

Antiretroviral Chess for Beginners

John Bartlett discusses the Use of HIV Treatment Guidelines by Physicians and Suggests a New Strategy for People on State ADAP Waiting Lists

— *John Hawes*

In 1996, the United States Department of Health and Human Services (DHHS) and the Henry J. Kaiser foundation convened the Panel on Clinical Practices for Treatment of HIV Infection to develop guidelines for clinical management of HIV-infected adults and adolescents. Since its inception, John Bartlett has served as co-chair of the Panel, along with Dr. Anthony S. Fauci from The National Institutes of Health. In 1998, the Panel published the first federal Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Since then, the Guidelines have been revised nine times to keep pace with discoveries in the field, with the latest revision issued on November 10, 2003.

Currently, the Panel includes 35 members involved in or concerned about HIV/AIDS care from academic, hospital, and community clinics; state and federal agencies; and patient advocacy

groups. The goal of the Panel's treatment recommendations is to provide evidence-based guidance for clinicians and other healthcare providers, and with nearly 800,000 visits to the Guidelines Web site in 2002, it continues to be a widely used resource. Dr. Bartlett spoke with Medical Advocates for Social Justice in September and October 2003 about the federal treatment guidelines, their revisions, and the challenges to provide antiretroviral drugs to people on state ADAP waiting lists.*

MASJ: How did you get involved in the DHHS Guidelines?

Bartlett: Eric Goosby [from the Pangea Global AIDS Foundation] approached me back in 1996 or 1997. Dr Goosby took the lead role in organizing this. He thought that there needed to be some sort of guidelines and I agreed.



MASJ: The Guidelines are continually being revised. What is the process the Panel goes through to determine what needs revision in the Guidelines and how to revise them?

Bartlett: There are 35 members of the Panel representing a number of organizations. For example, there are people from the FDA [Food and Drug Administration], HRSA [Health Resources and Services Administration], and CDC [Centers for Disease Control and Prevention] as well as

* Since the time of this interview, the DHHS Guidelines have been updated. The latest version of the Guidelines is available on the DHHS AIDSInfo Web site at: <http://www.aidsinfo.nih.gov>. The tables in this article were reproduced from the November 10, 2003, update of the DHHS Guidelines.



people from AIDS activist groups. It's a large group; in fact, we found that it's too large to be able to do very much at one time. So now we have a subset of about 15 members who are primarily in the clinic and experienced in HIV care plus a few others—some of the AIDS activists and some representatives from federal agencies. And this group of 15 has a conference call once a month—which means 10 to 12 will actually be on the call—the second Monday of every month, and it usually lasts about an hour.

Prior to the call, the Secretary pulls together an agenda for the meeting—it used to be Mark Dybul [from the

NIH] but now it's Alice Pau [also from the NIH]—based on feedback received from members of the Panel or from the outside. For example, we have the newly approved drug FTC and more information about atazanavir, and we need to put that information in the Guidelines, into every part of the Guidelines where it fits, in all the tables and the text where the various treatment options are discussed. There may be new information from conferences that needs to be considered. We will also discuss revisions to the different sections, such as updating the pharmacology information, drug interactions and complications, and so forth.

Another example of an agenda item might be an outside letter from the AIDS activist community to which we would respond. It would be great if we received more feedback from the outside world. I wish we would get more people that would send a comment to the Panel saying, "I don't like what you did here," rather than give a speech on Saturday and say "Well, those guys really blew it on this point." People should know that because this is a federal panel, it is required to respond to every comment it receives. All of these would be agenda items, and examples of what would be discussed during the monthly conference call.

MASJ: Is there a mechanism in place, such as on the Web site, that allows people to comment on the Guidelines or ask questions of the Panel?

Bartlett: You have raised a good point. I'm not sure that we have publicized our interest in having people do that. What we have done is to post the Guidelines on the Web and anybody can see them. And what we would really like is for people to com-

ment on the revised Guidelines before they come out in print.

I think the electronic media has changed how publications are done in such a way that everything seems to be sort of a moving target now. If we publish a *Mortality and Morbidity Weekly Report*, then there is a hard copy and it's going to last for a year. With a publication on the Web, it could be changed every month. We have not yet really taken advantage of this ability to update the Guidelines, and we probably should. In the past, what we've tended to do is to say that our next update is going to be one year from July, which was the time of our last update, but now the best way to do this in the electronic media world is to change the Guidelines as things happen.

MASJ: The last round of revisions was extensive, particularly for some topics.

