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“Au Revoir les Enfants” without leadership for HIV treatment in poor countries

D. William Cameron, MD, FRCPC

Editor, *JIA PAC*



River blindness no longer afflicts millions of people because of the donation of ivermectin by Merck & Co. in onchocerciasis control programs, celebrated by the World Health Organization (WHO). The WHO has stated a goal of “five million on HIV treatment by 2005.” It is not clear whether the blind man or the child will be leading us, but both the wisdom and vision of good leadership are badly needed in the provision of HIV medication to the poor.

Photo courtesy of WHO website at <http://terrance.who.int/mediacentre/photo/OMS/CARTER%20STATUE/RIVERBLINDNESS001.jpg>

I learned a lesson in health economics from a friend in Nairobi, Kenya, in the mid-1980s. We both worked at Kenyatta National Hospital in clinical research projects on sexually transmitted diseases and HIV. My friend was a shy, but experienced, insightful, and mature man. He worked in the city, away from his wife and children, to support them with a relatively good income. He discovered that he was HIV-positive, and would get *ukimwe* or “the end” which is the Swahili word for the slim disease. Treatment access was not an issue at the time because there was no medicine for HIV/AIDS. When I asked whether he would have preferred not to know about his disease, he laughingly told me that it was better to know because, “You can mourn yourself.” He talked about how long he might live, and where he might get money to provide for his family after his death. For the *mzungu*, the “white-faced foreigners,” he said, “The problem is not where to get money, but where to spend it.” After his death, I gave money to his family that may have helped only a little, but I know that it was appreciated a lot. I was angry that so much of it went to exorbitant bank transfer and exchange fees. Now I wish that I had given more than what I thought that I could spare at the time.

The world has AIDS, tuberculosis, and malaria. In developing countries, these are social sub-epidemics of poverty, politics, and other factors. Western industrial countries have money, and medical treatments that work for each of these diseases. If we do not provide these treatments generously, then the political memory of our selfishness in the face of millions of deaths, and millions of surviving orphans will leave a mark in history. We must not rationalize our ineffectiveness. We know right from wrong, and we have the means to help. What good we do will be measured against our resources, and the unmet needs. It will be measured as much by our genuine efforts, as by effectiveness. The record will say “we tried to help, and did so substantially,” instead of “we made an economic and political analysis of futility, and offered little help, no hope, and no comfort.” We cannot explain the economic and political realities to the orphans. They will learn from their experience, and they will blame our wealth for their misery and poverty.

As my friend in Kenya said, “The problem is not where to get money, but where to spend it.” It is ironic that discussion in the West revolves around the best choices among different medical HIV treatments and the optimal medical therapies for success, while countries with staggering burdens of disease are struggling at every step to get any treatments to those in need. This issue of *JIA PAC* considers the use of protease inhibitor drugs versus protease

inhibitor-sparing therapy around issues of tolerance and long-term safety. It also discusses some fine points in measurement of HIV plasma viremia. These remain privileged debates, unlike the case study of CNS cryptococcoma in an untreated HIV case. HIV-infected people in resource-limited settings die without any specific treatment.

The struggle to provide HIV medicines for people in dire need has been tough even in principle, with lawyers and politicians persuading the pharmaceutical industry to meet the needs in the face of inadequate healthcare systems and scarce resources. The next struggle will be to meet the predicted logistical difficulty of making the medicines actually reach the intended recipients. Recently, various news sources reported the fate of valuable anti-HIV drugs that were donated to the poor, and re-sold in richer countries. The great divide between the “haves” and “have-nots” where money flows west, is complex. We may be disappointed, but not discouraged in overcoming such uphill struggles.

The lessons from successful individual HIV treatments provide guidance in addressing HIV treatment in developing countries. Success of HIV treatment in individuals requires a hierarchy of factors:

- Ready, willing, and able patients.
- Reliable access to medicines.
- Reimbursement for the cost of medication.
- Predictable or known susceptibility of HIV to drugs.
- Adequacy of the prescription.
- Monitoring of therapy.
 - Tolerance and safety of treatment.
 - Compliance and adherence to therapy.
 - Drug absorption or bioavailability, and drug interactions.
 - Management of pre-existing and intercurrent medical problems.

Having addressed other factors, individual treatment success relies on the most important determinant, compliance and adherence to therapy.

Success of HIV treatment in a population has parallel requirements:

- A community receptive to the realities of AIDS, acceptance of persons with HIV, and a commitment to HIV treatment. Given the opportunity for treatment, a community will be inclined to respond.
- Reliable access to medicines. The infrastructure for the distribution of medicines, and stocking of pharmacies do not precede the availability of medications themselves. Develop the provision and distribution of medicine together.
- Reimbursement for the cost of medications. Even a reduction in cost to a few hundred dollars a month is still too expensive for the very poor.
- Drug resistance is a consequence of inadequate treatment. The best management of drug resistance is its prevention through good treatment.
- Medical education of healthcare providers in different settings must accompany the provision of medical treatments. We need practical learning and teaching programs, not just lengthy printed treatment guidelines. As well, one-way recruitment of physicians from poorer to richer countries needs a creative response to keep poor countries from becoming poorer.
- Monitoring HIV therapy for safety and adherence requires the same infrastructure as general medical healthcare for tuberculosis and malaria. This infrastructure will accompany or follow, but not precede the availability of treatments and care.

We have identified the problems. There will be more unforeseen problems, but we must not be discouraged from making the right response. History is watching us. We cannot become distracted and entangled in wars at the expense of engaging in international economic development and public health. The WHO goal of treating millions can be realized with the commitment of resources, and acceptance of leadership. ■

Protease inhibitor-sparing regimens

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Key words: HIV treatment, antiretroviral drugs, HAART, protease inhibitors, reverse transcriptase inhibitors

I will address three major issues that are the main benefits from using protease inhibitor (PI)-sparing regimens, such as efficacy of antiviral activity, metabolic side effects, and adherence. Anti-HIV efficacy is at least equal, and perhaps sometimes controversially superior to PIs because of fewer metabolic side effects, which results in better tolerance. Less controversial is the idea that PI-sparing regimens improve adherence because of decreased complexity, lower pill burden, and options for once-daily therapy.

Anti-HIV activity

There are many studies that compared PI-sparing to PI-based regimens. The DMP-006 study compared efavirenz (EFV) + Combivir (zidovudine (ZDV) + lamivudine (3TC)), to an indinavir (IDV) + Combivir, and to an EFV + IDV regimen. The as-treated (AT) and intent-to-treat (ITT) analyses showed that EFV did as well, if not better, in anti-HIV activity than IDV with Combivir. This suggested that PI-sparing regimens could match a PI-based regimen of the day. Data from Figure 1 show the first 48 weeks of anti-HIV treatment. Figure 2 shows the same type of activity after two years of therapy, in getting individuals to an undetectable level of plasma viremia and its durability, with the PI-sparing regimen EFV and Combivir. Eighty percent of individuals at 96 weeks maintained their response to therapy. There was significant decline in the group that received PIs.

Another study compared a nelfinavir (NFV)-based regimen to a nevirapine (NVP)-based regimen. It was one of the first studies that actually compared PI given twice daily to a PI-sparing regimen. In Figure 3, the ITT and AT analyses show the PI-sparing regimen performing at least as well, if not slightly better, than the PI-based regimen given twice daily.

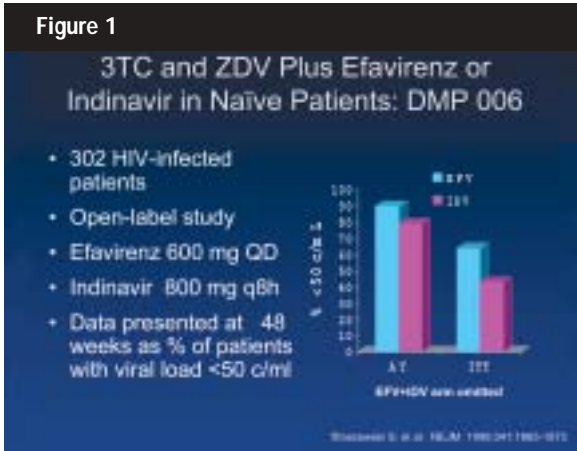
More recently, there were comparisons between abacavir (ABC)-based regimens or Trizivir (ZDV + 3TC + ABC), and twice-daily IDV + Combivir regimen. The ABC-based regimen was comparable in virologic outcome to the PI-based regimen. One of the controversies about these data and use of all nucleoside regimens has been whether performance is maintained in individuals who have lower CD4 cell counts and higher viral loads. This showed that the CD4 cell count rises were similar in the ABC and IDV arms, which has been true of the other studies.

What about individuals with higher viral loads? When you look at ITT analysis, Trizivir looked significantly better in individuals with lower viral loads up to 100,000 copies/mL. There was not much difference in individuals with greater than 100,000 copies/mL. The ITT analysis may have been biased, by presuming outcomes for individuals who drop out of the study, and so we were interested in looking at both the ITT as well as the AT analyses. Looking at the AT analysis, and at individuals with higher viral loads, the PI-based regimen tended to be better than the ABC. There were concerns about whether this particular PI-sparing regimen can be used in individuals with higher viral loads, and about the problem of using IDV-based regimens. We are currently moving away from regimens that require pills three times a day with food restrictions toward comparison of the Trizivir regimen with more commonly used PI-based regimens.

A more recent GlaxoSmithKline study compared Trizivir to Combivir + NFV twice daily, as well as stavudine (d4T) + 3TC + NFV. It looked at individuals with viral loads from 1,000 to 200,000 copies/mL, and stratified them on whether they were less than or greater than 100,000 copies/mL. The study was originally designed to focus on women, although it later recruited men to increase the study population. It remains important because it contained a greater proportion of women than in other studies. The study did not compare virologic outcomes from these three groups, but looked at some of the differences in metabolic complications. The 48-week data in Figure 4 were the observed ITT analysis, and looked like the AT analysis. The treatment groups

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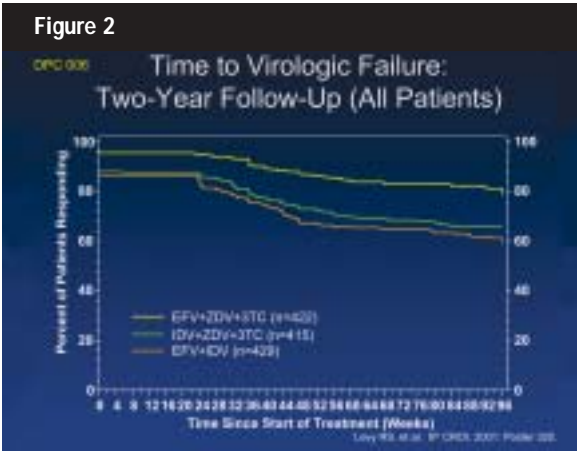
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appeared similar in outcome, showing regimens are comparable. In individuals with higher viral load, from 100,000 to 200,000 copies/mL, the proportions with viral load suppression less than 50 copies/mL appeared similar in the Combivir + NFV, and Trizivir treatment groups. The CD4 cell count rise was similar across the three groups.

Although the study made no comparison to a PI-based regimen, it led to the idea of the potential potency and efficacy of using once-daily combinations with didanosine (ddI), 3TC, and EFV. Recent data showed eighty percent of individuals responding at 48 weeks with plasma viremia less than 50 copies/mL, but no differences with individuals who had viral loads greater or less than 100,000 copies/mL.

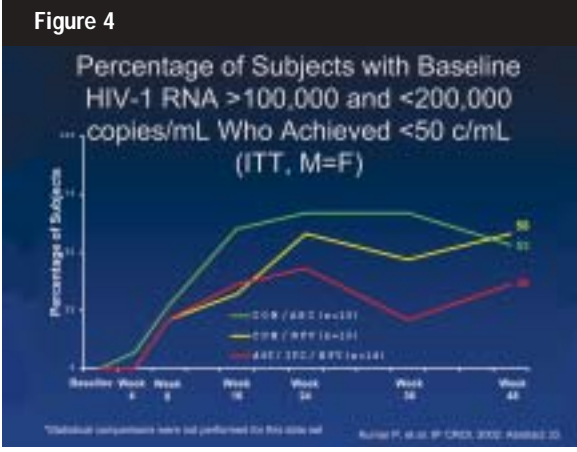
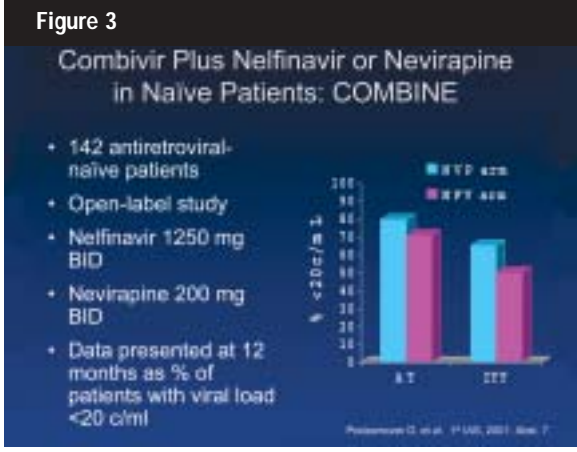
Another PI-sparing regimen that has gained attention is the "compact QUAD." A regimen of Combivir, ABC, and EFV may address questions about using a Trizivir or a triple nucleoside regimen in individuals with higher viral loads or lower CD4 cell counts when a PI is not initially desirable. This may be an interesting option because it adds to activity of Trizivir without additional problems with multiple doses. A current study in the AIDS Clinical Trial Group (ACTG) compares this

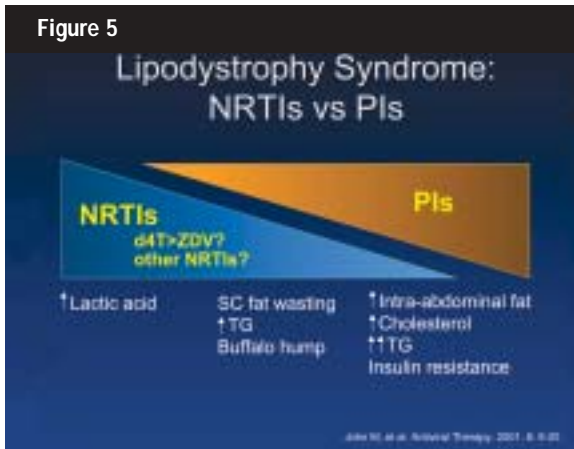


regimen with Trizivir alone, versus a regimen of Combivir and EFV. This leads to questions about whether some activity is gained over Trizivir alone, and whether anything is gained with this regimen rather than with EFV + Combivir.

