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Question and Answer Session

Moderator: KEVIN ROBERT FROST[1]

Participants: PAUL BELLMAN, M.D.,[2] CALVIN J. COHEN, M.D.,[3] JUDITH CURRIER, M.D.,[4] JAY DOBKIN, M.D.,[5] WAFAA EL-SADR, M.D.,[6] MARK HOLODNIY, M.D.,[7] AMY LEONARD,[8] SAMUEL MERRICK, M.D.,[9] LAURA PINSKY, C.S.W.,[10] DAVID RUBIN M.D.,[11] ANITA VAUGHN, M.D.,[12] and MICHAEL SAAG, M.D.[13]

PROPHYLAXIS OF OPPORTUNISTIC INFECTIONS

QUESTION: In your clinic do you stop prophylaxis for PCP when patients go up above a CD4 count of 200?

DR. CURRIER: Not routinely. I enroll the patients in the ongoing study, if they are interested. Sometimes patients stop prophylaxis on their own and do not tell me that they have decided to discontinue it. But I have not been routinely recommending discontinuation without more data.

MR. FROST (MODERATOR): What about *mycobacterium avium* complex (MAC)?

DR. CURRIER: It is [stopped]. But I do not go around discontinuing it as a matter of routine.

MR. FROST (MODERATOR): Dr. Rubin, do you discontinue MAC therapy or MAC prophylaxis?

DR. RUBIN: Yes. However, I am not doing a study, so I understand why you [Currier] do not. But I believe that CD4 count is probably the biggest risk for acquiring MAC. As a result, once my patients' CD4 counts bound over 100, I will routinely stop it. For those patients who do not respond to the HAART regimens, I will maintain it. Fortunately, it is a relatively small percentage. I will never stop *Pneumocystic carinii* pneumonia (PCP) prophylaxis unless there is some . . .

MR. FROST (MODERATOR): Is there a positive blood culture that you might use or a negative blood culture to guide you, or do you just look at the CD4 counts?

DR. RUBIN: If someone has what might be an incubated case of a disseminated MAC, that is a different issue. But that is a clinical judgment, and that has to be individualized. In terms of just as a way to approach it, it is one of the prophylaxes that I feel comfortable stopping.

[1]Director, Clinical Research and Information, American Foundation for AIDS Research, New York, New York.
[2]St. Vincent's Hospital, New York, New York.
[3]Research Director, Community Research Initiative of New England, Brookline, MA.
[4]Assistant Professor of Clinical Medicine, University of Southern California, Los Angeles, CA.
[5]Associate Professor of Clinical Medicine, Department of Medicine, Columbia Presbyterian, New York, New York.
[6]Director, Division of Infectious Diseases, Harlem Hospital Center, New York, New York.
[7]Assistant Professor, Stanford University, Director, AIDS Research Center, Palo Alto VA Medical System, California.
[8]Assistant Director of Education, AIDS Foundation Houston.
[9]Assistant Professor of Medicine, Associate Director, Center for Special Studies, The New York Hospital-Cornell University Medical College, New York, New York.
[10]Columbia University, New York, New York.
[11]Clinical Instructor of Medicine, Cornell University Medical College, Director AIDS Center, New York Hospital, Queens, New York.
[12]Newark Community Health Center, New Jersey.
[13]Associate Professor of Medicine, Director, AIDS Outpatient Clinic, University of Alabama, Birmingham.

DR. EL-SADR: There are two studies that I am going to refer to answer these questions. One is a study that Dr. Currier is leading, the ACTG. The other study I am leading, the CPCRA. There are many sites in New York City that are currently trying to enroll patients for these studies.

I am concerned that a lot of people are doing simply what they feel comfortable doing. How much are we going to be able to learn from these observational data? Obviously, a selection bias enters in with who we decide to stop and who we decide to continue on prophylaxis. Probably the only way we are going to learn definitively as much as possible is to enroll these patients in studies so in the end we can recommend something that is safe and effective.

MR. FROST (MODERATOR): What about CMV disease? Is there consensus around that? How many of you use prophylaxis with oral DHPG at less than 50 CD4 cells? Dr. Bellman, do you use it?

DR. BELLMAN: Yes.