Bartlett: Periodically, we will revise an entire section. For example, we didn't think that our section on salvage or rescue therapy was very good; we didn't think it helped anybody. What the Guidelines have always represented to me was a kind of state-of-the-art statement. In other words, what the Guidelines said is what we knew, but I didn't think that actually helped a practitioner who, for example, had a patient with multidrug-resistant HIV disease. So we are changing our approach to, "Here is what we know and here is what we suggest you do." In this case, we want to say, "We know that people who have had multiple drug regimens and have multidrug resistance are unlikely to respond to any current recommendations; however, there are several things that may be done which may work." To do this, we formed a subcommittee and got Trip

Antiretroviral Regimens Recommended for Treatment of HIV-1 Infection in Antiretroviral Naïve Patients

This table is a guide to treatment regimens for patients who have no previous experience with HIV therapy. Regimens should be individualized based on the advantages and disadvantages of each combination such as pill burden, dosing frequency, toxicities, and drug-drug interactions, and patient variables, such as pregnancy, co-morbid conditions, and level of Plasma HIV-RNA. Clinicians should refer to Table 2 to review the pros and cons of different components of a regimen and to Tables 14–17 for adverse effects and dosages of individual antiretroviral agents. Preferred regimens are in bold type; regimens are designated as "preferred" for use in treatment naïve patients when clinical trial data suggests optimal and durable efficacy with acceptable tolerability and ease of use. Alternative regimens are those where clinical trial data show efficacy, but it is considered alternative due to disadvantages compared to the preferred agent, in terms of antiviral activity, demonstrated durable effect, tolerability or ease of use. In some cases, based on individual patient characteristics, a regimen listed as an alternative regimen in the table may actually be the preferred regimen for a selected patient. Clinicians initiating antiretroviral regimens in the HIV-1-infected pregnant patient should refer to "Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States" at <http://aidsinfo.nih.gov/guidelines>.

	NNRTI-BASED REGIMENS	# OF PILLS PER DAY
Preferred Regimens	efavirenz + lamivudine + (zidovudine or tenofovir DF or stavudine*) – except for pregnant women or women with pregnancy potential	3-5
Alternative Regimens	efavirenz + emtricitabine + (zidovudine or tenofovir DF or stavudine*) – except for pregnant women or women with pregnancy potential**	3-4
	efavirenz + (lamivudine or emtricitabine) + didanosine - except for pregnant women or women with pregnancy potential**	3
	nevirapine + (lamivudine or emtricitabine) + (zidovudine or stavudine* or didanosine)	4-5
	PI-BASED REGIMENS	# OF PILLS PER DAY
Preferred Regimens	lopinavir/ritonavir (co-formulated as Kaletra®) + lamivudine + (zidovudine or stavudine)	8-10
Alternative Regimens	amprenavir + ritonavir† + (lamivudine or emtricitabine) + (zidovudine or stavudine)	12-14
	atazanavir + (lamivudine or emtricitabine) + (zidovudine or stavudine*)	4-5
	indinavir + (lamivudine or emtricitabine) + (zidovudine or stavudine*)	8-10
	indinavir + ritonavir† + (lamivudine or emtricitabine) + (zidovudine or stavudine*)	8-11
	lopinavir/ritonavir (co-formulated as Kaletra®) + emtricitabine + (zidovudine or stavudine*)	8-9
	nelfinavir§ + (lamivudine or emtricitabine) + (zidovudine or stavudine*)	6-14
	saquinavir (sgc or hgc)° / ritonavir† + (lamivudine or emtricitabine) + (zidovudine or stavudine*)	14-16
	TRIPLE NRTI REGIMEN - ONLY WHEN AN NNRTI- OR A PI-BASED REGIMEN CANNOT OR SHOULD NOT BE USED AS FIRST LINE THERAPY	# OF PILLS PER DAY
Only as alternative to NNRTI- or PI-based regimen	abacavir + lamivudine + zidovudine (or stavudine *)	2-6

* Higher incidence of lipodystrophy, hyperlipidemia, and mitochondrial toxicities reported with stavudine than with other NRTIs

** Women with child bearing potential implies women who want to conceive or those who are not using effective contraception

† Low-dose (100-400 mg) ritonavir

§ Nelfinavir available in 250 mg or 625 mg tablet

° sgc = soft gel capsule; hgc = hard gel capsule

Gulick [from Weill Medical College] to lead the effort to rewrite that section. The rewrite went out to the subcommittee assigned to this rewrite for comment. Then it went out for a vote to the whole Panel of 35 for approval and incorporation into the last revised Guidelines. This is basically the process for any revision of a section. There is a subcommittee to accomplish specific revisions, and then once the revisions are approved, the revised section goes out via the listserver to the entire 35-member Panel. One of the biggest changes in a recent revision [July 14, 2003] was evident in the recommendations for rescue therapy.

Once the conference call is over, the Secretary summarizes what has been said along with the recommendations for revisions, and the summary goes out to the entire Panel for comment via our listserver. It's a true working group with an active e-mail exchange among the members. The Secretary will then synthesize all of the comments and send out the final revisions to the committee for discussion and approval during the next month's conference call.

MASJ: Can any member of the Panel access the list server to see what the subcommittees are discussing during the month?

Bartlett: Yes, but many don't participate because they are representing an agency or they don't really feel that this is a primary part of their work. But they could participate if they wanted.

MASJ: Do you ever use experts outside of the Panel for help with revisions?