Side effects

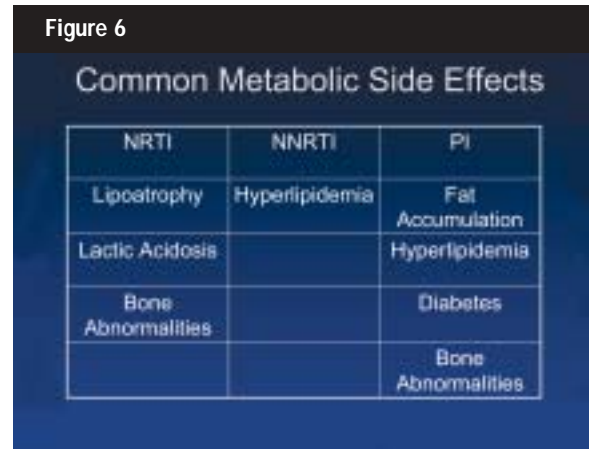
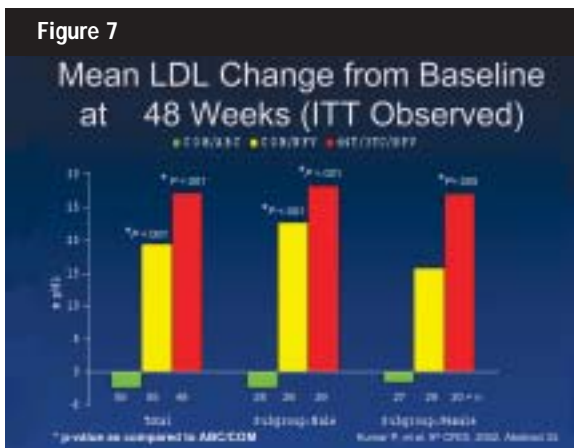
The second issue when looking at the benefits of PI-sparing regimens deals with metabolic side effects. Figure 5 shows that a combination of both PIs and nucleosides contributes to lipodystrophy syndrome. The nucleosides play a bigger role in fat atrophy and lactic acidosis, whereas PIs appear to be more involved in cholesterol and triglyceride elevation, insulin resistance, and fat accumulation. Figure 6 shows common metabolic side effects associated with particular drugs. Nucleosides are associated with lipoatrophy, lactic acidosis, and some bone abnormalities. Some studies controversially suggested that nucleosides contributed to osteoporosis and osteopenia. There are not many metabolic side effects in the non-nucleoside class, but clearly EFV contributes to lipid problems. PIs have been implicated in fat accumulation, serum lipids, diabetes, and controversially with bony abnormalities. Some studies showed osteoporosis that resulted from HIV disease improves in individuals on PIs.





The study comparing Trizivir to Combivir + NFV, and d4T + 3TC + NFV looked at metabolic complications, particularly lipid issues. Figure 7 shows the mean low-density lipoprotein (LDL) change in individuals from baseline at 48 weeks. The NFV-based arms show increases in LDL, whereas there are slight decreases in the individuals who receive Trizivir. Not only was there a difference in the triglycerides between the NFV-based regimen and the Trizivir, there actually seems to be a significant difference within the NFV-based regimen between the d4T arm and the ZDV arm. This is not well understood, and requires more study. There seems to be a trend of more elevated cholesterol and triglycerides with PI-based regimens than with a triple nucleoside regimen.

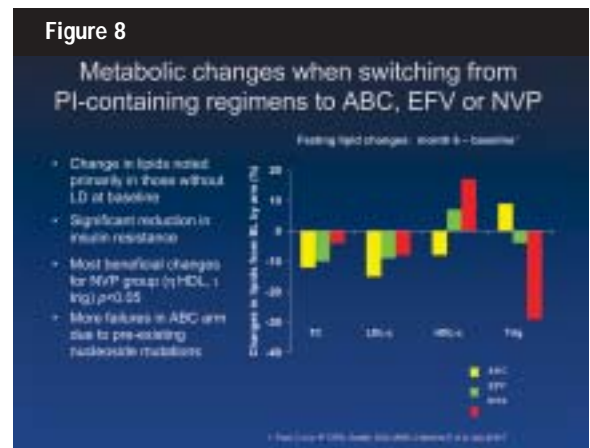
The study also addressed whether individuals have elevated lactate levels or lactic acidosis with triple nucleosides, as opposed to two nucleosides in combination with another class. It measured lactate levels of men and women over a period of 48 weeks. Women seemed to be at greater risk for elevated lactate issues, and some progressed to lactic acidosis. Overall, there were minor elevations for individuals on triple nucleosides, and for those on ZDV + 3TC + NFV. Most elevations occurred with the d4T-based regimen. This does not suggest that

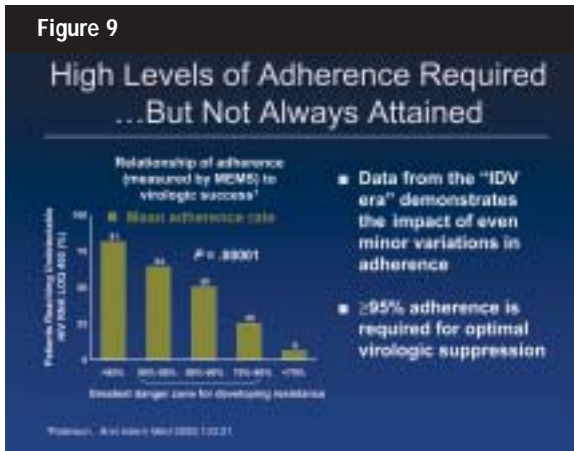


there are more lactate problems with three nucleosides than with two nucleosides.

Other studies looked at switching people away from PIs to regimens based on ABC, EFV, or NVP. Data in Figure 8 show improvement with triglycerides and LDLs when individuals switched to any of the three regimens. The high-density lipoprotein (HDL) levels suggest greatest improvement when switching from the PI to the non-nucleosides, and a lesser decline when switching to triple nucleosides. In triglycerides, the greatest decline was seen when switching to NVP.

What about concerns that PIs may be implicated with coronary heart disease through lipids and diabetes? Are we seeing excess cardiac disease in HIV-infected patients as a result of PIs or any type of HAART? Two recent abstracts were updates, particularly data from the Hobbs cohort. They assessed cardiac events in almost 6,000 patients, and found 15 myocardial infarctions (MIs). Thirteen were on PIs and two were on non-PIs, for an odds ratio of 4:9. This is a small number of events, and a short follow-up time. We are likely to see more events as individuals have a prolonged period of time with risk factors, particularly elevated lipids. The analysis also did not consider prior therapy.



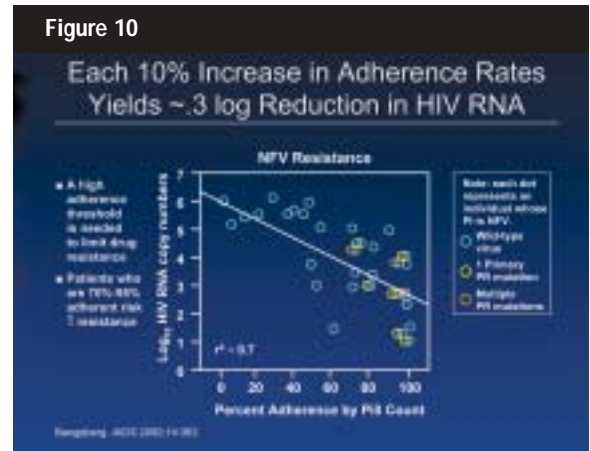
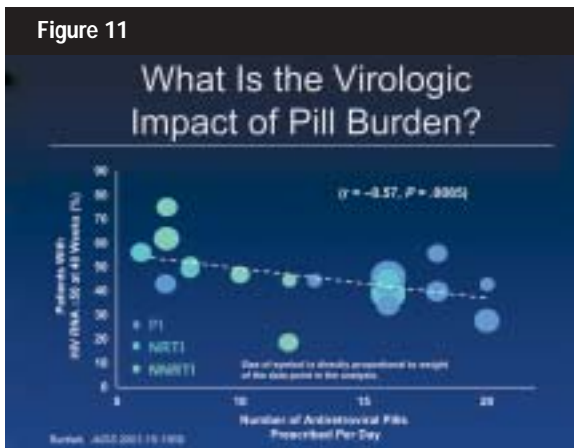


There could have been individuals who were not currently on PIs, although they had previous experience with PIs not included in that class. This also does not count for prescribing biases.

An updated Kaiser Permanente database study focused only on MIs among 4,000 HIV-infected patients, and 40,000 patients with no HIV disease. The study found 72 coronary events, and 47 MIs. There was no significant difference between individuals with or without HIV, although a trend seemed to suggest individuals with HIV had more events. There also seemed to be no differences between individuals on PIs and non-PIs.

Adherence

What about the benefit of improved adherence with PI-sparing regimens? A high level of adherence is critical to successful therapy, but not always attained by individuals. Figure 9 refers to the early PI era with regimens that required dosing several times a day. Nowadays this might be a little bit different as suggested by studies using triple nucleosides. Clearly, a very high level of adherence, greater than 95 percent, is necessary for successful antiretroviral therapy.



This point is reinforced with data from NFV-treated patients in Figure 10. Lesser adherence is accompanied with an increase in the plasma HIV RNA levels, or higher viral loads. Resistance mutations occur with individuals who take most, but not all, of their medications, rather than with individuals who take their medications very little, if at all.

What are some of the characteristics of a complex regimen with doses more than twice a day? Studies about hypertension showed that regimens with dosing three or more times a day impaired adherence more than regimens with twice-daily dosing. There are no clear studies showing that once-daily dosing is better than twice-daily dosing.

Clearly, pill burden is important. Lower adherence has been associated with taking more than four drugs, along with food and water restrictions and special storage requirements that accompany PI therapy. Figure 11 demonstrates a recent meta-analysis of the virologic impact of pill burden by John A. Bartlett, from Duke University Medical Center in Durham, North Carolina. Bartlett's group looked at numerous studies that used PIs and triple nucleosides, as well as non-nucleoside regimens. The analysis showed the proportion of individuals who respond decreases as the number of pills increases.

There has been an important transition from taking many pills during the pre-HAART period, to taking a single pill such as ddI and EFV. Benefits were clear in moving away from complex regimens with time restrictions for IDV, 3TC, and ZDV, to simpler regimens such as Combivir + ABC, or Trizivir.

Is there a difference in patient response based on pill burdens and simplicity of medications? A comparison between ABC + Combivir, and IDV + Combivir shows the self-reported adherence of patients over a one-month period of time. Only 46 percent of the individuals

had 100 percent adherence. In the Trizivir arm, there were twice as many adherents, when compared to the IDV + Combivir arm. The number of individuals who had greater than 95 percent adherence was good. Clearly, a simpler regimen results in better adherence in the patient.

In conclusion, lower pill burden is a major benefit of PI-sparing regimens, compared to a PI-based regimen, leading to increased simplicity and better adherence. A PI-sparing regimen may also have superior anti-HIV efficacy, and fewer long-term metabolic side effects, particularly in relation to lipid abnormalities. It remains to be seen whether these advantages may be balanced by acute toxicities such as hepatitis or drug rash and hypersensitivity. ■

Sources

Staszewski S, Morales-Ramirez J, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J* 1999; 341(25):1865-73.

Levy R, Labriola D, Ruiz N. Low two-year risk of virologic failure with first regimen HAART. 8th Conference on Retroviruses and Opportunistic Infections. February 4-8, 2001. Chicago, USA. (Abstract 325).

Podzamczar D, Ferrer E, et al. Final 12-month results from the Combine Study: A randomized, open, multicenter trial comparing Combivir plus nelfinavir or nevirapine in naïve patients. 1st IAS Conference on HIV Pathogenesis and Treatment. July 8-11, 2001. Buenos Aires, Argentina. (Abstract 7).