MR. FROST (MODERATOR): Prophylactically, at a CD4 count of less than 50?

DR. BELLMAN: Not as a standing recommendation, but certainly in selected patients, and certainly in patients who have positive cytomegalovirus polymerase chain reaction results, which I check every couple of months in patients who have less than 50 CD4 cells.

MR. FROST (MODERATOR): What if their T-cells go above 50 as a result of . . .

DR. BELLMAN: My feeling is that there is a clinical response to these drugs that is quite apparent in terms of patients who are very immune compromised. Too often they develop a whole host of major and minor infections. For patients who have this clinical response, even if it is not a complete virologic response, and even if some of that virologic response is lost over time, the clinical response, the immunologic response that occurs makes me very comfortable trying to minimize using medications other than the antiretrovirals themselves—because once again, there are drug interactions, particularly with rifabutin (Mycobutin), although there are alternatives. Of course, it is always possible to get burned with a patient off TMP-SMX (Bactrim) or a relapse of CMV.

But to be honest, with a large group of patients, I would really have to think hard of a single patient that I regret taking off prophylaxis who afterward developed either a recurrence of an infection they already had or had a new infection.

ANTIVIRALS AND DISCONTINUANCE OF PROPHYLAXIS

QUESTION: Do you apply the same kind of intellectual process when dealing with antiretrovirals [as with opportunistic infections]? If you have a patient whose viral or CD4 count goes up to 700 to 800, and who has been on antiretroviral therapy, would you consider a "drug holiday" from antiretroviral agents for them?

DR. COHEN: There are two reasons why you would consider it. Number one is because somebody comes in the door and says, "You know, doctor, I need a drug holiday. My CD4s are up high enough. I would like to take a break. Is that okay with you?" And to which I can only say, "If you take a drug holiday and we monitor and things stay quiet for a while, and your CD4s are up here, and even if there is a rebound of virus, well, then in theory, you are not resistant to any of these agents we started. We can just restart it [antiviral therapy] at some future time point." That is one reason I am comfortable with the idea of drug holiday.

The second reason is that probably most of the audience is aware that there are a few anecdotes from Europe where people with an extremely good prognosis did take a regimen, and then stopped. A year later they still had viral suppression even in lymph node biopsy samples where once there was replication.

I think we have more to learn about this than we know. And while I agree, almost every time we stop therapy, the virus comes back quickly, there may be some amount of drug or some duration of suppression that allows a patient to take a safe drug holiday and just have a break from all these pills.

DR. EL-SADR: Do you stop all of them?

DR. COHEN: If I am going to stop, I stop the group. I do not believe in the partial suppression. I am too afraid of resistance to the regimen.

DR. EL-SADR: It is interesting to hear this

because I have told my patients that if they feel they are getting tired of the pills they should just give me a call. I have had patients who did that, call me and say, "I woke up this morning, and I am tired of taking these pills." And we talk about it. I tell them, "Everybody has bad days and good days, but keep on taking the pills." It is almost like a support group, because I am convinced it is important to maintain individuals on antiretroviral therapy if they are doing well, and to try to support them over moments of doubt and moments of sort of battle fatigue.

d4T AND ddI IN COMBINATION

MR. FROST (MODERATOR): This appears to be an interesting question.

QUESTION: Early on, d4T and ddI seemed like an unfavorable combination because of the levels of associated peripheral neuropathy. Has that changed or has something else changed, because I certainly hear a lot of people talking about d4T–ddI as a combination, and I am wondering if our perception of this combination has changed or if something actually biologically has changed?

FEMALE SPEAKER: I think one thing that has changed is that there is some information to suggest that ddI can be safely given once a day. That is very attractive to a lot of people. Also, I think it improves the tolerability if it is taken at bedtime once a day. At least in the clinic where I worked, that caused a lot of people to gravitate toward that combination. I also think the idea of 3TC sparing or saving regimens has increased the popularity of the d4T–ddI combination.

DR. MERRICK: And then there were data that showed there was no increased incidence of neuropathy, and that is what made people feel alright.

MR. FROST (MODERATOR): Maybe not as much [neuropathy] as what we were afraid of early on.