Bartlett: The answer is yes and no. One of the things we have done is to say that there are some things that

our committee and Panel are good at and some things that we're not very good at, and the things that we're not very good at are often done by other groups. Rather than have two guidelines with overlap, we ought to simply work with another group. So, for example, for maternal-child transmission, there is a separate group that writes their own guidelines; they have their own panel and they go through a similar process to keep their guidelines updated. In this case, we simply refer to their guidelines or we have a brief summary that they approve. Same thing with pediatrics, for which a similar but separate group also exists.

Where it has become somewhat confusing for our group is something like prevention. We weren't the experts in prevention but we put recommendations in anyway because we thought this was important. It turned out that that the CDC wrote their own prevention guidelines, and we will probably agree to have theirs merged with ours. In other words they'll have their full document with 50 pages about prevention, and we'll have a short synopsis of what they say which needs to be reviewed and approved by the CDC Panel. I think it becomes very confusing to people if the DHHS has a set of guidelines that are different from those of another federal agency.

MASJ: What's your opinion on the acceptance of federal treatment guidelines by the medical community?

Bartlett: I think most HIV treatment guidelines in general are good, including these. But if you ask people who do a lot of AIDS work, they will likely say, "The Guidelines are fine, but I don't need them because that's what I already do." That's the response by most people that do a lot of HIV care.

On the other hand, there are a number of people who don't see a large number of patients and who don't go to the conferences; those are the ones who would probably find the Guidelines useful.

For credibility, I trust guidelines if they come from the right source, not from a drug company and not from somebody that has an axe to grind, but from a source that's neutral, experienced, and respected. Our Guidelines have that ingredient.

Although most people in HIV care in the United States probably don't think they really need the DHHS Guidelines, another place where the DHHS Guidelines are very useful is with HMOs, third party payers, Ryan White CARE Act, the Title I, Title II, Title III activities, and so forth because a lot of the quality assurance monitoring is done on the basis of guidelines. A number of state ADAPs [AIDS Drug Assistance Programs] will approve drugs that are on the DHHS Guidelines list, and sometimes the use of a drug will be limited according to the Guidelines. For example, a state ADAP might say, "You can give T-20, but you have to give it according to what it says in the Guidelines." So the Guidelines may be more helpful for some of the medical organizations than they are for the individual provider. I also think they may help providers in some areas where they are not that comfortable, such as in some of the more specialized areas. They may also be useful for quality assurance.

MASJ: Can you give an example?

Bartlett: One example is in corrections. Providers in correctional facilities would probably be much better off if they used the Guidelines. If these providers follow the DHHS

Guidelines they are doing good HIV care and at the same time avoiding criticism. Also, a lot of the care provided under the Ryan White CARE Act is done by quality assurance around guidelines. Many HMOs have their own guidelines, but by-and-large, they follow the DHHS Guidelines very closely. New York State has their own set of guidelines; they have very extensive guidelines, thousands and thousands of pages of guidelines. The New York State guidelines are similar to the DHHS Guidelines, but there are some differences. In many cases, the DHHS Guidelines become a source document for others. Quite frankly, if somebody in Oklahoma who is running a clinic and is told that he or she ought to write guidelines for how that clinic should deal with HIV infection, the person in Oklahoma most likely is just going to take the federal guidelines and adapt them for that clinic. So a lot of organizations are influenced by the DHHS Guidelines in some way, but I don't think the average HIV care provider thinks he or she needs them.

MASJ: You mentioned that New York State has its own set of guidelines. Were these guidelines put together in collaboration with the Johns Hopkins [Division of Infectious Diseases Clinical Guidelines Program] staff?

Bartlett: The New York State guidelines are a product of the New York State AIDS Institute under Bruce Agins. They cover a diverse array of topics and are compiled by experts in the appropriate fields from New York State. Johns Hopkins orchestrates the meetings, helps with the reviews, and arranges for the publications in print media and Web-based presentation. These guidelines are available at the New York State AIDS Institute Web site (<http://www.hivguidelines.org>).

They cover nearly all relevant topics including many topics not covered in the federal guidelines, such as psychiatric issues, neurologic complications, and post-exposure prophylaxis for nonoccupational exposure. They also have occasional differences from the federal guidelines in what they recommend. For example, with occupational exposure, they routinely recommend three antiretrovirals rather than the two- or three-drug regimens recommended by the CDC. I should emphasize that Hopkins does not supply content for the New York State guidelines, but we have the grant to facilitate administration, external review, and methods of presentation.

MASJ: How often are the New York State guidelines updated?

Bartlett: They are updated, usually at 6- to 12-month intervals. Like most guidelines, they tend to get behind because of the velocity of AIDS information.

MASJ: Would you recommend the New York guidelines as a guide for other states?

Bartlett: I would strongly recommend the New York guidelines. This is not because they are better than the federal guidelines, but because they cover areas not covered in federal guidelines and they also use a somewhat different style of presentation that I think is easier for the user.

MASJ: Do you have a criticism of the DHHS Guidelines in any way?

Bartlett: My major criticism of them is that it is very hard to find specific information. The federal Guidelines make recommendations on almost everything, but if you try to figure out, for example, how often should a CD4 count be obtained, the informa-

tion is in there, but it's buried. I think there could be a much easier way to present the information.