Vibhagool A, Cahn P, Schechter M, et al. Abacavir/Combivir (ABC/COM) is comparable to indinavir/Combivir in HIV-1 infected antiretroviral therapy naïve adults: Preliminary results of a 48-week open label study (CNA3014). 1st IAS Conference on HIV Pathogenesis and Treatment. July 8-11, 2001. Buenos Aires, Argentina. (Abstract 63).

Combivir, full prescribing information, GlaxoSmithKline, 2001.

Trizivir, full prescribing information, GlaxoSmithKline, 2001.

Kumar P, Rodriguez-French A, et al. Prospective study of hyperlipidemia in ART-naïve subjects taking Combivir/abacavir (COM/ABC), COM/nelfinavir (NFV), or stavudine (d4T)/lamivudine (3TC)/NFV (ESS40002). 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle, USA. (Abstract 33).

Maggiolo F, Migliorino M, et al. Once-a-day treatment for HIV infection: Final 48-week results. 8th Conference on Retroviruses and Opportunistic Infections. February 4-8, 2001. Chicago, USA. (Abstract 320).

Ruane P, Parenti D, et al. The PI-sparing compact QUAD regimen of Combivir (COM)/abacavir (ABC)/efavirenz (EFV) is potent and well-tolerated in antiretroviral therapy (ART) naïve subjects with high viral loads: 24-week data. 1st IAS Conference on HIV Pathogenesis and Treatment. July 8-11, 2001. Buenos Aires, Argentina. (Abstract 221).

John M, Nolan D, Mallal S. Antiretroviral therapy and the lipodystrophy syndrome. *Antivir Ther* 2001; 6(1):9-20.

Fisac C, Fumero E, et al. A randomized trial of metabolic and body composition changes in patients switching from PI-containing regimens to abacavir (ABC), efavirenz (EFV) or nevirapine (NVP). 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle, USA. (Abstract 699-T).

Martinez E, Podzamczar D, et al. Switching protease inhibitors to nevirapine (NVP), efavirenz (EFV) or abacavir (ABC): A randomized, multicenter, open-label, simplification trial. 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle, USA. (Abstract LB17).

Holmberg S, Moorman A, et al. Protease inhibitor use and adverse cardiovascular outcomes in ambulatory HIV patients. 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle, USA. (Abstract 698-T).

Klein D, Hurley L. Hospitalizations for coronary heart disease and myocardial infarction among HIV+ patients in the HAART era. 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle, USA. (Abstract 696-T).

Paterson DL, Swindells S, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med* 2000; 133(1):21-30.

Bangsberg DR, Hecht FM, et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *AIDS* 2000; 14(4):357-66.

Cramer JA, Mattson RH, et al. How often is medication taken as prescribed? A novel assessment technique. *JAMA* 1989; 261(22):3273-7.

Eisen SA, Miller DK, et al. The effect of prescribed daily dose frequency on patient medication compliance. *Arch Intern Med* 1990; 150(9): 1881-4.

Fischl MA. Antiretroviral therapy in 1999 for antiretroviral-naïve individuals with HIV infection. *AIDS* 1999; 13 Suppl 1:S49-59.

Bartlett JA, DeMasi R, et al. Overview of the effectiveness of triple combination therapy in antiretroviral-naïve HIV-1 infected adults. *AIDS* 2001; 15(11):1369-77.

Stone VE, Adelson-Mitty J, et al. Adherence to protease inhibitor therapy in clinical practice: usefulness of demographics, attitudes and knowledge of predictors. 12th World AIDS Conference. June 28-July 3, 1998. Geneva, Switzerland. (Abstract 32337).

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Antiretroviral therapy 2002: Old and new paradigms

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Key words: antiretroviral strategy, protease inhibitors, sequencing, pharmacology, forgiveness

It is my pleasure to speak on the merits of antiretroviral regimens containing protease inhibitors (PIs). I would like to address an old paradigm in HIV therapeutics, as well as to raise important new paradigms. There are three classes of anti-HIV drugs in clinical practice: the nucleoside reverse transcriptase inhibitors (NRTIs), the non-nucleoside reverse transcriptase inhibitors (NNRTIs), and the PIs. I will discuss some changes in HIV epidemiology, and later PI-sparing and PI-inclusive regimens. I will consider new paradigms, particularly drug resistance in relation to pharmacology, the initial use of potent antiretroviral regimens, and of once-daily therapy versus more frequent dosing. I will also discuss toxicity, tolerability, and adherence. These are the factors that make or break anti-HIV treatment, and lead to successful therapy.

Data from Chicago mirror reports from the US Centers for Disease Control and Prevention (CDC) during the rise of the HIV/AIDS epidemic (Figure 1). From 1995 to 1998, mortality in persons living with HIV declined 65 percent with no differences between Caucasians, African-Americans, and Hispanics. Decline in mortality was equal across racial groups for both men and women. These data span the highly active antiretroviral therapy (HAART) era and the introduction of PIs, and provide direct evidence of the remarkable benefits of HAART in an urban population.

The most important consideration in starting antiretroviral therapy is to successfully gain a patient's confidence and prepare for optimal adherence in initial therapy. Margaret Fischl, from the University of Miami in Florida, compared a clinical trial cohort to a treatment cohort of incarcerated persons. She showed that patients who take and tolerate their medications have extremely good outcomes. The group that had directly observed therapy (DOT) even with a complicated indinavir (IDV)-based regimen approached 90 to 100 percent therapeutic

success. This was in contrast to a group of patients, in a clinical trial setting, who achieved only a 72 percent success rate.

A crucial lesson of adherence is the need to emphasize adherence at the initiation of therapy, and to ensure the patient understands and accepts the regimen before prescription. Patients need to understand what is in store for them, how the clinicians will be available to them in an ongoing way if there are complications or toxicities, and the different tools that have been used to improve adherence. This issue cuts across different regimens and classes of drugs, and is clearly at the heart of the success for antiretroviral therapy.

Let me briefly address some of the earlier arguments about the value of PI-inclusive versus PI-sparing regimens. The clearest epidemiologic and clinical trial information for the use of drugs in reducing HIV morbidity and mortality can be attributed to protease inhibitors in the AIDS Clinical Trial Group (ACTG) 320 and a variety of other clinical endpoint studies. There is reason to expect that the control of virus load and the increase of CD4 count are associated with declines in morbidity and mortality with the other regimens, but we still await definitive data for PI-sparing regimens such as triple nucleoside, and the NNRTI-based treatments.

The list of preferred regimens from the US Department of Health and Human Services (DHHS) guidelines is shown in Table 1. Among the preferred agents are efavirenz (EFV), two single PIs such as indinavir and nelfinavir (NFV), and then the boosted PIs (lopinavir (LPV)/ritonavir (RTV) known as Kaletra (LPV/r)), or ritonavir/saquinavir (SQV)). Table 2 shows the outcomes of numerous trials by an intent-to-treat (ITT) analysis with at least 100 patients per arm showing virologic success between 50 and 70 percent of patients. This includes treatments with three nucleosides, or two nucleosides in an NNRTI-based regimen with nevirapine (NVP) or EFV, and in both non-boosted and boosted PI-based treatments.

Table 2 shows three examples of the durability of regimens. For example, the EFV DMP-006 study extension at three years showed 52 percent of patients still below the level of detection by intent-to-treat analysis. The

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extension of Merck 035 showed that 48 percent at five years were still below detection in the ITT analysis. Regarding boosted PI studies which included IDV and LPV, the Abbott 720 long-term Phase II study found undetectable viral load levels in 76 percent, and the five-year RTV/SQV study found the same in 70 percent, suggesting that we can achieve long-term success across different classes. A 50 to 70 percent success rate also implies substantial failure rates. Because of observation, attention to sequencing drug classes in successive antiretroviral treatments has been a priority.

I will review the advantages of protease inclusive regimens in Tables 3,4, and 5 that are from the DHHS guidelines. We have documented clinical, virologic, and immunologic activity, and we have also seen benefit in several different cohort studies with PI-based regimens, even when a patient has ongoing smoldering viremia and relatively low CD4 cells. As noted above, there was a marked mortality benefit described in Chicago. These data speak to an intrinsic strength and effectiveness with PI-based regimens.

There is a resistance advantage with PIs. A PI-based regimen that includes nucleosides targets HIV at two steps of virus replication, unlike a nucleoside-only regimen, and preserves the NNRTI class. Cross-resistance within a drug class is a problem. Other past problems with PIs included difficulty of use, the long-term side effects, inhibition and induction of the cytochrome systems, and real and potential drug interactions. These drug interactions are not limited to the PI class, but are greater with the PI class, particularly RTV. In comparison to NNRTIs, side effects related to the protease class are more prominent, and generally there is a higher pill burden and less ease of adherence. There are also exceptions that will be addressed later.

In terms of disadvantages for the NNRTIs, we do not really have the desired data about clinical endpoints with NNRTIs, although cohort studies do suggest

Table 1

Initial Treatment
Strongly Recommended

One Choice Each From Column A and B

Column A	Column B
• Efavirenz	• Didanosine + Lamivudine
• Indinavir	• Stavudine + Didanosine†
• Nelfinavir	• Stavudine + Lamivudine
• Ritonavir + Indinavir*†	• Zidovudine + Didanosine
• Ritonavir + Lopinavir**†	• Zidovudine + Lamivudine
• Ritonavir + Saquinavir* (SGC§ or HGC§)	

*The combination of zalcitabine plus didanosine is not recommended because of the risk of peripheral neuropathy. †The combination of didanosine plus zalcitabine is not recommended because of the risk of peripheral neuropathy. **The combination of zalcitabine plus zidovudine is not recommended because of the risk of peripheral neuropathy. ‡The combination of didanosine plus zalcitabine is not recommended because of the risk of peripheral neuropathy. §The combination of didanosine plus zalcitabine is not recommended because of the risk of peripheral neuropathy. © 1998, CDC

comparability for NVP and EFV. NNRTIs have a low genetic barrier to evolution of resistance that can be conferred by a single or a few mutations. Resistance occurs in two-drug classes more frequently with NNRTI failures than with PI failures. This may be an important issue, but we have not yet demonstrated the long-term clinical consequences. Finally, NNRTIs also cause drug interactions, such as induction of methadone withdrawal due to lower serum methadone levels when co-administered with NVP or EFV. The rapid and sustained immunologic benefits continue to be an important advantage for the PIs. Figure 2 shows data from the ABT 720 study that the Phase II long-term follow-up from LPV/r up to 144 weeks. There were 100 drug-naïve patients enrolled in this study regardless of the CD4 count at which a patient entered a study. A robust CD4 cell increase of a 100 or greater was noted within the first 24 weeks. When starting therapy in someone with advanced disease who may have had an opportunistic infection, a prompt and early CD4 cell response is desirable. The CD4 cell increases were seen if the baseline level was less than 50, 50 to 200 cells/mL, or higher. Another feature of PIs is the sustained CD4 rise in the second and third year, and the continuing in the third year. In the five-year RTV/SQV study, a 100 CD4 cell gain was observed in patients in their fourth year of therapy. PIs appear to have the ability to continue to provide increasing immunologic benefit long into treatment. Whether this occurs equally with NNRTIs and NRTIs remains to be shown.

Convenience and low pill burden are important issues. Nevirapine is available as one pill twice a day or two pills once daily; EFV as one pill once a day; and Trizivir (abacavir (ABC) + zidovudine (ZDV) + lamivudine (3TC)) as one pill twice daily. There are also some advances in the protease class that are worth noting such as a simplified regimen of LPV/r as three pills twice a day or six pills once daily; boosted IDV as three pills twice a day; and the amprenavir (APV) pro-drug 908 as two pills twice a day. So there is improved simplification of the PI class as well.

Table 2

**Recommended Treatment:
Durability of First Line Regimens**

Drug +2 nRTIs	Reference	Result (VL cps/ml)
EFV	Tashima/IAS '01	52% <50 @ 3 yrs ITT
IDV	Gulick/IAS '01	48% <50 @ 5 yrs ITT
NVP	Petersen/ECMO '99	60% <50 @ 2 yrs OT
RTV/IDV	Boyd/CROI '00	66% <50 @ 48 wks ANS
LPV/RTV	White/IAS '01	76% <50 @ 3 yrs ITT
RTV/SQV	Farthing/IAS '01	70% <200 @ 4 yrs ITT

Figure 3 contains a cartoon illustrating one of the advantages of the early use of the boosted PIs that is true for LPV/r and for the other boosted PIs. There is a significant advantage to the development of clinically relevant resistance through stepwise resistance mutation that is especially apparent when used earlier. With a current PI such as IND, there are low troughs that lead to accumulation of two, three, and four resistance mutations. With NNRTIs, the pharmacologic advantage with EFV and NVP with quite high drug levels comes with a large change with each resistance mutation, so that the K103N (eg, one single resistance mutation) confers resistance. So the boosted PIs when used early have a theoretical advantage over the NNRTIs, and some evidence suggests this may be important.

As the HIV epidemic evolves, one problem is that treatment in 2002 is different from treatment in 1998 because of a changing pattern in drug resistance in newly infected individuals. Viviana Simon, of the Aaron Diamond AIDS Research Center, reported any resistance mutations in 13 percent in 1998 and 1999, increasing to 20 percent in 2001. There was also a change in the nature of the resistance with a substantial rise in the number of NNRTI resistance mutations of about 6 percent, and the emergence of PI resistance mutations. Similarly, Susan Little, from the University of California in San Diego, showed that that frequency of resistance in primary HIV infection appeared to be between 6 and 15 percent for the nucleoside classes.