DR. DOBKIN: I also wonder if the fact that we are in an era where we can suppress viral load for long periods of time has changed the way the adverse effects of the nucleosides are seen in our patients as opposed to the monotherapy era. For instance, how often do we see AZT-related anemia as compared with prior to 1995? Same thing with pancreatitis from ddI, etc. So I think that something may have changed in terms of how the patients handle the drugs.

DR. BELLMAN: I would like to disagree somewhat in the sense of one concern that I have, with respect to drug toxicities in the combination regimens. I am not sure how accurate my sense is, but it seems that I am seeing an awful lot of neuropathy with d4T. In fact, when I go over the risks and benefits of regimens with patients comparing, let us say, AZT–3TC–Crixian versus d4T–3TC–Crixian, it is important, in my mind, that patients understand that the kind of toxicity that they may get from d4T could, indeed, be irreversible.

I am seeing this also in healthier patients—patients who are maximally suppressed on the regimens who have been doing well for awhile and have good T-cell counts. Then when you add d4T and ddI together, or d4T and ddC (which I am not sure why in a formal way is not considered the equivalent of d4T and ddI, and easier to take), I am very concerned about that.

DR. EL-SADR: I just want to mention that the CPCRA study with acupuncture shows that there was not a clearer benefit to using acupuncture in the treatment of peripheral neuropathy, although we have used it for over 5 years now, and I have seen that it has been beneficial.

MALE SPEAKER: My sense of it is that people are opposed to AZT–ddI because they just do not like nausea. I think nausea always loses because nobody likes to experience it. AZT just tends to have a little more of it, which is why I think you are hearing more about d4T–ddI rather than AZT–ddI.

MALE SPEAKER: We have always argued from a regional aspect how everybody in New England or Boston seems to tolerate ddI well, and here patients have more nausea than they do with AZT. I do not know what the difference is.

INDIVIDUALIZING THERAPIES

MR. FROST (MODERATOR): Dr. Saag talked about issues relevant to dosing with

women, and that there may be some important discussion involved. This question takes that issue from a broader perspective.

QUESTION: How much tailoring of doses do you really do on an individualized basis? And how do you get at that lacking information on bioavailability?

DR. SAAG: The bottom line is you really cannot. D4T is adjusted based on weight, and ddI to some degree. That is about it.

MR. FROST (MODERATOR): Do you adjust the others or not?

DR. SAAG: It is actually an interesting point. If I am not misquoting, I think Dr. Markowitz made a comment about the combination saquinavir–ritonavir, which is that he feels that a lot of patients are underdosed on the ritonavir arm, and their regimen really calls for pushing people up to 600 twice daily. Those who will tolerate it are probably metabolizing it more effectively.

DR. COHEN: Sure, it makes perfect sense. However, we are left with a conundrum of sorts. On the one hand, we want the drugs available as soon as possible for obvious reasons, and I think we should always err on that side. On the other hand, we are dealing with the consequences, and that is widespread use of drugs for which we do not have a full data set. It is going to take another 5 to 7 years for that to come into being. What we have to be willing to do is live with the consequences, which is what has obviously happened.

MR. FROST (MODERATOR): Tell me how you live with the consequences? Other than d4T and ddI, which obviously have some dose recommendations, do you dose adjust for proteases, for example?

DR. COHEN: We dose adjust for protease combinations and protease in combination with non-nucleosides. We know there are likely to be interactions. We have a chart which I suppose most everybody has some version of in their clinic. It shows the predicted area under the curve (AUC) changes based on one column with one set of drugs; the same drugs are listed the other way. Then we look at their predicted AUC changes, and we make a best guess.

MR. FROST (MODERATOR): But that is based, at least in part, on pharmacokinetic data. We have seen what delavirdine does, for example, with protease inhibitors. We also know, to a degree, what nevirapine does with protease inhibitors.

I would like to propose this question. If one patient comes to your clinic who weights 300 pounds, is 6'2", a big person, and another person comes to your clinic who is 120 pounds and a very small person, are there any differences in how you dose those two patients? Let us say, in both cases, you have chosen AZT–3TC–indinavir.

DR. SAAG: Not right now, But I am worried about it.

MR. FROST (MODERATOR): Would anyone else on the panel like to comment?