MASJ: Why not provide an index or a search engine?

Bartlett: I think that's a good idea. What we did with the last revision for the initial treatment section is that we put our specific treatment recommendations upfront in the first paragraph, which appears in bold type. Now, we're going to go through the entire Guidelines and do that that for every section. This should make it easier to find information on specific recommendations.

MASJ: Earlier you touched on the speed with which information in the HIV field changes. Could you comment on any initiatives to provide updates of the Guidelines on a more frequent basis?

Bartlett: We will be in fact changing how we release updated Guidelines and do plan to provide updates on a more frequent basis. In the past, we have not provided updates to the extent that I think we need to. We ought to take advantage of the fact that in the age of electronic media, it becomes very easy to update information and provide it to an audience very fast.

MASJ: To follow up on the need to provide more timely updates regarding treatment guidelines, it seems that an increasing number of physicians may be basing their treatment decisions on data presented at major AIDS conferences in advance or in lieu of published data. What's your opinion on this?

Bartlett: My personal opinion is that this has been a very unfortunate part of the AIDS information network. There's an enormous amount of infor-

Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy

ARV CLASS	ANTIRETROVIRAL AGENT(S)	ADVANTAGES	DISADVANTAGES
NNRTIs		<ul style="list-style-type: none"> • Less fat maldistribution and dyslipidemia than PI-based regimens • Save PI options for future use 	<ul style="list-style-type: none"> • Low genetic barrier to resistance • Cross-resistance among NNRTIs • Skin rash • Potential for CYP450 drug interactions
	Efavirenz	<ul style="list-style-type: none"> • Potent antiretroviral activity • Low pill burden and frequency (1 tablet per day) 	<ul style="list-style-type: none"> • Neuropsychiatric side effects • Teratogenic in nonhuman primates, contraindicated in pregnancy and avoid use in women with pregnant potential
	Nevirapine	<ul style="list-style-type: none"> • More safety experience in pregnant women • No food effect 	<ul style="list-style-type: none"> • Higher incidence of rash than with other NNRTIs, including rare serious hypersensitivity reaction • Higher incidence of hepatotoxicity than with other NNRTIs; including serious cases of hepatic necrosis
PIs		<ul style="list-style-type: none"> • NNRTI options saved for future use • Longest prospective study data including data on survival benefit 	<ul style="list-style-type: none"> • Metabolic complications - fat maldistribution, dyslipidemia, insulin resistance • CYP3A4 inhibitors & substrates – potential for drug interactions (esp. with ritonavir-based regimens)
	Lopinavir/ritonavir	<ul style="list-style-type: none"> • Potent antiretroviral activity • Co-formulated as Kaletra® 	<ul style="list-style-type: none"> • Gastrointestinal intolerance • Hyperlipidemia • Little experience in pregnant women • Food requirement
	Amprenavir/ritonavir	<ul style="list-style-type: none"> • No food effect • FDA-approved once-daily regimen 	<ul style="list-style-type: none"> • Less extensive experience • Frequent skin rash • High pill burden and capsule size
	Atazanavir	<ul style="list-style-type: none"> • Less adverse effect on lipids than other PIs • Once daily dosing • Low pill burden 	<ul style="list-style-type: none"> • Hyperbilirubinemia (indirect) • PR interval prolongation – generally inconsequential unless combined with another drug with similar effect • Interaction with tenofovir and efavirenz—avoid concomitant use unless combined with RTV (ATV 300mg qd + RTV 100mg qd) • Food requirement
	Indinavir	<ul style="list-style-type: none"> • Long-term virologic and immunologic efficacy experience 	<ul style="list-style-type: none"> • 3-times-daily dosing and food restriction reduced adherence • High fluid intake required (1.5–2 liters of fluid per day) • Nephrolithiasis
	Indinavir/ritonavir	<ul style="list-style-type: none"> • Low-dose ritonavir + indinavir T? & Cmin allows for twice-daily instead of 3-times-daily dosing • Eliminates food restriction of indinavir 	<ul style="list-style-type: none"> • Possibly higher incidence of nephrolithiasis than with IDV alone • High fluid intake required (1.5–2 liters of fluid per day)
	Nelfinavir	<ul style="list-style-type: none"> • More extensive experience in pregnant women than with other PIs 	<ul style="list-style-type: none"> • Diarrhea • Higher rate of virologic failure than with other PIs in comparative trials • Food requirement
	Saquinavir (hgc or sgc) + ritonavir	<ul style="list-style-type: none"> • Low-dose ritonavir reduces saquinavir daily dose and frequency -? Cmax, Cmin, & T? 	<ul style="list-style-type: none"> • Gastrointestinal intolerance (sgc worse than hgc)
NRTIs		<ul style="list-style-type: none"> • Established backbone of combination antiretroviral therapy 	<ul style="list-style-type: none"> • Rare but serious cases of lactic acidosis with hepatic steatosis reported with most NRTIs
Triple NRTI regimen	Abacavir + zidovudine (or stavudine) + lamivudine only	<ul style="list-style-type: none"> • Abacavir + zidovudine + lamivudine - Co-formulated as Trizivir® • Minimal drug-drug interactions • Low pill burden • Saves PI & NNRTI for future option 	<ul style="list-style-type: none"> • Inferior virologic response when compared to efavirenz-based and indinavir-based regimens • Potential for abacavir hypersensitivity reaction
Dual NRTIs: backbone of three or more drug combination therapy	Zidovudine + lamivudine	<ul style="list-style-type: none"> • Most extensive and favorable virological experience • Co-formulated as Combivir® – ease of dosing • No food effect • Lamivudine – minimal side effects 	<ul style="list-style-type: none"> • Bone marrow suppression with zidovudine • Gastrointestinal intolerance
	Stavudine + lamivudine	<ul style="list-style-type: none"> • No food effect • Once-daily dosing (when extended release stavudine formulation becomes available) 	<ul style="list-style-type: none"> • Peripheral neuropathy, lipoatrophy, hyperlactatemia and lactic acidosis, reports of progressive ascending motor weakness, potential for hyperlipidemia • Higher incidence of mitochondrial toxicity with stavudine than with other NRTIs
	Tenofovir + lamivudine	<ul style="list-style-type: none"> • Good virologic response when used with efavirenz • Well tolerated • Once-daily dosing 	<ul style="list-style-type: none"> • Data lacking for tenofovir use in patients with renal insufficiency • Tenofovir – reports of renal impairment • Tenofovir – food requirement
	Didanosine + lamivudine	<ul style="list-style-type: none"> • Once-daily dosing 	<ul style="list-style-type: none"> • Peripheral neuropathy, pancreatitis – associated with didanosine • Food effect – needs to be taken on an empty stomach
	NRTI + emtricitabine	<ul style="list-style-type: none"> • Long half-life of emtricitabine allows for once daily dosing (of emtricitabine) 	