If there is more circulating resistant virus in newly infected patients, and in chronically infected but treatment-naïve patients at the start of therapy, there is a rationale for doing baseline resistance tests before treatment. The initiation of very highly potent regimens in the naïve state may also be an important strategy partly to accommodate this growing problem of primary resistance. Taken together, early use of resistance tests and the use of more potent agents up front, comprise a reasonable strategy.

Table 3

PI-Based ART Regimen

Advantages	Disadvantages
<ul style="list-style-type: none"> Documented clinical, virologic and immunologic efficacy Benefit despite viral breakthrough Resistance requires multiple mutations Targets HIV at two steps of viral replication Preserves NNRTI use 	<ul style="list-style-type: none"> May be difficult to use and adhere to May have long-term side effects (lipodystrophy, insulin resistance and hyperlipidemia) Mild to severe inhibition of cytochrome P450 Cross resistance with other PIs

Figure 4 shows data from Christopher Alexander, at the BC Centre for Excellence in HIV/AIDS in Vancouver, about the effect of the initial regimen on subsequent resistance profile. Several different studies have shown similar results. Treatment-naïve patients were started on regimens recommended by their clinicians, and were genotyped at first virologic failure. PI-based regimens were more frequently associated with single-class resistance to nucleoside drugs. For PIs, about 39 percent had one-class failure such as the mutation M184V for 3TC, and 15 percent had two-class resistance. The opposite was true for the NNRTI-based regimens. Thirty-eight percent of NNRTI-treated individuals had two-class resistance to NVP or EFV, as well as M184 resistance to 3TC, or the development of NRTI early treatment-associated mutations (TAMS). Only 16 percent had single-class mutations. It is not proven that this has any clinical significance, or implications in terms of drug class sequencing, but is unlikely to be favorable. Ongoing trials such as the Community Programs for Clinical Research on AIDS (CPCRA) First Study, the ACTG 384, and Initio might shed some light. It is unclear whether patients under salvage therapy after virologic or clinical failure with a NNRTI-based regimen, are less likely to have a successful outcome because of more genotypic resistance mutations.

There is another example of the relative uncertainty about the impact of the genetic vulnerability of the NNRTI class. From treatment interruption data, we have learned that M184 is the most common single mutation that is seen when the regimen contains 3TC. In NNRTIs, the K103 or the Y181C single mutations have been commonly seen after treatment interruption, suggesting the resistance that emerges with treatment interruption may be at these weakest genetic links. This is unlike the multiple mutations required to confer PI resistance. This finding has implications in clinical practice because it is uncommon for patients to have 100 percent adherence. More common are adherence levels between 55 and 85 percent, which have been associated with the greatest

Table 4

PI vs. NNRTI: Advantages	
PI	NNRTI or 3-NRTI
<ul style="list-style-type: none"> ● Clinical, virologic, and immunologic efficacy well-documented ● Continued benefits seen despite viral breakthrough ● Resistance requires multiple mutations ● Targets HIV at two steps 	<ul style="list-style-type: none"> ● Sparing of PI-related side effects ● Generally easier to use and adhere compared with PIs

likelihood of the development of virologic treatment failure and resistance mutations.

Susan Little and Eric Daar, from the University of California in Los Angeles, studied the apparent durability of NNRTI resistance mutations by looking at the diverse patterns of resistance mutations in six patients. Five patients had a reduced phenotypic susceptibility persisting up to 450 days, suggesting that NNRTI resistance mutations may be stable for prolonged periods of time. Some have argued for early genotypic testing of patients who are drug-naïve prior to starting therapy. The implications are that resistance may persist for many months without drug pressure, and be transmissible. These data support susceptibility testing before treatment at least during the first year of infection. It is necessary to determine whether there is a difference in the persistence of resistance depending on the initial drug, or on the resistance mutation.

Diane Havlir, from the University of California in San Diego, also showed limited protease inhibitor resistance with the first triple regimen. With ZDV, 3TC, and IDV, almost all the resistance was to 3TC, with none to IDV. In another setting, there were five out of 23 patients with a PI resistance mutation, but that was overshadowed by M184V.

In the Abbott 863 trial, which was a comparison of treatment-naïve patients treated either with NFV or LPV/r PI-based regimen, no resistance mutations were detected as defined by the L90M or D30N for NFV, nor any of 10 common PI mutations for LPV/r. Over two years, there were no PI mutations in the LPV/r group of about 500 drug-naïve patients treated, as compared to 43 percent in the NFV group. There was an interesting difference in the presence of the M184V. There appeared to be some effect of the PI on the emergence of 3TC resistance, where 37 percent of patients in the LPV/r group developed the M184V, as compared to 81 percent in the NFV group.

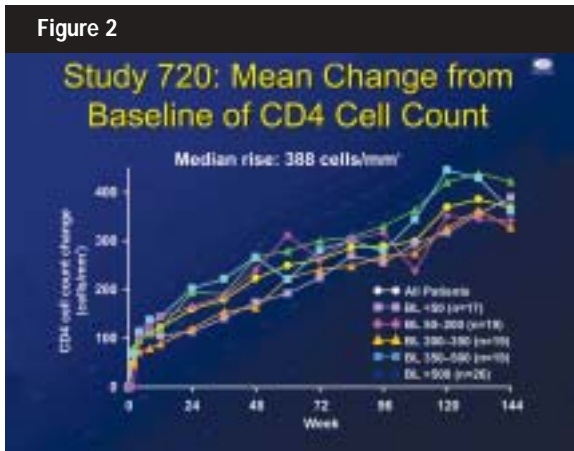
Table 5

PI vs. NNRTI: Disadvantages	
PI	NNRTI
<ul style="list-style-type: none"> ● May be difficult to use and adhere to ● Long-term side effects, including lipid disorders ● Drug interactions 	<ul style="list-style-type: none"> ● Effect on clinical endpoints unknown ● Resistance conferred by a single or few mutations ● More multi-class resistance w/ failures ● Drug interactions

C. Charpentier, from Hôpital Bichat-Claude Bernard in Paris, studied the evolution of drug resistance on PI-based antiretroviral therapy, and showed that PI resistance is not a simple process. There is a stepwise evolution of resistance mutations in the protease. There are multiple clones with different primary resistant mutations evolving different secondary mutations of different advantage in resistance and fitness, at different rates. This is distinct from the view of a single dominant resistance clone within a single infection, as for NNRTIs or 3TC. How we fit this information into what we understand about the development of resistance in a population is unclear.

What about the early use of potent antiretroviral therapy? Bill Cameron, from the University of Ottawa in Ontario, studied patients on RTV/SQV who were identified by baseline virus load above and below 100,000 copies/mL, and showed comparable outcomes in the two strata. With a potent regimen such as RTV/SQV in five-year follow-up, the CD4 cell increased steadily for many years. The Abbott 720 study looked at the virologic outcomes with a boosted PI when used in a naïve state. After three years, 96 percent of patients were still below the level of detection in the on-treatment (OT) analysis, and 76 percent in the ITT analysis. Six percent stopped therapy due to intolerance from a boosted PI over a period of three years. Good tolerability is one of the keys to good adherence. It has been used as an argument favoring the triple nucleoside or the NNRTI-based treatment option. There is substantial evidence that one can achieve good tolerance within the PI class, as shown in the long-term LPV/r trials.

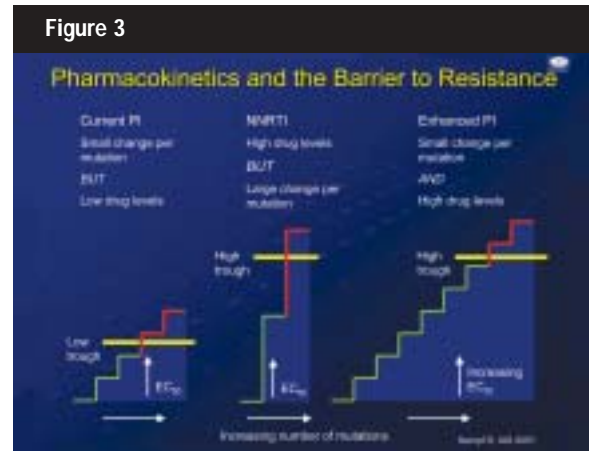
Initial potent antiretroviral therapy does not necessarily mean the inclusion of a protease inhibitor. In the QUAD Study using ZDV, 3TC, ABC, and EFV, Peter Ruane, of Tower Infectious Disease Medical Associates in Los Angeles, studied patients with a mean virus load of 100,000 copies/mL and low T-cells. The mean CD4 count was 285 cells/mL, and half the patients had a



clinical diagnosis of AIDS. Two-thirds, or 68 percent of patients had virus loads over 100,000 copies/mL. Results were good at 24 weeks by ITT and in the on-treatment (OT) analysis at both less than 400 and less than 50 copy threshold. Treatment was also very well tolerated except for 6 or 7 percent of patients who stopped treatment. Note that this strategy breaks the paradigm. Rather than asking whether or not first-line therapy should be a PI or an NNRTI-based regimen, it deploys a tolerable, relatively convenient regimen, on which a patient may be able to stay for a prolonged period of time, measurable over many years and not just 24 weeks or even two years. More data are needed on the long-term durability and tolerability of this regimen before making recommendations.

To summarize, PIs have a proven track record of decreasing morbidity and mortality; a significant resistance advantage which is augmented with the use of pharmacologically boosted PIs; an impressive early immunologic benefit which is particularly desirable in patients with advanced disease; and some recent improvements in convenience and tolerability which allow for highly potent and well-tolerated regimens of durable efficacy. Currently available clinical trial data suggest that LPV/r is the best performer among the boosted PIs, and that the best management of resistance is its prevention.

Let us turn our attention to toxicity. Protease inhibitors have common enteric, hepatic, skin, and metabolic toxicities in initial use. Long-term problems are lactic acidosis, lipodystrophy, and osteopenia that overlap with effects of other anti-HIV drug classes, and of HIV itself. Data from the ATHENA and other studies show that the percentage of discontinuations from clinical or virologic failure has been small, and discontinuations are largely the result of toxicity. Enteric side effects are common reasons for discontinuation, and are associated with the PI class, and with certain nucleosides as well. Some side effects are related to single drugs



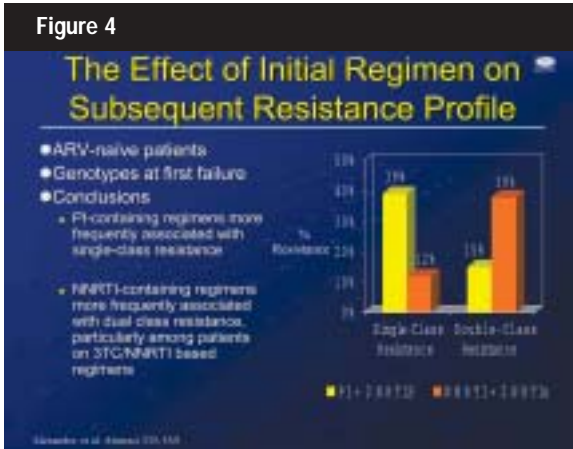
such as urolithiasis with IDV, or altered sleep and mood with EFV.

Sometimes what is seen in clinical practice differs substantially from what is reported in clinical trials. For example, we reported 15 percent discontinuations during our first use of EFV in 150 patients at the CORE Center, most commonly from dizziness, which contrasted sharply with a 6 percent discontinuation rate in the DMP-006 study.

The strongest association with hyperlipidemia occurs with the protease inhibitors, except atazanavir. However, high lipids lead to discontinuation infrequently. For example, Hans Jaeger, from KIS-Curatorium for Immunodeficiency in Munich, Germany, looked at discontinuations over a period of sixteen months in 151 patients, and found that greater than 90 percent of patients remained on therapy. Here again is evidence of an evolution in the tolerability of the boosted protease class.

Princy Kumar, from Georgetown University in Washington, DC, looked at an NRTI versus NFV-based regimen, comparing ABC + Combivir (ZDV + 3TC), to NFV + ZDV + 3TC, or NFV + stavudine (d4T) + 3TC in a 48-week study. There clearly was a difference in cholesterol and triglyceride levels between the two regimens. Literature on the degree of lipid elevations agrees with the Kumar data. Increases occurred in low-density lipoprotein (LDL) cholesterol of about 20 to 30 mg/dL in the NFV arm, compared to no change in the ABC + ZDV + 3TC arm.

I use the following paradigm to interpret these levels of lipid changes in clinical practice. A small percent of patients may have documented ischemic heart disease, such as a 50-year-old smoker with hypercholesterolemia, so that a 20 to 30 mg/dL increase in cholesterol might have serious consequences. It is probably appropriate to avoid medications that might increase cholesterol in this setting. For other patients, this degree of elevation



has to be put in context with other risks and benefits affecting the selection of antiretroviral therapy. My point is the pendulum in HIV medicine may have swung a little too strongly towards concerns about long-term cardiovascular complications, versus the need for effective HIV treatment options. It is reasonable to ask how important are these lipid changes, and what management options are open to the HIV clinician and the patient in the event of their occurrence?

Note that PIs are not the only agents that have been associated with cholesterol elevations. In the EFV + IDV arm of the DMP-006 study, there was twice the lipid elevation as the IDV or EFV arms, with a 20 to 30 mg increase in total cholesterol. Similar increases have been seen in other trials of EFV. More recently, there is evidence that the NRTI class, in particular stavudine, is associated with hyperlipidemia.