DR. DOBKIN: It is counterintuitive not to adjust dosage, but we do not because we do not know how.

DRUG MONITORING AND INTERACTIONS

DR. EL-SADR: I think there are other factors, in addition to weight, that influence drug metabolism. Even more than resistance testing, therapeutic drug monitoring will probably be something that we will be doing in the future. The problem is, right now, most of the companies claim that they do not know what level of their drug is the one that is useful in predicting what the best response is. But I think we are going to have to start making some assumptions because I believe there is a lot of variability, particularly in protease inhibitor metabolism, that may relate to more than weight alone.

MR. FROST (MODERATOR): Dr. Dobkin, you said something I thought was important—that it is intuitive to adjust dosage, but we simply do not know how.

DR. JAY DOBKIN: Yes, I cannot understand why we are debating spending $800 on tests for genotyping, which we clearly do not understand how to apply, and not performing high-performance liquid chromatography (HPLC) for drug levels, which I could certainly make a good crack at applying. If somebody is way below the published levels, then I would increase the dose.

With a drug like Crixian, for instance, we are

afraid to push the dose because of toxicity. And yet something that I would not have expected to work seems to be working. Giving Crixian twice a day with ritonavir does boost the levels. It looks like it may be a very attractive regimen. I would feel a lot better doing that if I had drug monitoring to go along with it.

DR. SAAG: It is really a carryover of the differences between pediatric and adult medicine. There are not many infectious diseases in pediatrics that you do not dose on a milligram-per-kilogram basis. There are few diseases outside of oncology in adults you do dose on a milligram-per-kilogram basis. Maybe amphotericin is one of the exceptions. I think that the reason that we have done that is a tradition with antimicrobial therapies for bacteria. The therapeutic window is so enormous that it does not matter. But here, we are dealing with much narrower therapeutic windows. In retrospect, I think we just made some mistakes.

DR. EL-SADR: Somehow, collectively, we have not made a strong enough point about the need for us to look at whether there are any correlations between these levels and outcome.

DR. SAAG: I do not know that there are data out there. The problem is to measure protease inhibitors. It is more than HPLC, and it is not so easy to do. There may be specimens that are stored. But then you have to track those specimens back to the actual dosing time to be able to interpret. I think we would have to do it prospectively.

DR. BELLMAN: There are a lot of drug interactions that can affect the drug levels of protease inhibitors that are not listed on the package inserts. For example, to my knowledge, Tegretol is an inducer for the enzyme that breaks down Crixian, and there is no mention of that in the package insert. I found this out the hard way. One of my patients who was on Tegretol failed therapy very early on when Crixian first became available. I think to this day, it was probably an example of a drug interaction that is underrecognized, and that is not formally reported.

So I think there needs to be a mechanism, maybe every an inclusion in the guidelines, because that would actually be very useful for people to have a very complete list of drug interactions and suspected drug interactions.

DR. CURRIER: I want to make one more comment regarding the differences between men and women and drug metabolism. What is interesting is that when people have looked, they have found some differences. Data on delavirdine presented by Upjohn Pharmacia revealed that when they looked at trough levels of the drug in men and women, the women had significantly higher trough levels than men. It was not of any obvious clinical consequences during the follow-up time, but there clearly was a difference between men and women. I think it is something we really have to continue to try to look at.

DR. SAAG: Two additional comments. One is that in many phase I studies, including some of the ones that we are doing, the sponsors clearly want a very homogenous population, and you have to do anthropomorphic measurements. We want to make sure they have the same volume of distribution. That is clear as you are trying to dose escalate into people that you want to understand the bioavailability of that drug. But that is a problem as then it puts the results into a box. The second phase studies are designed for efficacy in a wide variety of people, and therefore, all bets are off.

The second comment is that, yes, we have to pay attention to blood levels. But, again, the way AZT was first dosed was based on pharmacokinetic principles. Now, the dosage has evolved from every 4 hours to twice a day, and we are moving to using ddI once a day. Treatment is clearly changing, and it is important to know that it is getting to a significant level. But that may not be the whole story.