Antiretroviral Regimens or Components That Should Not Be Offered At Any Time

ANTIRETROVIRAL REGIMENS NOT RECOMMENDED

	RATIONAL	EXCEPTION
Monotherapy	<ul style="list-style-type: none"> • Rapid development of resistance • Inferior antiretroviral activity when compared to combination with three or more antiretrovirals 	<ul style="list-style-type: none"> • Pregnant women with HIV-RNA < 1,000 copies/mL using zidovudine monotherapy for prevention of perinatal HIV transmission* and not for HIV treatment for the mother
Two-agents drug combinations	<ul style="list-style-type: none"> • Rapid development of resistance • Inferior antiretroviral activity when compared to combination with three or more antiretrovirals 	<ul style="list-style-type: none"> • For patients currently on this treatment, it is reasonable to continue if virologic goals are achieved
Abacavir + tenofovir + lamivudine - combination as a triple NRTI regimen	<ul style="list-style-type: none"> • High rate of early virologic non-response seen when this triple NRTI combination was used as initial regimen in treatment naïve patients 	<ul style="list-style-type: none"> • No exception
Tenofovir + didanosine + lamivudine – combination as a triple NRTI regimen	<ul style="list-style-type: none"> • High rate of early virologic non-response seen when this triple NRTI combination was used as initial regimen in treatment naïve patients 	<ul style="list-style-type: none"> • No exception

ANTIRETROVIRAL COMPONENTS NOT RECOMMENDED AS PART OF ANTIRETROVIRAL REGIMEN

	RATIONAL	EXCEPTION
Saquinavir hard gel capsule (Invirase®) as single protease inhibitor	<ul style="list-style-type: none"> • Poor oral bioavailability (4%) • Inferior antiretroviral activity when compared to other protease inhibitors 	<ul style="list-style-type: none"> • No exception
Stavudine + didanosine	<ul style="list-style-type: none"> • High incidence of toxicities – peripheral neuropathy, pancreatitis, and hyperlactatemia • Reports of serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women 	<ul style="list-style-type: none"> • When no other antiretroviral options are available and potential benefits outweigh the risks*
Efavirenz in pregnancy	<ul style="list-style-type: none"> • Teratogenic in nonhuman primate 	<ul style="list-style-type: none"> • When no other antiretroviral options are available and potential benefits outweigh the risks*
Amprenavir oral solution in: <ul style="list-style-type: none"> • pregnant women; • children < 4 yr old; • patients with renal or hepatic failure; and • patients treated with metronidazole or disulfiram 	<ul style="list-style-type: none"> • Oral liquid contains large amount of the excipient propylene glycol, which may be toxic in the patients at risk 	<ul style="list-style-type: none"> • No exception
Stavudine + zidovudine	<ul style="list-style-type: none"> • Antagonistic 	<ul style="list-style-type: none"> • No exception
Stavudine + zalcitabine	<ul style="list-style-type: none"> • Additive peripheral neuropathy 	<ul style="list-style-type: none"> • No exception
Didanosine + zalcitabine	<ul style="list-style-type: none"> • Additive peripheral neuropathy 	<ul style="list-style-type: none"> • No exception
Atazanavir + indinavir	<ul style="list-style-type: none"> • Potential additive hyperbilirubinemia 	<ul style="list-style-type: none"> • No exception
Emtricitabine + lamivudine	<ul style="list-style-type: none"> • Similar resistance profile • No potential benefit 	<ul style="list-style-type: none"> • No exception
Hydroxyurea	<ul style="list-style-type: none"> • CD4 count • ddl-associated side effects – such as pancreatitis & peripheral neuropathy • Inconsistent evidence of improved viral suppression • Contraindicated in pregnancy (Pregnancy Category D) 	<ul style="list-style-type: none"> • No exception