One option for the management of hyperlipidemia is switching from a PI-containing regimen to a non-PI regimen of ABC, EFV, or NVP. Several studies have shown that there is an improvement with the switch. The improvement in low-density lipoproteins (LDLs) appears to be equal, with some evidence showing the greatest improvement with NVP. The magnitude of the change for the LDL is around 10 percent, so that a 200 baseline cholesterol or LDL represents a change of 20 mg/dL.

What about head-to-head comparisons between PIs? Again, I will rely on trials comparing LPV/r with NFV, specifically a non-boosted PI with a boosted PI. For triglycerides in the 863 Trial there was a significant difference between the two favoring NFV. The mean increase from baseline for LPV/r was 125 mg/dL and 47 mg/dL for NFV. But, looking at the percentages of patients who are at less than 400 or 400 to 750 mg/dL (recall again that these are not fasting specimens), there is a fair comparability between LPV/r and NFV. Most patients who were subsequently fasted and had levels redrawn

Table 6

Is Lipoatrophy Reversible with ART Switch?

Three Prospective, Randomized Trials

Study design	DEXA	CT scan	Comment
PartB 48 weeks, n=40 2 NRTIs + PI → ABC/CDV	8.5-2.8% fat gain in arms, no change in legs	stable	No lipid improvements
Carri n=40, 24 weeks d4T or AZT → ABC	0.3kg fat gain (18%)	Improvement	No patient or MD reported improvement
TARHEEL n=134, 6 mo d4T → ABC or AZT	5-6% fat gain in leg & trunk; 22% in arms	Improvement	+ Patient self-reported improvement

Concise: Small studies, early data, and small changes seen
 Jones et al. *JGIM* 2004
 Carr et al. *JAMA* 2004
 McCauley et al. *AIDS*

went down one or two grades. Only about 6 percent had very high triglyceride elevations. In contrast, there was no significant difference in cholesterol in this trial between the boosted LPV and NLF. Most of the elevations were in the grade 1 or grade 2 level, and most patients reduced by one or two grades when fasted.

What are the predictors of having high triglycerides and high cholesterol in clinical practice? The strongest predictors in the LPV/r trials were having a baseline cholesterol or triglyceride elevation. There were LPV/r trials done in PI experienced patients, so the data included some patients who had elevations due to the prior PI-based regimen. The LPV/r dose also made a difference. Four LPV/r pills (for use with a NNRTI) twice a day conferred almost a fourfold increase in cholesterol level, and a threefold increased likelihood of increased triglyceride.

Another option for the management of hyperlipidemia is the use of statins and gemfibrozil or fenofibrate. In the LPV trials, 44 percent of patients with grade 3 elevations of cholesterol, and a similar proportion with elevated triglycerides were treated. There was a 17 percent decrease in cholesterol, and a 48 percent decrease in triglycerides. As I noted above, the degree of change from switching anti-HIV therapy are in the same range as these changes. Triglyceride reductions averaged 191 mg/dL (the average triglyceride elevation in that trial was 121), and cholesterol reductions were similarly 48 mg/dL.

Another example of switch therapy was from whatever regimen patients were on to Trizivir (ABC + ZDV +3TC). The majority was on PI-containing regimens, and the study had a PI continuation arm. Comparable values were achieved in the as-treated and intent-to-treat analyses. There was better adherence, and cholesterol fell by 50 mg/dL and triglyceride by 22 mg/dL in the Trizivir group. The results are comparable to what has been seen with pravastatin, gemfibrozil, or fenofibrate.

There is evidence that all lipid elevations may not be the same, and may not necessarily have the same implications for the development of cardiovascular disease. A study by Werner Richter, from the University of Munich in Germany, found that the strongest analogy for the HAART-associated hyperlipidemia is familial hypertriglyceridemia, which does not carry an increased cardiovascular risk compared to the general population. That is in contrast to familial combined hyperlipidemia, which is known to have a markedly increased cardiovascular risk. Richter's hypothesis is based on the similarity in the distribution of apolipoprotein B (apo-B) and very low-density lipoproteins (VLDLs) and fat micelles in the blood between HAART-associated lipid elevations and familial hypertriglyceridemia.

The other major long-term toxicity that may be associated with the PI class is morphologic change. The long-term RTV/SQV trial from Cal Cohen, from the Community Research Initiative of New England in Boston, and Charles Farthing, from the AIDS Healthcare Foundation in Los Angeles, showed that when you add nucleosides, most commonly d4T + 3TC, you see much more of all of the morphologic changes, particularly lipoatrophy, as compared to just dual PIs alone. The only parameter that was higher in the dual PI alone was the increase in waist size.

Regarding the potential management of lipoatrophy, three studies have suggested that there was an improvement in lipoatrophy by DEXA or by CT scan with a switch from NRTIs or PIs in patients with clinically significant lipoatrophy (Table 6). These are very modest improvements and these data are preliminary. This suggests that a protease-sparing group, or a switch to ABC + ZDV + 3TC (or in one case ABC + ZDV) may improve lipoatrophy.

Liver toxicity merits attention. In a study by M. E. Moreno, from the Hospital Ramón y Cajal in Madrid, Spain, 62 percent of 200 patients were co-infected with hepatitis C (HCV), or 5 percent with hepatitis B (HBV). One-third continued to use alcohol. The incidence of grade 3 to 4 toxicity changes in transaminase levels in this observational cohort was 15 percent, with only 4 percent discontinuations. The most common drug associated with hepatotoxicity was NVP. Overall, the data do not favor one drug over another. Similarly, the large review of 10,000 patients by the ACTG found the incidence of HIV treatment-related hepatotoxicity to be 6.2 percent. There was more toxicity seen in the NNRTI arms. It was of limited clinical significance, 8 percent versus 5 percent. This analysis really did not lead a clinician to one clear choice of classes or agents, in the presence of underlying risk for hepatotoxicity. The study recommended patients should be monitored more closely with the use any of

the antiretroviral agents in the presence of underlying hepatitis.

What about DOT and once-daily therapy? Is that going to take us to PI-sparing or PI-inclusive treatment? I want to make a couple of points from the CNA 3014 study of reasons for non-adherence with a simplified regimen. There was better adherence with ABC + ZDV + 3TC than with a difficult IDV + ZDV + 3TC. The most common reason for non-adherence is people forget about a simple as well as a complicated regimen. The second most common reason for non-adherence was discontinuation due to an adverse event for IDV, or lacking privacy for ABC. Other reasons were being out in public, depression, or continuing adverse events. Thus, non-adherence may occur even with a simplified regimen,

The DOT program from Margaret Fischl had almost 100 percent success when an incarcerated patient was watched taking pills. By comparison, a study from Brian Conway, from the University of British Columbia in Canada, looked at a methadone program where 89 percent of patients still had positive tests for cocaine. All individuals were co-infected with hepatitis C and HIV, representing a difficult group in which to achieve good outcomes in on antiretroviral therapy. Both NNRTIs and PI-based regimens were used for either DOT for all doses, or modified DOT for a morning dose after which patients took their own afternoon dose. After 48 weeks, between 55 and 70 percent of patients were below the level of detection. Potential success might have more to do with the manner in which patients are given medications, and how well patients are able to adhere to their medications.

Tenofovir (TFV) may add a new option in the treatment of naïve patients, though data are as yet unpublished. It has been used in highly treatment-experienced patients with risk for opportunistic infections (OIs) and other concurrent treatments. Tenofovir appears to be well tolerated, offers an additional 0.5 log₁₀ decline in plasma virus load (VL) in such patients, and is convenient with one pill daily. **A study compared TFV to d4T + EFV + 3TC in treatment-naïve patients, and demonstrated no difference between the d4T and TFV-containing arms. Eighty percent of patients had viral loads below 50 copies/mL after 48 weeks by an ITT, missing-equals-failure analysis. Mean CD4 cell increases were 160 cells/μL in both arms. It is noteworthy that lipid elevations were significantly greater in the stavudine arm than the tenofovir arm.**

What about once-daily options within the PI class? Julio Montaner, from the University of British Columbia in Canada, presented one of the once-daily saquinavir + low dose ritonavir (SQV/r) studies, comparing SQV/r to EFV.

The Focus study included patients who did not have advanced illness with T-cells of about 350 cells/mL. It demonstrated virologic inferiority at 24 weeks by ITT, compared to EFV in a once-daily setting. The dose format of 100 mg of RTV and 1,800 mg of SQV once a day resulted in substantially more gastrointestinal toxicity. Nausea and vomiting were only seen in the SQV/r group. Once-daily use for most of the traditional boosted PIs still may have tolerance problems.

In contrast, the use of LPV/r once daily has greater variation in pharmacokinetics than twice-daily dosing. The trough is getting closer to a threshold of inhibition (IC₅₀) of the drug, although remaining well above it. It also appeared in 19 patients to have similar virologic efficacy to twice-daily therapy over a period of 48 weeks, by ITT analysis for an outcome of less than 50 copies/mL. Although tolerability appeared to be similar, it is necessary to have long-term and larger studies to compare it. The authors concluded that once-daily therapy with LPV/r would be reasonable in naïve patients, but raised concern for the lower IQ in treatment-experienced patients, with higher IC₅₀ or partial PI resistance.

Upon US Food and Drug Administration (FDA) approval, atazanavir will be another protease inhibitor with potency or activity comparable to NFV, which has less than LPV/r. Atazanavir also causes an indirect hyperbilirubinemia in about a third of patients, some of whom appear jaundiced, which may be an issue in its long-term use. A potential advantage seems to be no or little increase in serum lipids. More comparative studies will help place this drug among the PIs for optimal individualized treatments.

I want to finish by thinking about other novel paradigms, such as NRTI-sparing regimens. To my knowledge, only two regimens have been reported in the published literature: the SQV/r cohorts, and the IDV/EFV arm of the DMP-006 trial. One conference presentation looked at 42 patients on HAART with RTV, SQV, and EFV with no nucleosides in the regimen. Half those patients were already well controlled when they were switched, making the study a comparison of apples and oranges. Eighty-three percent of those patients maintained good virus load suppression, and 14 percent stopped because of adverse events. This was probably one of the more difficult regimens to take with 1200 mg of SQV and 100 mg of RTV. **Christophe Allavena, from the Institut de Biologie in Nantes, France, recently presented preliminary results of 75 patients treated with LPV/r and EFV without nucleosides over 48 weeks, showing 84 percent of them below 50 copies/mL. It will be of interest to see the long-term virologic and immunologic outcomes of this study, as well as the relative incidence of metabolic and morphologic complications.** Clearly the most

important thing about the NRTI-sparing regimens, in addition to virologic outcomes and short-term tolerability, is the incidence of morphologic and metabolic problems.

What is the appropriate role for the boosted PI? Should it be used earlier or later in HIV treatment sequencing? Salvage therapy is easiest with boosted protease inhibitors. Some evidence of the superiority of high drug level of dual PIs comes from the early ritonavir-saquinavir trials published by O. Kirk from the University of Copenhagen in Denmark. There is clearly a pharmacokinetic advantage to boosted PIs, and a higher inhibitory quotient. But there are also a number of uncertainties. What is the salvageability for a boosted PI when it is used early but leads to failure? What is the incidence and severity of the lipodystrophy syndrome? Current evidence suggests that the metabolic and lipid problems are mostly mild and manageable for the majority of newly treated patients.

The pharmacologic advantage of boosting PIs is a major benefit. The “forgiveness” quotient in pharmacology, or the extent to which a regimen remains effective without resistance after missing doses, should be considered when thinking of successful regimens. The best examples of more forgiving regimens are EFV, in the DMP-006 follow-up data, and LVP/r in the extended 720 study. One of the reasons for the success of those drugs is the pharmacology of the agents, or the elimination half-life compared with the dosing interval. Less forgiving regimens include the non-boosted PIs, 3TC, and once-daily NVP. Important questions are whether once-daily regimens will reduce the “forgiveness” quotient, and whether this will be offset by improved adherence. Some sequencing answers may hopefully emerge from the First trial from CPCRA, the Initio trial, and the ACTG 384. These trials may also answer important questions. Does it do any better to start one versus another form of therapy? Do they all switch as well to another?

In sum, I have argued for initial PI use in patients with advanced disease and low CD4 cells. It is an open question whether this is a worthwhile strategy in patients with higher CD4 cells, who have several other options for initial therapy. With boosted PIs there is a resistance advantage. We are still learning about the implications of this advantage, including the intriguing data from the LPV/r trials describing a lack of observed protease resistance mutations. Clearly a major lesson in the current era is the importance of the pharmacologic advantage and its greater “forgiveness,” a characteristic enjoyed only by EFV and the boosted PIs. The early use of potent antiretroviral therapy, including the compact QUAD or members of other classes, is an important strategy that needs to be tested, particularly for greater durability. In terms of toxicity, the concern of HIV clinicians with lipids may be out of proportion to all the

other issues in patient care. Greater simplicity, including once-daily therapy, is likely to continue to improve therapy, particularly in patients who are reluctant to take pills more than once a day, and also for its use in DOT. We need to study more of the alternative regimens, including the nucleoside sparing regimens, and that is where our sequencing trials are going to help us. ■

Sources

Whitman S, Murphy J, Cohen M, Sherer R. Marked declines in human immunodeficiency virus-related mortality in Chicago in women, African Americans, Hispanics, young adults, and injection drug users, from 1995 through 1997. *Arch Intern Med* 2000; 160(3):365-9.