DRUG ESCALATION

QUESTION: Now that we are talking in an era of triple-drug therapies [possibly more], is it reasonable to consider a strategy that would begin with fewer drugs, but over a relatively short amount of time introduce the rest of the regimen in an attempt to minimize toxicities? Is it a reasonable scenario to suggest perhaps two nucleosides, and maybe a month or 6 weeks later the addition of a protease?

DR. COHEN: There is one instance in which that was done successfully, and that is in the ritonavir–saquinavir trial. What we did in that study was to start with just two protease inhibitors (ritonavir–saquinavir) and wait 12 weeks. For anybody whose viral load was not less than 200, we added two nucleosides, often d4T–3TC. With that strategy of allowing patients to kind of declare themselves responders or not, and then adding two nucleosides for the people who were inadequate responders, we actually have achieved over 90% suppression with success 1 year later.

But to my understanding, that is the only example of a successful staggered approach. My sense would be that that would probably be the best way to do it. Meaning, use a regimen that is likely to work for most everybody, and then intensify before you are going to see resistance. The worst thing you could do would be to give an AZT–3TC regimen for 8 weeks because we know 3TC resistance occurs within a month. We also know that nevirapine and delavirdine are lost in a month unless full suppression is achieved before the 2-week period.

And so, I think if you are going to use that strategy, you have got to use a regimen that is unlikely to be lost within the period of time that you are going to use before you decide to intensify.

MR. FROST (MODERATOR): Were heavily pretreated patients included among those patients in the trial, Dr. Cohen?

DR. COHEN: Almost all of them had experiences on all the nucleosides before entering the study, and they all stopped their nucleosides. The study was done at a time when d4T and 3TC were relatively new, and most of the patients had added those two agents, which they had not taken before. It is probably why it was so effective.

MR. FROST (MODERATOR): How many patients had to add nucleosides?

DR. COHEN: About 20%.

FEMALE SPEAKER: There is also a European ritonavir study where they started with ritonavir alone for 3 weeks, and then added the nucleosides after that time. I think as long as that period of time is kept relatively short, it may improve the ability to tolerate the medication. But I would not feel comfortable with monotherapy using a protease inhibitor like that for probably more than 4 to 6 weeks.

MR. FROST (MODERATOR): Does everybody else feel comfortable with that?

MALE SPEAKER: No, I would try to avoid that if at all possible, except in the specific situation with saquinavir–Norvir. If you feel you are giving a really potent regimen, perhaps that is one thing. But I think if you are starting off with two nucleosides and protease monotherapy, I do not think it is worth taking that chance. Norvir is going to be hard to tolerate regardless of what drugs a patient is taking it with, and I am not sure that the toxicity issue is very different when it is used as monotherapy or as triple therapy.

MUTATIONS AND TREATMENT EFFICACY

QUESTION: Is it true that, even with the 30N mutation present that is associated with nelfinavir, it is possible to utilize a protease in the future?

MR. FROST (MODERATOR): David Ho, at the Interscience Conference of Antimicrobial Agents and Chemotherapy (ICAAC), called this story folklore. I recall that a side of Dr. Cohen's kind of did it in the reverse. It said the 90 mutation was present, and therefore without the 30N mutation there was still resistance. But if you flip that question, which has been done out there, we have all probably been some of it in one form or another.

DR. COHEN: We are now beginning to get an inkling of at least the clinical correlation of the data. And that is some data that were presented, a study at ICAAC, I think Keith Henry's presentation, looked at patients who were nelfinavir failures. They were small numbers, a dozen patients or so. What was there status in terms of mutations when they had virologic failure on a nelfinavir-containing regimen? Probably about three quarters of those patients had the 30N mutation. Two or three of the patients did not have a 30N mutation; they had the 190M mutation, which was interesting. Again, there was no saquinavir exposure, nel-

finavir being the only protease inhibitor they had.

Subsequently, patients went on to a ritonavir–saquinavir containing regimen. All of those patients went to undetectable viral loads in short-term follow-up. So in the presence of a 30N mutation and nelfinavir exposure, at least in small numbers of patients short-term follow-up, they were able to get a virologic response with other protease inhibitors.

MR. FROST (MODERATOR): Take me further for a second here, Dr. Cohen. First, you put these patients on dual protease after nelfinavir failure. Second, they also had two nucleosides on board. Third, you saw a positive response.