* When constructing an antiretroviral regimen for an HIV-infected pregnant woman, please consult "Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States" in <http://aidsinfo.nih.gov/guidelines>.

mation that's presented at meetings that never makes it into press, any place. And that's a problem in two ways. One is that it means that the data have not really been peer reviewed. If an ACTG trial reports something, then you can depend on it, but there's a lot of other information that doesn't necessarily come from such a credible source. The second problem is that the reader that wants to get the information can't get it because most people don't have the book of abstracts, and even if you do you've got one paragraph. So I have tried very hard to have the Guidelines refer as much as possible to published literature rather than abstracts. For example, if I look at a reference and it is an abstract from CROI [Conference on Retroviruses and Opportunistic Infections] in 1999, and there has been no subsequent publication, I conclude this is not very good data because it was presented four years ago and has never been published or the authors are simply lazy about getting this information into print. There are 67 publications that either have HIV or AIDS in their titles, so there are plenty of places to publish. It is terribly disappointing that more data from major AIDS meetings do not get into the medical literature.

MASJ: But don't abstracts submitted to meetings like CROI undergo a peer review?

Bartlett: Yes, but if you been a reviewer on those, you know that all you get is a paragraph. One paragraph. You read through it, and the bottom line says that the full database is now undergoing analysis and will be presented at the meeting. So you say, it sounds like they may have something good here. I remember one time somebody was presenting a study on impaired replication capacity, with a title stating

“impaired replication capacity of resistant HIV strains in treatment-naïve patients results in reduced viral load after the set point is established.” The presenter started the presentation stating that a slight change in the title is needed, “It should say the results showed no effect on the viral load because we have done more experiments.” [laughing] And it completely changed the bottom line of the study.

MASJ: With that caution in mind, at what level of experience in HIV management should a physician consider not following the Guidelines but rather base treatment decisions on personal experience or judgment? Also, is there any liability involved in deciding not to follow the Guidelines, such as when using nonrecommended therapies?

Bartlett: We have dealt with this in two ways. One is that we put a disclaimer in the beginning, like all guidelines do, that physician judgment supersedes whatever is in the Guidelines. I do not know how much clout that has; lawyers tell me that it doesn't have much clout at all. The second thing is that there is an enormous amount of grayness to our recommendations. So, for example, where it says when to start treatment, the recommendation is that everybody ought to start treatment when their CD4 count is under 200 cells per microliter, and there's really a consensus on this; it's above that level where there is controversy. If you read our recommendations, we say things like “For CD4 counts less than 350 and above 200 however, some experts recommend therapy. This is because there is no clear consensus on the CD4 threshold to start treatment. We have found that it is better to qualify our statements; that is, it is much easier to put in a bit of fudge factor, such as the supporting evidence is not

robust or consistent. We also do this because of just what you're asking about: we don't want people to get nailed because they don't follow the Guidelines to the letter of the law.

Interestingly, our feedback to date has not been that a physician in Florida got sued because he or she didn't follow the Guidelines. What we have had been told is that a Southern state has decided not to put drug X on their ADAP formulary because of something that's in the Guidelines. In this case, the Guidelines had been misinterpreted, and we've written to an ADAP to say, “You've misinterpreted what we've said.”

MASJ: What happened with that state exactly?

Bartlett: I really do not know the details of the case about the ADAP that made an erroneous decision based on misinterpretation of the Guidelines. I was told about this at a meeting, took it at face value, and wrote the administrator of the ADAP program. The most important message is to make sure that our Guidelines are absolutely clear about what we are recommending and some of the limitations in the knowledge base. For example, in the section on antiretroviral regimens, we state preferred regimens and have several alternatives. Some might interpret this to mean that the only acceptable regimens are in the “preferred” category. Therefore, it is important to add a statement such as: “The alternative regimens may be the preferred treatment in selected patients.”

MASJ: What is your opinion on the value of providing an addendum to the Guidelines on questions regarding potential areas of misinterpretation to help prevent similar misinterpretations like the one you cited?

Bartlett: We are in the process of a major overhaul of the Guidelines in order to address some of the areas of confusion and also to make the document more “user friendly.” This project will be finished about spring 2004. We had not considered an addendum for questions, but that might not be a bad idea.

MASJ: What about the physician with minimal experience in treating patients with HIV who is providing treatment with a regimen not recommended according to the DHHS Guidelines. Would such treatment be considered inappropriate? In other words, would he or she be at risk of malpractice?