Dicenzo R, Forrest A, Smith P, Squires K, Hammer S, Fischl M, et al. Comparing intensive and sparse sampling for estimating the population pharmacokinetics (PK) of indinavir (IDV) in efavirenz (EFV)-containing regimens. 8th Conference on Retroviruses and Opportunistic Infections. February 4-8, 2001. Chicago, USA. (Abstract 751).

Dybul M, Fauci AS, Bartlett JG, et al. Guidelines for using antiretroviral agents among HIV-infected adults and adolescents. The Panel on Clinical Practices for the Treatment of HIV. *Ann Intern Med* 2002; 137(5 Part 2):381-433.

Bartlett J. Severe liver toxicity in patients receiving two nucleoside analogues and a non-nucleoside reverse transcriptase inhibitor. 8th Conference on Retroviruses and Opportunistic Infections. February 4-8, 2001. Chicago, USA. (Abstract 19).

Staszewski S, Morales-Ramirez J, Tashima KT, Rachlis A, Skiest D, Stanford J, Stryker R, Johnson P, Labriola DF, Farina D, Manion DJ, Ruiz NM. *N Engl J Med* 1999; 341(25):1865-73.

Gulick RM, Melors JW, Havlir D, et al. 3-year suppression of HIV viremia with indinavir, zidovudine, and lamivudine. *Ann Intern Med* 2000; 133(1):35-9.

White, AC Jr, Brun S, King M, et al. Lopinavir/ritonavir (Kaletra) in antiretroviral naive HIV⁺ patients: Week 144 follow-up. 1st IAS Conference on HIV Pathogenesis and Treatment. July 8-11, 2001. Buenos Aires, Argentina.

Alexander C, Yip B, Wynhoven B, et al. The effect of initial antiretroviral therapy regimen on subsequent resistance profile. 1st IAS Conference on HIV Pathogenesis and Treatment. July 8-11, 2001. Buenos Aires, Argentina. (Abstract 235).

Cohen C, Shen Y, Rode R, et al. Effect of nucleoside (NRTI) intensification on prevalence of morphologic abnormalities (MoAs) at year 5 of ritonavir (RTV) plus saquinavir (SQV) therapy in an HIV-infected cohort. 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle, USA. (Abstract 683-T).

Kempf D, Isaacson JD, King MS et al. Analysis of the virologic response with respect to baseline viral phenotype and genotype in protease-inhibitor experienced HIV-1 infected patients receiving lopinavir/ritonavir therapy. In press.

Max B, Sherer R. Management of Adverse Effects of Antiretroviral Therapy and Medication Adherence. *Clin Inf Dis* 2000;30(Suppl 2):S96-116.

Simon V, Vanderhoeven J, et al. Evolving patterns of HIV-1 resistance to antiretroviral agents in newly infected individuals. 1st IAS Conference

on HIV Pathogenesis and Treatment. July 8-11, 2001. Buenos Aires, Argentina. (Abstract 122).

Simon V, Vanderhoeven J, et al. Infectivity and *in vitro* replication of sexually transmitted drug-resistant HIV-1 variants. 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle, USA. (Abstract 376).

Little SJ, Daar ES, et al. Persistence of transmitted drug resistance among subjects with primary HIV infection not receiving antiretroviral therapy. 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle, USA. (Abstract 95).

Daar ES, Frost SDW, et al. Mixed infection with multidrug resistant (MDR) and wild type HIV strains in primary HIV infection (PHI): Early viral rebound suggests loss of immune control. 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle, USA. (Abstract 96).

Havlir DV, Hellmann NS, et al. Drug susceptibility in HIV infection after viral rebound in patients receiving indinavir-containing regimens. *JAMA* 2000; 283(2):229-34.

Charpentier C, Dwyer DE, et al. Co-existence and co-evolution of viral populations with distinct genotypes in patients failing treatment with protease Inhibitors. 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle, USA. (Abstract 555-T).

Cohen C, Ryan J, Jiang P, Cameron D, et al. Effect of nucleoside (NRTI) intensification on prevalence of morphologic abnormalities (MOAS) at year 4 of ritonavir (RTV) plus saquinavir (SQV) therapy in an HIV-infected cohort. 1st IAS Conference on HIV Pathogenesis and Treatment. July 8-11, 2001. Buenos Aires, Argentina. (Abstract 93).

Jambroes M, Weverling GJ, et al. HIV-1 therapy in the Netherlands: virological and immunological response to antiretroviral therapy. *Ned Tijdschr Geneesk* 2001; 145(33):1591-7.

Kumar P, Rodriguez-French A, et al. Prospective study of hyperlipidemia in ART-Naïve subjects taking combivir/abacavir (COM/ABC), COM/Nelfinavir (NFV), or stavudine (d4T)/Lamivudine (3TC)/NFV (ESS40002). 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle, USA. (Abstract 33).

Fisac C, Fumero E, et al. A randomized trial of metabolic and body composition changes in patients switching from PI-containing regimens to abacavir (ABC), efavirenz (EFV) or Nevirapine (NVP). 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle, USA. (Abstract 699).

Lowe MR, Chuck SK, Penzak SR. Efficacy & safety of pravastatin in protease inhibitor-related hyperlipidemia (PIH). 41st Interscience Conference on Antimicrobial Agents and Chemotherapy. October 27-31, 2001. Chicago, USA. (Abstract I-228).

Cameron DW, Angel JB, et al. Durability of ritonavir (RTV) plus saquinavir (SQV) dual protease inhibitor therapy in HIV infection: 5-year follow-up. 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle, USA. (Abstract 550-T).

Katlama C, Fenske S, Gazzard B, et al. Switch to Trizivir versus continued HAART provides equivalent HIV-1 RNA suppression at 48 weeks (TRIZAL-AZL30002). 41st Interscience Conference on Antimicrobial Agents and Chemotherapy. December 16-19, 2001. Chicago, USA. (Abstract I-671).

John M, James I, et al. A randomized, controlled, open-label study of revision of antiretroviral regimens containing stavudine (d4T) and/or a protease inhibitor (PI) to zidovudine (ZDV)/Lamivudine (3TC)/abacavir (ABC) to prevent or reverse lipodystrophy: 48-week data. 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle, USA. (Abstract 700).

Carr A, Smith D, et al. Switching stavudine or zidovudine to abacavir for HIV lipodystrophy: A randomized controlled, open-label, multicentre, 24-week study. 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle, USA. (Abstract 32).

McComsey G, Loneragan T, et al. Improvements in lipodystrophy (LA) are observed after 24 weeks when stavudine (d4T) is replaced by either abacavir (ABC) or zidovudine (ZDV). 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle, USA. (Abstract 701).

Moreno ME, Moreno A, et al. Hepatotoxicity associated with antiviral therapy in HIV-infected adults: Seriousness and predictive factors. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy. December 16-19, 2001. Chicago, USA. (Abstract I-207).

Reisler R, Liou S, et al. Incidence of hepatotoxicity and mortality in 21 adult antiretroviral treatment trials. 1st IAS Conference on HIV Pathogenesis and Treatment. July 8-11, 2001. Buenos Aires, Argentina. (Abstract 43).

Jordan J, Cahn P, et al. Predictors of adherence and efficacy in HIV-1-infected patients treated with abacavir/combivir (ABC/COM) or indinavir/combivir (IDV/COM): Final 48-week data from CNA3014. 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle, USA. (Abstract 543).

Conway B, Prasad J, et al. Nevirapine (NVP) and protease inhibitor (PI)-based regimens in a directly observed therapy (DOT) program for intravenous drug users (IDUs). 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle, USA. (Abstract 545).

Max B, Garrey KW, Schwartz DN, Sherer R. Efavirenz (EFA) toxicity, discontinuations, and relation to mental illness and substance abuse in 122 patients at a large public hospital HIV clinic. XIIIth World AIDS Conference. July 8-13, 2000. Durban, South Africa. (Abstract WePeB4288).

Montaner JSG, Saag M, et al. FOCUS Study: Saquinavir QD regimen versus efavirenz QD regimen 24 week analysis in HIV infected patients. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy. December 16-19, 2001. Chicago, USA. (Abstract 670).

Bertz R, Foit C, et al. Pharmacokinetics of once-daily vs twice-daily Kaletra (Lopinavir/ritonavir) in HIV+ subjects. 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle, USA. (Abstract 125).

López-Cortés LF, Viciano P, et al. Pharmacokinetics, efficacy, and safety of once daily saquinavir-sgc plus low-dose ritonavir (1200/100 mg) in combination with efavirenz in HIV-pretreated patients. 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle, USA. (Abstract 441).

Kirk O, Lundgren JD, et al. Can chemoprophylaxis against opportunistic infections be discontinued after an increase in CD4 cells induced by highly active antiretroviral therapy? *AIDS* 1999; 13(13):1647-51.

Sanne I, Cahn P, et al. Comparative results (Phase II 48-week): BMS-232632, stavudine, Lamivudine as HAART for treatment-naïve HIV(+)

patients (AI424-008). 41st Interscience Conference on Antimicrobial Agents and Chemotherapy. December 16-19, 2001. Chicago, USA. (Abstract 667).

Allavena C, Lefeuvre A, Bentata M, et al. Lopinavir/ritonavir-efavirenz: Preliminary assessment of a potent nucleoside-sparing dual antiretroviral regimen (the BIKS Study). XIV International AIDS Conference. July 7-12, 2002. Barcelona, Spain. (Abstract WePeB5904).

Staszewski S, et al. Efficacy and safety of tenofovir disoproxil fumarate (TDF) versus stavudine (d4T) when used in combination with lamivudine (3TC) and efavirenz (EFV) in HIV-1 infected patients naïve to antiretroviral therapy (ART): 48-week interim results. XIV International AIDS Conference. July 7-12, 2002. Barcelona, Spain. (Abstract LbOr17).

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CNS cryptococcoma in an HIV-positive patient

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Abstract

This is the first case of brain cryptococcoma in an AIDS patient reported in Argentina. The patient was a 28-year-old white heterosexual man with AIDS who presented with altered mental status, seizures, visual hallucinations, headache, and fever without significant focal neurological deficit. He had a lumbar puncture, and was treated for cryptococcal meningitis. Subsequent brain CT scanning and MRI disclosed a mass lesion in the occipital lobe. Histopathological examination of biopsy was compatible with cryptococcoma, and tissue culture revealed *Cryptococcus neoformans*. Resolution of the mass and edema resulted after treatment with intravenous amphotericin B for six weeks, which was followed with maintenance oral fluconazole.

Intracranial mass is an uncommon complication in AIDS patients with cryptococcosis, and cryptococcoma should be considered as differential diagnosis of brain mass lesion in these patients. The etiologic diagnosis is necessary because central nervous system (CNS) toxoplasmosis, lymphoma, and tuberculoma can produce similar clinical syndromes and MRI or CT findings to cryptococcoma. Also, these pathologies may coexist with meningeal cryptococcosis.

Key words: *cryptococcoma, HIV infection, central nervous system, neurologic complications*

Introduction

Cryptococcosis is the most frequent systemic mycosis observed among AIDS patients at the Francisco J Muñiz Hospital in Buenos Aires, Argentina, where approximately 100 new cases are diagnosed annually. Its prevalence is 15 percent of HIV/AIDS cases.¹

Cryptococcal infection of the CNS may produce symptoms and signs of meningitis, meningoencephalitis, or manifest as single or multiple space-occupying lesions with focal neurologic deficit, which is referred to as cryptococcoma.^{1,2} Three different forms of focal lesions have been described as intracerebral abscesses, gelatinous pseudocysts, and rarely septated lesions within the intraventricular spaces around the choroid plexus.²

Cryptococcosis is present in most AIDS patients at our hospital as meningitis or meningoencephalitis with clear cerebrospinal fluid (CSF), and is only occasionally observed as mass, or space-occupying lesion.³ We report on an HIV-positive patient with cryptococcal meningitis and CNS cryptococcoma, diagnosed by microscopy and cultures of tissue after stereotactic brain biopsy.

Case report

A 28-year-old white heterosexual man with a history of intravenous drug use had been diagnosed with HIV infection eight years earlier. He became ill two weeks prior to his admission with symptoms of fever, severe headache, visual hallucinations, seizures, and altered level of consciousness. At the time, his medications included double-strength trimethoprim-sulfamethoxazole tablets three times weekly. His only previous opportunistic infection had been tuberculosis.

Physical examination showed reduced alertness, hepato- and splenomegaly, pseudomembranous oropharyngeal candidiasis, hairy leukoplakia, tachycardia, and fever. Kernig, Brudzinski, and Romberg signs were negative, and the Babinski reflex and nuchal rigidity were absent. Pupils were equal and reactive. There was no papilledema. Skin sensation, reflexes, muscle tone, and cranial nerves were intact. Deep tendon reflexes were normal without clonus.