DR. COHEN: Right.

MR. FROST (MODERATOR): Does that validate these data?

DR. COHEN: No, it does not. It simply suggests people were showing early signs of response. I think the punchline will be first of all, it does not always work, but why not? Is there a way to make this work by switching at low viral loads, for example? And second, how long does this have to last for us to feel confident that it is safe to rely on? I think 16 weeks is too soon to judge an approach as successful. At some point, enough time will have passed to reach a greater certainty. Keith Henry mentioned one patient who is now at week 52 and has less than 20 viral copies on the ritonavir–saquinavir regimen.

Now, if that one patient is joined by 10 more patients, at that point should we feel confident or not? I think that is going to be when we feel a bit more certain. Right now, though, it is kind of a hint rather than enough data to rely on.

PROTEASE INHIBITOR THERAPY

QUESTION: How do you reconcile the much published data from the Merck protocol 035 and the ACTG 320 trial with a decision not to start a protease inhibitor?

DR. CURRIER: I think that the case that you gave [in the roundtable discussion] as an example was somebody who had higher a T-cell count and a lower viral load. Clearly, for people who have a CD4 count of less than 200, and in ACTG 320 that was the population that was studied, I always use a protease inhibitor in their therapy. I would not have any reservation to use it. Sometimes, given the results of that study that not everybody who was on the protease inhibitor an achieved undetectable viral load, I might even use more than three drugs, and use four drugs in some of the patients who have higher viral loads.

In Merck 035, patients had an average CD4 count of about 140 and viral loads of approximately 40,000. I would not hesitate to use a protease inhibitor in somebody with more advanced disease.

DR. SAAG: I would look at the glass as half full rather than half empty in that question. In other words, if we think further about the Merck 035, first you have a more advanced patient, heavily AZT experienced for 12 months on average, but 85% to 90% did well. Second, it appears that many also received nucleoside monotherapy, sometimes considered a sort of cardinal sin, and still had a response. And third, the same patients could be rescued later, at least for 2 years.

MR. FROST (MODERATOR): Is that really what is driving your thinking?

DR. SAAG: That is a lot of what is driving my thinking. The other aspect though, which I had trouble reconciling, is the discrepancy of the results between Merck 035 and ACTG 320. I expected the data to show in the two-drug therapy 50 to 60 progressions, and then in the three-drug, perhaps two regressions, like the Merck 035. Well, that was not what we saw. We saw only, and I underscore only, a 50% reduction in clinical events, including mortality. Well, why is that?

The investigators say, "The CD4 count was a little bit lower still." And maybe adherence was more of a problem. Maybe the population was more heterogeneous in terms of the past nucleoside experience. So there are a lot of problems interpreting clinical trial data. You have to know the details of the study, the criteria for admission, and the homogeneity or heterogeneity of the population, and so on.

But I would take a lot of that data as some degree of evidence, ironically, in favor of someone like our case presentation [see roundtable

discussion] and going a little bit slower. ACTG 175 was really what I am basing a lot of my thought on. That is a study using nucleosides early on for naive patients. We have about half of our patients now rolling into yet another iteration of that study and doing just fine, thank you. That is also where I am thinking from.

DR. COHEN: One really important point, though, is that for both of those studies, the patients were 3TC naive. I think that has been very critical to their success. They could have been on ddI in the past. I think many of them were, and they were still successful. Some people have said, "Well, the participation of the Merck 035, those must have been the most extraordinary people because they did so well, and why am I not seeing that in my practice or my clinic?"

And I think the reason that we are not seeing that success, and the reason that Steve Deecks reported 50% of people not being suppressed with protease inhibitors is that they are not the same patient. These were people who had an average viral load of 40,000, and had never been on 3TC. So we have to understand the population that was studied, and how we can reliably generalize those results.

The other success story that we have of people who are pretreated is the DMP–indinavir study. Ninety-five percent of those on just those two drugs are suppressed a year later, and all of them could have taken all the nucleosides they wanted and still had this very successful regimen next.

So, again, I think it is the cross-resistance within a class that is our undoing. And that is why there is an increasing feeling that we should use one class at a time because the other class will be fresh and ready. I actually intend to go right to left, protease to nucleoside.