Bartlett: I think one can do a lot of harm in this disease. It was a lot different before 1995. In 1995, it was very hard to harm with therapy because we didn’t have anything that worked well. But in 2003, one can do a lot of harm. So, I would say in some cases, the answer would be yes.

MASJ: In terms of what you said earlier about how the Guidelines are revised, could you comment on the general design of studies from which the results would be included to form the basis for a treatment guideline or recommendation?

Bartlett: I have always wished we put these criteria in the Guidelines somewhere. The problem is that the Panel members get very concerned when you start to write down specific details because they can always think of exceptions. But in general what is needed for the initial antiretroviral regimen recommendation is a comparative trial in treatment-naïve patients with a sufficient sample size—which is really not defined—with a study duration of at least 24 weeks but

preferably 48 weeks. The study should compare a new regimen with one that is already accepted in the Guidelines as an appropriate comparison. The results should show the number of subjects that reached 50 and 500 HIV RNA copies per milliliter; they need to account for the outcome of all of the patients; there needs to be a tabulation of side effects, and the data analysis performed has to be both an as-treated analysis and an intent-to-treat analysis. The panel requires all of this, which is now pretty standard.

MASJ: Could you comment on the process by which the only protease-inhibitor-based regimen specifically recommended for initial treatment was Kaletra [lopinavir/ritonavir] plus lamivudine with either zidovudine or stavudine? How did that process develop?

Bartlett: It was developed primarily on a basis of the available controlled trials, although other factors such as patient convenience and pill burden were also considered. This protease inhibitor regimen seemed to be as good or better than anything tested at the time the review was done. The obvious concern is that there are no published data on lopinavir/ritonavir compared with another protease-inhibitor-boosted regimen.

So we can’t say for certain that it’s better than other regimens that a lot of us use. Nevertheless, it has never been beaten and it clearly has a very good track record, including 5-year durability. We chose the specific nucleoside analogues that it is paired with because we have become a bit nervous about a general recommendation of “two nucleosides and a protease inhibitor” as a good way to go because of some of the drug interac-

tions and problems that have been seen with certain combinations, such as the triple nucleoside analogue regimen and didanosine/stavudine.

MASJ: Regarding the lack of published data, what about the Context study, which compared lopinavir/ritonavir with boosted fosamprenavir?

Bartlett: There are several ongoing studies of lopinavir/ritonavir versus other boosted protease inhibitors, so I think the problem of sparse comparative studies will be corrected very soon. There is also a large ACTG study comparing efavirenz versus lopinavir/ritonavir. However, remember that the panel likes a “full deck” in making comparisons. This means a good sample size, comparable patients, follow-up for at least 48 weeks, and good data regarding virologic response, immune response, and toxicity. We are also interested in convenience, long-term toxicity, pill burden, drug interactions, food effects, and so on.

MASJ: With adherence being a key predictor of long-term virologic success, what is your opinion on the potential impact on adherence with once-daily compared with twice-daily therapy? There’s new information about once-a-day therapy in the Guidelines and an explanation now about missed doses and minimum concentration (Cmin) in relation to the inhibitory concentration (IC50), but could you comment further on this?

Bartlett: I think that we now are at a point where we can offer once-daily therapy. It’s probably going to be a nonnucleoside-analogue-based once-a-day therapy because we now have drugs with long half-lives that show once-daily dosing can be done. However, there are some important differences based on pharmacokinetics.

For example, a missed dose with unboosted atazanavir could be a disaster; yet, with efavirenz, it would not be such a problem because of its half-life. So, by discussing missed doses in the Guidelines, we tried to point out that once-a-day therapy is not necessarily the same among all of the drugs that are going to be offered as once-a-day drugs. But we think that we're at a point where once-a-day therapy can be standard care.

MASJ: Several agents and drug combinations have been removed from the preferred and alternate regimens for initial recommendations in treatment-naïve patients. What are the reasons for removing the triple nucleoside analogue regimen as a preferred initial treatment?

Bartlett: The Trizivir triple nucleoside regimen was removed because of the results from the ACTG 5095 trial, which seemed to be solid science. I personally was not surprised because I thought that if a drug regimen does not work very well in a patient with a high viral load, then it probably would not work in patients with a lower viral load if you had a large enough sample size. It just means it is a weaker regimen, a less potent regimen. At the same time, there were a number of members on the Panel who have had very good experiences with a triple nucleoside regimen. They felt that for a lot of patients, it may not be the best regimen in terms of the likelihood of a durable viral response, but it was their best shot at therapy. It's now in the "alternative" category and may be preferred for some patients.

MASJ: The guidelines make a distinction between patients with "limited" prior treatment experience versus "extensive" prior experience. What's your definition of those two terms?

Bartlett: [laughing] Well, don't ask that because we don't know. "Extensive" means patients who have been exposed to multiple drugs and have a resistance profile that really limits their options with all three drug classes. We were reluctant to try to define these terms because it's such a gray area. However, we did think that was very important to tell a provider that if a patient fails his or her first regimen, their probability of success with another one is very good. Likewise, we also thought it was important to tell a provider that if the patient has had extensive exposure to all drug classes with many resistance mutations, they should not spend a lot of time changing from one regimen to another because it's probably not going to work. So we thought that the differences in the approach to those two patient populations was important to convey, but we also felt we couldn't get into too many specifics because there are so many variables involved.