Blood chemistry was unremarkable except for a white blood cell count of 2,100/ μ L, and hemoglobin of 10.9 g/dL. CD4 lymphocyte count was 28 cells/ μ L, and HIV-1 plasma viral load greater than 750,000 copies/ μ L. Lumbar puncture was done. The CSF fluid was under

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CT and MRI have revolutionized the diagnosis and management of CNS mass lesions. The radiological evaluation of the lesions included both CT scan and MRI with gadolinium enhancement, that are shown to be more sensitive than a standard MRI in identifying focal brain lesions of specific cause, or in the evaluation of patients with meningeal findings when other studies are inconclusive. Contrast enhancement is also beneficial in differentiating a mass lesion from surrounding edema in preparation for a stereotactic biopsy, and in defining multiple lesions that may not be apparent or that appear as solitary lesions on a CT scan.¹³

Our patient had a subacute presentation of illness. CSF was negative for *Toxoplasma gondii* DNA by polymerase chain reaction (PCR). The lesion did not have a typical appearance of a lymphoma or a metastatic carcinoma, and there was no evidence of a primary tumor outside the CNS. We considered *Mycobacterium tuberculosis* and non-tuberculous mycobacterial infections in the differential diagnosis, particularly in this setting of HIV and past tuberculosis. Mycobacterial abscesses are also frequently multiple and occur in the setting of meningitis or disease outside the central nervous system.^{1,14,15} We performed the stereotaxic procedure to obtain the etiologic diagnosis because of the similarity among the lesions produced by different etiologic agents in the brain, the occasional concomitance of these various lesions, and a lack of initial therapeutic response observed in our patient.

Delay in specifically diagnosing a treatable space-occupying lesion can lead to increased mortality. When assessing these patients, it is important to remember that HIV patients may have concomitant conditions with a variety of noninfectious and infectious diseases that mimic cryptococcoma (eg, toxoplasmosis, lymphoma, tuberculosis). Parasitic causes such as Chagas' disease (*Trypanosoma cruzi*) deserve inclusion, despite being an unlikely pathogen, because they can occur in South America.¹⁶ Biopsy may be helpful in certain contexts, such as lack of a specific diagnosis, or likelihood of identification of a specifically treatable second condition. This case illustrates the presentation, diagnosis, and course of treatment of cryptococcal meningitis with cryptococcoma in AIDS. ■

References

1. Bava AJ, Negroni R, Arechavala A, Robles AM, Bianchi M. Cryptococcosis associated with AIDS in the Muniz Hospital of Buenos Aires. *Mycopathologia* 1997; 140(1):13-7.
2. Andreula CF, Burdi N, Carella A. CNS cryptococcosis in AIDS: spectrum of MR findings. *J Comput Assist Tomogr* 1993; 17(3):438-41.
3. Negroni R, Arechavala A, Robles AM, Bianchi M, Bava AJ. Revisión clínica y evolución terapéutica de pacientes con criptococcosis asociada al SIDA. *Revista Iberoamericana de Micología* 1995; 12:12-5.
4. Tirelli U, Spina M, Gaidano G, et al. Epidemiological, biological, and clinical features of HIV-related lymphomas in the era of highly active antiretroviral therapy. *AIDS* 2000; 14(12):1675-88.
5. Ammassari A, Murri R, Cingolani A, et al. AIDS-associated cerebral toxoplasmosis: an update on diagnosis and treatment. *Curr Top Microbiol Immunol* 1996; 219:209-22.
6. Evaluation and management of intracranial mass lesions in AIDS. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 1998; 50(1):21-6.
7. Iacoangeli M, Roselli R, Antinori A, et al. Experience with brain biopsy in acquired immune deficiency syndrome-related focal lesions of the central nervous system. *Br J Surg* 1994; 81(10):1508-11.
8. Mitchell TG, Perfect JR. Cryptococcosis in the era of AIDS—100 years after the discovery of *Cryptococcus neoformans*. *Clin Microbiol Rev* 1995; 8(4):515-48.
9. Mulanovich VE, Saag MS. Cryptococcal meningitis. In: Berger JR, Levy RM, eds. *AIDS and the Nervous System*. Lippincott-Raven Publishers, Philadelphia, 1997. Pp 661-75.
10. Khanna N, Chandramuki A, Desai A, et al. Cryptococcal infections of the central nervous system: An analysis of predisposing factors, laboratory findings and outcome in patients from South India with special reference to HIV infection. *J Med Microbiol* 1996; 45(5):376-9.
11. Wispelwey B, Dacey RG, and Scheld WM. Brain Abscess. In: Scheld WM, Whitley RJ, and Durack DT, eds. *Infections of the Central Nervous System*, 2nd ed. Lippincott-Raven Publishers, Philadelphia, 1997. Pp. 463-92.
12. van der Horst CM, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. *N Engl J Med* 1997; 337(1):15-21.
13. Ammassari A, Scoppettuolo G, Murri R, et al. Changing disease patterns in focal brain lesion-causing disorders in AIDS. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; 18(4):365-71.
14. Bava AJ, Negroni R. The epidemiological characteristics of 105 cases of cryptococcosis diagnosed in the Republic of Argentina between 1981-1990. *Rev Inst Med Trop Sao Paulo* 1992; 34(4): 335-40.
15. Gildenberg PL, Gathe JC Jr, Kim JH. Stereotactic biopsy of cerebral lesions in AIDS. *Clin Infect Dis* 2000; 30(3): 491-9.
16. Corti M. AIDS and Chagas' Disease. *AIDS Patient Care and STDs* 2000; 14(11): 581-8.

The significance of HIV viral load assay precision: A review of the package insert specifications of two commercial kits

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Abstract

Quantification of HIV-1 RNA levels is a vital tool in the medical management of individuals infected with HIV. The commercially available US Federal Drug Administration (FDA)-approved assays vary in their ability to accurately measure and detect significant changes in plasma viral load. A more precise assay can accurately distinguish true clinically significant biologic changes in viral plasma load from background noise, or systematic variation. These differences in precision between assays are profound at low, near-cutoff levels, but also occur throughout the dynamic range of the assays. This review examines the precision specifications, expressed as fold changes in test and retesting, across the dynamic ranges of the Bayer Versant bDNA assay, and the two available versions of the Roche Amplicor Monitor PCR assays. Highly validated data from their respective package inserts are analyzed to confirm each assay's performance throughout its dynamic range. The precision of a viral load assay is critical to patient management, and gives the clinician a clearer picture of the patient's true virologic status that is attributable to infection or treatment as opposed to systematic variation in assays.

Key words: HIV-1 plasma viremia measurement, precision, viral load, variation

Introduction

Since the mid-1990s, quantitative HIV-1 RNA testing in plasma has become the standard of care in predicting progression of HIV disease, and for the therapeutic monitoring of individuals on antiretroviral drug treatment regimens. The early comprehensive Multicenter AIDS Cohort Study (MACS) described the clinical association of baseline viral load and the rate of disease progression, independent of peripheral blood CD4 T-lymphocyte

count, allowing a prognostic correlation between viral load values and clinical disease.¹⁻³ With the introduction of an arsenal of anti-HIV therapies, viral load testing was quickly adopted in clinical practice to monitor patient response to these regimens.^{4,5}

The first commercially available viral load assays were capable of measuring at their lower limits of detection from 400 to 500 copies/mL. An evolving understanding of HIV disease and treatments, coupled with increasing therapeutic options, saw the advent of increasingly more sensitive HIV viral load assays. These assays are generally capable of measuring levels below 100 copies/mL. Even these extremes of plasma viremia have been shown to predict "virologic success" of therapies. This paper compares the precision of two commonly utilized viral load assays, and explores the impact that assay precision has on HIV patient management.

Guidelines for use of viral load tests

According to the current guidelines for the treatment of patients with HIV-1 infection from the US Department of Health and Human Services (DHHS), the objective of antiretroviral therapy is maximal suppression of viral replication to levels below the limit of detection by a sensitive viral load assay.⁶ The recommendation to use more sensitive versions of viral load assays is driven by evidence that increased levels of viral suppression lead to better treatment outcomes. In a clinical trial using a research assay, suppression of plasma HIV RNA levels below 20 copies/mL was associated with a longer response to antiretroviral therapy, compared with that achieved when viral suppression was below 500 copies/mL.⁷ The evidence that viral replication persists in patients with undetectable viral load has also prompted interest in the ability of an HIV RNA assay to measure very low viral load levels.⁸ It is currently unknown whether a true, clinically relevant difference exists between suppression of viral load below 100 copies/mL versus 50 copies/mL. However, increasing attention is being paid to the meaning of very low, but detectable viral loads, at or near the cutoff of commercial viral load assays.

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Definition of sensitivity, precision, and dynamic range

Sensitivity: There are currently four FDA-approved assays for measuring HIV-1 viral load: Bayer VERSANT® HIV-1 RNA 3.0 Assay (bDNA), the Roche Amplicor® HIV-1 MONITOR® Test versions 1.0 and 1.5 (PCR), and the bioMérieux NucliSens™ HIV-1 QT Test. According to package inserts, the sensitivity claim of the Bayer bDNA is 75 copies/mL, the Roche PCR assay is 50 copies/mL, and the bioMérieux NASBA assay is 176 copies/mL. The assay sensitivity is defined as the lowest viral load level that can be detected 95 percent of the time. This statistical method of assessing sensitivity is generally

considered to be the standard to determine the lower quantitative “limit of detection” (LoD) for quantitative HIV RNA assays.

Prior to FDA approval, the bDNA assay had a cutoff of 50 copies/mL based on the point at which 95 percent of HIV RNA negative samples would produce a below-cutoff result. The current, FDA-approved bDNA assay now utilizes the industry-wide standard based on 95 percent detection of samples at the assay cutoff (LoD). From clinical trial studies this was demonstrated to be 75 copies/mL.⁹

Table 1. Performance characteristics of assays for HIV viral load

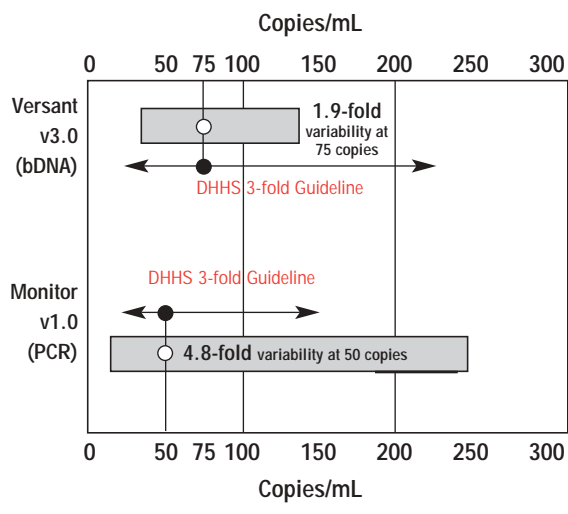
Performance attribute	Description	Clinical significance
Sensitivity	Lowest level of HIV RNA that can be detected consistently (eg, ≥95% of the time). Defined as Limit of Detection.	Important to detect virus at very low levels to assess the degree of viral suppression during therapy.
Accuracy	Refers to the ability of the assay to determine the true value of an analyte. Very difficult to establish “gold” standard for viral load (VL). Calibration of assays to common standard should result in consistency of quantification between assays.	Results from clinical trial with one assay can be applied in management of patients with any of the assays. Treatment (International AIDS Society and DHHS) guidelines describe a viral load threshold for initiation of therapy. Standardization will result in common management thresholds across all assays.
Precision (reproducibility)	Capacity to achieve very similar viral quantification values regardless of the laboratory, day, operator, instrument or kit lot. Determines the change in viral load that is statistically significant.	Physician and patient need to understand if viral load decreases or increases are significant, or within the variability expected from biological variation plus systematic (assay) variation. Treatment guidelines describe viral load changes of 3-fold (or 0.5 log ₁₀) as the minimum change that is considered significant.
Specificity	High specificity means that HIV-negative samples will not be positive in a viral load test for HIV.	HIV viral load assays designed to be used only in individuals who are known to be HIV-positive (eg, antibody-positive). High specificity gives physicians and patients confidence that the assay is really only assessing HIV RNA.
Linearity	Refers to the degree to which the assay standard curve approximates a straight line. Used to determine the linear range of the assay. Linearity is a measure of how accurately the assay measures changes in viral load throughout its dynamic range.	Important to know that changes in viral load reflect actual changes in amount of virus (without contributions from quantification biases in specific areas of the dynamic range).
Equal quantification of all genotypes	Capacity of assay to accurately measure viral load regardless of sequence variation in HIV RNA.	Since treatment guidelines depend on specific viral loads, then assay must accurately quantify virus regardless of HIV group or subtype. Assays that under-quantify certain subtypes have yielded viral loads that are inconsistent with CD4 counts and/or the clinical status of the patient.

Table 2. A comparison of the low-end reproducibility (fold changes) of two commercially available HIV-1 RNA assays, using calculations that consider the expected variation from a single measurement

	<i>Versant HIV bDNA 3.0 clinical trial data generated at five independent labs and Bayer Reference Testing Laboratory using single measurement method¹¹</i>			<i>Amplacor HIV Monitor Test (version 1.0) PCR, Ultrasensitive Specimen Processing Procedure (data from Roche package insert)¹²</i>		
Copy level:	50 c/mL	75 c/mL	>75 c/mL	50 c/mL	75 c/mL	>75 c/mL
Log change:	0.33	0.29	0.30	0.68	0.44	0.39
Fold change:	2.2	1.9	2.0	4.8*	2.8	2.5
Copy/mL range	23-110	39-143	50-200	10-240	27-210	40-250

*Fold changes if they exceed 3-fold.

