow you to test specific hypotheses, that design, that trial has a lot of value.

Now, however, there's a down side to them in terms of quantitatively understanding a PK/PD relationship, because now you may narrow in on a smaller range of concentration exposures. You may not have this broad understanding of what the overall concentration effect relationship is, but I think that the up side of specifically testing two different concentrations, or one concentration versus standard, really is the strength of that.

And then, just to mention that it's come up several times, but it's not just one drug in a

regimen that contributes to the effect, it's all the drugs in the regimen. And so if one goes down this road, I think we need to be careful about presuming that we could control the concentrations of one drug in a regimen, and that that is going to be important enough that it will make the regimen work or not work.

As we learn in particular about nucleoside triphosphates, their intracellular concentrations on the data available so far are going to be even more variable than the plasma concentrations of PIs and NNRTIs. So that's going to be an issue we won't be able to ignore.

CHAIRMAN GULICK: So I guess what we're hearing today is that, first and foremost, that we need additional studies to relate specific PK parameters with virologic outcome and safety. That therapeutic drug monitoring is going on right now in pretty large trials.

That an interesting design would be a prospective but concentration-controlled approach to drug levels, which currently isn't being done. That we can't forget about the other drugs that patients

take that also have affects on the antiretrovirals. And then issues of adherence also remain paramount.

So with that, we'll sum up and stop. I'd like to thank all the presenters and the discussants for a very lively, far-reaching discussion which I think has been very helpful in crystalizing the issues. Thanks.

(Whereupon, the foregoing matter concluded at 4:57 p.m.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Antiviral Drugs Advisory Committee

Before: Food and Drug Administration

Date: July 25, 2000

Place: Gaithersburg, MD

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.

Rebecca Davis