MASJ: There are many physicians and other caregivers globally who try to utilize the DHHS Guidelines. Many of them are from resource-limited nations where some, and often most, antiretrovirals are not available. Do you have any advice on ways that the Guidelines can be adapted in such situations?

Bartlett: Our guidelines are sponsored by the US government and are directed primarily at treatment in this country. However, we are sympathetic to the use of these guidelines elsewhere and feel that the information is useful but not always relevant because of some exceptions. You mentioned one, which is a limited drug supply. Other confounders are the problem of concurrent diseases such as TB, drug storage issues like refrigeration, and the importance of economics with a drug price structure that is entirely different

than ours. We simply cannot cover all of this ground. I also feel that there are many AIDS experts in every area of the world who are better equipped to address regional issues and most have done this.

MASJ: You have talked about the process on how the Guidelines are updated and about some of the specific revisions that were made recently, but perhaps you could also comment on the state AIDS Drug Assistance Programs (ADAPs). There were recent press reports of deaths of several people in West Virginia and Kentucky who were on those states' ADAP waiting lists because there was no funding to purchase antiretroviral drugs for those people who died. At what point is the failure to initiate antiretroviral therapy for HIV patients potentially harmful for a patient and, with more than 700 people on ADAP waiting lists, is there a way that treatment might be prioritized so that this doesn't happen again? Could recommendations be made based on the DHHS Guidelines?

Bartlett: One of the things you need to say right up front is that ADAP and Medicaid are state-based systems; so there are 50 of them, and they are all different. People on ADAP in Maryland are not going to suffer because Maryland has a great ADAP, and the reason it has a great ADAP is because it has great Medicaid. Maryland has risk-adjusted rates for AIDS. I don't know what the rate is in West Virginia, but in Tennessee, it's something like \$150 per member per month. Well, you can't provide care with that. In Maryland, it's \$2600 per member per month for a patient with AIDS. That's a colossal difference and something that a lot of people are simply not aware of. So if you are in Tennessee—and it looks like West

Virginia and Kentucky may be the same way—Medicaid is broke; reimbursement is under funded, and this places an increased burden on ADAP. So if you've got a good Medicaid, you've usually got an ADAP that can supply the patient needs, and if you've got a bad Medicaid, you don't. This means that they may need to prioritize.

MASJ: So what recommendations would you make for evaluating people for prioritizing treatment if you had to?

Bartlett: There needs to be a way to prioritize by saying that these are the drugs that are most critical, and these drugs are less critical on the basis of cost. So Serostim, for example, may not be very important compared to an antiretroviral drug, and you may have to bite the bullet and say that. And then the second thing is you may have to say that patient X may have only recently got on the ADAP rolls but needs medicine more than others who have been there longer. I don't know of states that do this. If people are dying in West Virginia and Kentucky, they either need more funds or a way to prioritize. ADAPs are coming to the point of rationing, which is where many are—I think there are nine states [10 as of November 2003—Ed] that have waiting lists—those that have to ration probably need to find a way to prioritize. I do think there could be guidelines but they need to come from HRSA because HRSA holds the purse strings for ADAP programs.

MASJ: Would HRSA get their information from the DHHS Panel on how to make their recommendations?

Bartlett: They could. I think if they asked us, we would probably provide whatever kind of information they wanted.

MASJ: That leads me to my next question. Would national guidelines on rationing HIV drugs and prioritization of those on ADAP waiting lists be of benefit to those affected by the lack of ADAP funding? It sounds like you are saying yes and that HRSA needs to do that.

Bartlett: Yes, but Medicaid and ADAP are state based, and people are very reluctant to mess with the prerogative of a state. HRSA might say, "We don't think that's our role. We think our role is to allocate the money to the states, and they then have the prerogative of deciding how they're going to spend that money. And if they want to have a list that is simply by number, then that's their prerogative. If they want to do it by some method in which they judge severity of need and so forth, then that's their prerogative too." On the other hand, I think that if HRSA became alarmed by this, they could set up some sort of guidance. Ultimately, HRSA can apply an enormous amount of pressure on states because it could make funding contingent on demonstrating such plans. Many probably have them.

MASJ: Assuming HRSA gets involved, would the Panel consider developing

some supplemental guidelines for the prioritization of care for people with HIV on state ADAP waiting lists? You seemed to imply that if HRSA approached you that you would.

Bartlett: Well, you know, I'm speaking as an individual. Would the Panel respond? I think we would respond to almost anything that HRSA or another federal agency asked us to do. How we would go about doing it, I'm not sure. Most of us on the Panel, and in medicine for that matter, are running on a fast treadmill. Personally, I would try to do it because I see it as a very high priority, a very important issue. However, we are all volunteers who are already pretty busy. Further, we may not have the right expertise to do the necessary cost-effective analysis. It might require a different panel.

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