I personally am in the dual-protease mode first, and maybe even triple-protease mode first, and then going to a nucleoside second. I am interested, at least, in exploring that because I personally have a sense that that might provide a more successful opening move. And having done ritonavir–saquinavir, that feels like it is worth exploring. I do not think it always has to go left to right (nucleoside to protease). It is just the way we have done it.

POSTEXPOSURE PROPHYLAXIS

QUESTION: I am wondering among the physicians who may have seen this, or potentially could see this, how many are applying post–sexual exposure prophylaxis, and in what circumstance?

DR. RUBIN: I can say I have not used it. I think it is a bit of a slippery slope.

MR. FROST (MODERATOR): Would you use it? Let's say I show up in your clinic and say, "Listen, last night I had a few beers . . ."

DR. RUBIN: I would never say never. I think that there certainly are situations where it may be appropriate.

MR. FROST (MODERATOR): Could you tell me what those are?

DR. RUBIN: A discordant couple would be the obvious situation. I think that in those cases it would be appropriate. I am saying I have not been in a situation where I have been asked to do that.

DR. DOBKIN: If anyone is unhappy about the U.S. Public Health Service antiretroviral guidelines, then they should prepare themselves, because New York State is about to issue guidelines on postexposure prophylaxis for sexual exposure. In fact, I have already told those of us who have AIDS Institute education programs to get ready to start disseminating this material when it is ready. But they have not told us what the guidelines are yet, so we will have to wait.

DR. VAUGHN: I think in instances of rape or something similar that we currently do a poor job of reinforcing prevention of HIV disease. This came up with one of our community forums. One of the patients was going on about participating in risky sexual activities again. I think that we really have to do a better job educating at every encounter with patients and the community, as far as prevention because the toxicity of the medications just does not make sense to many them. Some think postexposure prophylaxis is feasible, in that we can just take the top tail and have sex the good old ways as in the good old days.

With rape situations or something like that, I would apply it. But to possibly encourage post-

exposure in settings of sexual exposure, I am not comfortable with that at all.

DR. CURRIER: But I think that the slippery slope is to declare that if a health-care worker gets exposed, we will do something, but in other situations, we will make further judgments. We need to have some sort of consistency. How do you define what is a potentially unavoidable exposure? I think if somebody has an exposure that could not be avoided for whatever reason, without passing a lot of judgment on them, you have to consider what you might be able to do to prevent them from getting infected.

MR. FROST (MODERATOR): Well, I am going to be a bit of the devil's advocate here. In the health-care setting, there is a significant body of data gathered by the Centers for Disease Control. There are no data regarding a sexual environment. And clearly, I think, the exposure sexually could be different than the exposure in a hospital setting or an emergency room setting. Should that influence our judgment in any way?

DR. SAAG: If the sexual exposure actually is a much higher risk than the needle stick, perhaps. I received a call once of someone who had unprotected anal receptive intercourse with a known HIV-positive partner. That is a pretty high risk. I think it would be ridiculous not to treat in that situation when we are treating people for needlesticks where the cumulative incidence is less than 1%. And although there are data now, when we started doing prophylaxis in needle sticks, there were no data. Therefore, I do not believe not having the data is a reason not to do it. I think you need to quantify the risk as best we can the same way we quantify a needle stick, as high, moderate, and low risk.

DR. EL-SADR: I agree with some of what has been said. We have to be careful not to have hard and fast rules. You have to make a judgment. In the right setting, where an assessment has been made and there is significant risk, I find it very difficult to withhold the potentially favorable treatment. But I think we have to be careful that this is not done, sort of across the board repeatedly, in individuals who are repeating high-risk behaviors. But I think it is hard in certain settings to say, "No, I will not give you the benefit of this treatment."

Another issue that was raised as being neglected in New York City, New York State, and perhaps elsewhere, is that there are very few interventions given in relation to HIV per se for rape victims, either male or female.

FEMALE SPEAKER: I think it is important to add to what Dr. Currier said that there are not data available which indicate that responsible availability of postexposure prophylaxis will increase nonadherence to using condoms for intercourse. It may be that people who feel like if the condom breaks, or they have one episode, they have a chance of getting treatment—it may increase their compliance with safer sex. I think we should not make that assumption.

If a patient comes in with a high-risk exposure, I feel it is my obligation to try to prevent an infection in them. I cannot sit there and be judgmental about why they were exposed. But the difficulty is, again, an access because it is impossible to expect a third-party payer to pay for medicines for somebody who has been exposed in that situation. A healthcare worker has protection through the hospital or the healthcare employer to pay for their medicines. And in the case of rape, at least in some states, that it is paid for by the state or by the institution.

All to say, when there is no means of payment, that becomes a rate-limiting step. Nobody pays for people's condoms, for the most part; they are provided in clinics. But the point is, contraception is generally something that is considered a personal responsibility that people purchase for themselves. With postexposure prophylaxis in this setting, the cost is going to be the rate-limiting step. And that, I think, is going to probably dampen a lot of the repeat request for medicines.

MALE SPEAKER: Just one small point. I think one of the things we learned from the needle stick experience, and I do not know that we learned a great deal more, is that education has been very effective at getting people to realize when they have had a low-risk exposure. I think that is going to be important to do a lot

of educating about postsexual exposure, perhaps not to the public, but to contact healthcare workers so they can counsel patients if they have not had an obviously serious exposure. Otherwise, every bathroom across the country is going to have antiretroviral drugs in it pretty soon.

THIRD-PARTY PAYMENT OF INNOVATIVE COMBINATIONS

QUESTION: What is the risk that innovative therapeutic combinations, which lie outside the guidelines, may not be reimbursed by third-party payers, or third-party payers may look askance at it?

DR. SAAG: A distinction should be made between regimens that are sort of outside the guidelines with respect to initiation of therapy for treatment-naive patients, and treatments that are outside the guidelines for patients who have failed therapy, because actually there are no really meaningful guidelines for patients who failed therapy, regardless of what is in the guidelines. I think that it is important for us as physicians to take a very proactive approach toward the issue of third-party payers, and not treat the guidelines as something objective and immutable. Otherwise, they will just deny patients' treatment options when we think something might be helpful to them.

I believe we need to have an understanding at this point. It is true that salvage therapies are indeed experimental, whatever they may be. On the other hand, salvage therapies are part of the medical care of the patient. The fact that that medical care has now gone to an "experimental" level does not mean that we should not support the drugs that those patients need, because there are patients who do respond to salvage therapies—those that are in the guidelines, and also those that are outside of the guidelines.

MR. FROST (MODERATOR): Is this a problem? Does it come up?

DR. VAUGHN: This issue came up when I initially started using the combination of Norvir and saquinavir, depending on what type of insurance the person had, such as if the person was on city welfare. There was one particular individual. His viral load was going way, way up after it had been initially suppressed. He was compliant. It took 6 weeks before the pharmacist in Trenton would authorize the combination Norvir–saquinavir. The only reason he finally received it was that I hammered the pharmacist, wrote letters, sent reprints from the Antiretroviral Meeting, and the results of the study. Finally they approved it.

You have people who are wedded to the guidelines, and if the request is anything else outside of them they will not approve it. I have the benefit of knowing the patient and all the other medications that he was on, but somebody in Trenton is just going to decide that since he had never heard of that combination before or actually heard that it was contraindicated, the patient could not have the benefit of these therapies.

DR. EL-SADR: I think that is the area where sometimes guidelines are tricky, especially in a field such as HIV care which changes every minute of every day and at every meeting. How can guidelines keep up with reasonable options for our patients? I wish that the guidelines had just dealt with the principles of treatment, which I think are solid and probably will be with us, at least, for a while. I think once you start adding names of drugs and doses and so on, it is going to be almost obsolete by the time it is printed. So by the time these come out, and the interactions that these have to go through, they are going to be obsolete. I think that is the danger. Although the writers were well-meaning, and wanted the guidelines to provide broad access, on the other hand, they already are obsolete and behind the current recommendations.

MS. LEONARD: Just to supply reality, in Texas, if you're on the program, you can get three drugs. You can only get three drugs. So if you want two proteases or need two protease inhibitors and two reverse transcriptase inhibitors, you can get three out of the four paid for. That is how the guidelines have been overinterpreted.