Figure 1. The graph represents the low-end precision (fold changes) for two commercially available HIV-1 RNA with reference to the DHHS definition of “significant changes” in viral load. Precision calculations consider the expected variation from a single measurement.



Clinically, the goal of therapy is to suppress viral load to below the LoD. It is yet to be determined if the differences in LoDs between commercial assays would result in different treatment practices, or patient outcomes.

Precision: The precision or reproducibility of an assay is defined by its ability to obtain the same answer when tested repeatedly. Traditionally, manufacturers of viral load assays measure precision by the ability of the assay to detect “fold changes,” or the ability to detect a significant change from one measurement to the next. The statistical methods used to calculate and report precision claims have not been standardized in the industry. For example, Roche defines fold change for its polymerase chain reaction (PCR) assay as the expected

variation calculated from multiple determinations of a *single measurement*. Another statistically relevant method of assessing fold change uses sequential time point analysis that reflects the use of viral load assays in clinical practice.¹⁰ The bDNA assay utilizes this method. Bayer defines fold change as the expected variation between *two independent measurements*.

The DHHS guidelines state: “A *minimally significant change in plasma viremia is considered to be a 3-fold or 0.5 log₁₀ increase or decrease... In general, viral loads and trends in viral load are felt to be more informative for guiding decisions regarding antiretroviral therapy than are CD4+ T cell counts.*”

The concept of a fold change refers to two serial measurements taken at different points in time, or trends in viral load. The formula used by the bDNA assay for calculating fold changes is appropriate because it considers the variation between two measurements from different time points.

Dynamic range: The dynamic range of an assay is defined as the quantitative range over which the assay can reliably report results. Since viral levels are obtained at varying time points during treatment regimens, it is essential that the assay be able to accurately follow changes in HIV RNA across the wide range of clinically expected values. The bDNA methodology utilizes a single assay to span the entire dynamic range of 75 to 500,000 copies/mL. By comparison, the PCR methodology uses two separate assays: an ultrasensitive version that has a dynamic range of 50 to 75,000 copies/mL, and a standard version that has an overlapping dynamic range of 400 to 750,000 copies/mL.

An “ideal” quantitative HIV RNA assay

Table 1 describes the performance characteristics and their corresponding clinical significance for HIV viral load assays. The overall reliability of an HIV RNA viral

Table 3. A comparison of the low-end reproducibility (fold change) of two commercially available HIV-1 RNA assays, using calculations that consider the expected variation from serial measurements

	<i>Versant HIV bDNA 3.0 clinical trial data generated at five independent labs and Bayer Reference Testing Laboratory¹³</i>			<i>Amplicor HIV Monitor Test (version 1.0) PCR, Ultrasensitive Specimen Processing Procedure (calculated from Roche package insert data using the serial measurement method)¹⁴</i>		
Copy level	50 c/mL	75 c/mL	>75 c/mL	50 c/mL	75 c/mL	>75 c/mL
Log change	0.47	0.41	0.33	0.96	0.63	0.55
Fold change	3.0	2.6	2.2	9.2*	4.2*	3.5*
Copy/mL range	17-150	29-195	45-220	5-460	18-315	29-350

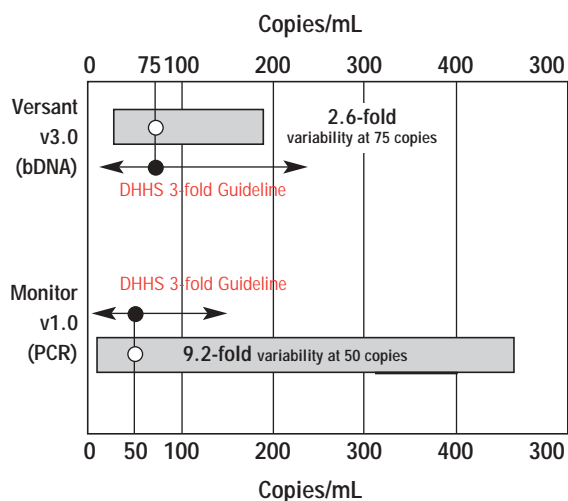
*Fold changes if they exceed 3-fold.

Table 4. A comparison of the reproducibility (fold changes) of two commercially available HIV RNA assays for HIV RNA levels above 500 copies/mL

	<i>Versant HIV bDNA 3.0 clinical trial data generated at five independent laboratories¹⁵</i>			<i>Amplicor HIV Monitor Test (version 1.0) PCR, Standard Specimen Processing Procedure (data from Roche package insert)¹⁶</i>		
Approximate copy level	620 c/mL	6,203 c/mL	62,028 c/mL	620,282 c/mL	500 c/mL	>1000 c/mL
Log change	0.30	0.28	0.31	0.30	0.76	0.50
Fold change	2.0	1.9	2.0	2.0	5.8*	3.2*

*Fold changes if they exceed 3-fold.

Figure 2. The graph represents the low-end precision (fold changes) for two commercially available HIV-1 RNA with reference to the DHHS definition of “significant changes” in viral load. Precision calculations consider the expected variation from serial measurements.



load assay is determined by a combination of interrelated performance characteristics. For example, true sensitivity is achieved when the assay remains reproducible at viral RNA concentrations that are near the assay's low-end

cutoff. Similarly, a precise (reproducible) assay should identify changes in viral load that are biologically and statistically significant (3-fold). Finally, the assay should remain reproducible across a wide dynamic and clinically relevant reporting range. Therefore, an “ideal” viral load assay would have good sensitivity while being able to maintain excellent precision throughout a wide dynamic range. These specifications are critical performance characteristics of an HIV RNA assay, and should be considered by clinicians when choosing a viral load assay.

A critical look at precision and fold changes

The DHHS guidelines state that in order for an HIV RNA assay to reliably and reproducibly assess clinically significant changes in viral load, the assay must be able to distinguish a 3-fold (or 0.5 log₁₀) change in viral load from the assay's inherent or background variability.⁶

Table 2 compares the reproducibility of the Bayer bDNA version 3.0 (bDNA 3.0) and the Roche PCR version 1.0 (PCR 1.0) assays at values near their cutoffs, as performed in approved labs, according to the package insert.

The data show the fold change performance for the two assays in question, using a statistical method that does not take into account serial measurements. The data illustrate that the fold change at each viral concentration listed, using the bDNA 3.0 assay, is less than three. The fold change value at the 50 copies/mL

Table 5. A display of various HIV RNA input values spanning the dynamic range of the Roche Amplicor HIV-1 Monitor test, version 1.5, and the associated precision specifications, using the method of calculating fold changes from serial viral load measurements

<i>Input HIV RNA (copies/mL)</i>	<i>Fold change for version 1.5 using Standard Specimen Preparation Procedure¹⁸</i>	<i>Input HIV RNA (copies/mL)</i>	<i>Fold change for version 1.5 using Ultrasensitive Specimen Preparation Procedure¹⁸</i>
175	6.24*	25	8.4*
250	4.25*	40	3.45*
400	4.06*	50	4.06*
500	4.75*	60	4.86*
600	3.88*	80	3.62*
2,000	2.63	100	3.37*
7,000	2.26	400	2.38
35,000	2.77	1,000	2.63
100,000	2.84	5,000	10.39*
350,000	9.08*	25,000	8.31*
500,000	5.30*	35,000	6.37*
650,000	6.89*	50,000	8.46*
750,000	5.88*	75,000	3.97*
850,000	3.62*	100,000	6.00*

* Fold changes if they exceed 3-fold.

level utilizing the PCR 1.0 assay is 4.8. This represents a range of values between 10 and 240 copies/mL, shown in Figure 1.

Typically, patients on antiretroviral therapy are tested every three to four months to monitor their viral load levels. This sequential monitoring of viral load is an essential tool for assessing therapy success or failure because significant changes in viral load can predict changes in treatment efficacy and clinical status of the patient. Additional variability is introduced when looking at sequential or serial HIV RNA measurements. Table 3 compares the fold change specification of the same two HIV RNA assays, using a statistical method of calculating fold change that takes into account the additional biological variability associated with serial viral load measurements.

When the effect of serial determination of viral load measurement is taken into account, the data show that the bDNA 3.0 assay is able to reproducibly detect 3-fold changes at 75 copies/mL. By comparison, the PCR 1.0 assay's precision at 75 copies/mL is 4.2-fold. At the sensitivity claim of 50 copies/mL, the PCR 1.0 assay precision is 9.3-fold. This represents a range of values between 5 and 460 copies/mL, shown in Figure 2.

Table 4 compares the precision of the bDNA 3.0 assay and the PCR 1.0 assay (Standard Procedure) at concentrations greater than 500 copies/mL.

The data indicate that the bDNA 3.0 assay maintains good precision for levels above 500 copies/mL and meets the DHHS guidelines for ability to detect 3-fold changes in viral load. Conversely, the Standard Procedure PCR 1.0 assay has fold changes that exceed three for both concentrations that are reported in their package insert.

A newer version of the Roche HIV assay (Amplicor HIV-1 Monitor Test, version 1.5) has recently been approved. According to the package insert for the 1.5 assay,

"For the Standard specimen preparation procedure of the AMPLICOR HIV-1 MONITOR test, version 1.5, Coefficients of Variation (CV's) in the linear range were between 30% and 94%, while the prior version of the assay had CV's of between 32.2% and 45.3%. For the Ultrasensitive specimen preparation procedure of the version 1.5 assay, the CV's over the linear assay range of the assay were 32% to 102%, compared to CV's between 30.2% and 41.9% for the prior version."¹⁷

When Coefficients of Variation (CVs) are converted to fold changes for the Roche PCR version 1.5 (PCR 1.5) assay, using the method of calculating fold change that takes into account serial viral load measurements, the data in Table 4 can be derived.

Package insert data demonstrate that the new PCR 1.5 assay is able to detect 3-fold changes only in the range of 2,000 to 100,000 copies/mL for the standard specimen

preparation procedure and 400 to 1,000 copies/mL for the ultrasensitive specimen preparation procedure.

Peer-reviewed publications evaluate comparative performance of bDNA and PCR

Several studies published in peer-reviewed journals have evaluated the performance characteristics of the bDNA 3.0 and PCR 1.0 assays. A multicenter study in Canada and the United States showed that the bDNA 3.0 assay displayed a higher level of precision than the PCR 1.0 or Biomérieux assays.¹⁹

Likewise, the multilaboratory study, conducted with the AIDS Clinical Trials Group (ACTG), stated that both the bDNA 3.0 assay and PCR 1.0 ultrasensitive have “comparable low levels of HIV-1 RNA... for the assessment of viral suppression in clinical trials and in clinical practice.” The authors of the study also stated that the bDNA 3.0 assay has “excellent reproducibility, a broad linear range and a good sensitivity for the quantitation of HIV-1 RNA in plasma down to 100 copies/mL.” They indicated that the within run standard deviation (SD) for the PCR 1.0 assay was “higher than the SD for the bDNA assay at all concentrations.” (Note: ACTG uses a method other than LoD to determine assay sensitivity).²⁰

Similarly, a new paper stated that bDNA 3.0 was more reliable and accurate than PCR 1.5, in studies that compared multiple serially diluted viral isolates of HIV-1 Group M, subtypes A through F. Accuracy analysis showed that the “data points more closely distributed about their respective regression lines.” According to the authors, bDNA 3.0 demonstrated greater reliability than PCR 1.5.²¹

The impact of assay performance in managing HIV patients in clinical practice

The precision of a viral load assay is significant for the HIV-treating clinician who relies on the accuracy of the HIV RNA levels, and on the reproducibility of the measurements. If an assay is unable to distinguish 3-fold changes across its full dynamic range, the laboratory findings may not correlate with the patient's clinical presentation. Increases or decreases in serial measurements of HIV RNA could be due to assay variation or poor precision, rather than actual changing virologic response to treatment. The issue is further complicated by the occurrence of transient viremia or “viral blips” that can be seen in HIV RNA levels. Recent studies considered the significance of transient viremia and viral rebound,²²⁻²⁴ and showed that viral blips are probably not clinically significant because they did not predict disease progression or subsequent treatment failure. These studies illustrate the importance of being able to distinguish between true viral rebound and what is most likely a transient viral blip, whether these may

be due to varying treatment adherence, virologic breakthrough, or systematic assay variation.

As more research studies look at the significance of viral kinetics, it is important to use a precise assay so that the rise and decline in viral load can accurately be categorized as true biologic variation versus an artifact of systematic assay variation.²⁵ If an assay is unable to distinguish clinically significant changes due to poor precision, it is less likely to give accurate answers for HIV RNA values. As described in Table 1, knowledge that viral load changes are statistically and clinically significant offers a better assessment of therapeutic success or failure and greater confidence in treatment decisions.

Discussion

Studies are in progress to assess the clinical relevance of plasma HIV RNA levels that approach the limits of detection for available viral load assays. The results of these studies should provide additional evidence supporting the need for accurate and precise viral load determinations below 100 copies/mL. For the present, sensitivity, or the ability to measure as low as possible, is not the only specification that contributes to the strength of a commercial HIV RNA assay. Perhaps a more important clinical characteristic of an HIV RNA assay is the ability to reproducibly measure HIV RNA levels across its entire dynamic range. Inherent in this performance characteristic is an assay's ability to accurately measure and appropriately characterize fold changes from one viral load measurement to the next, thereby demonstrating virologic response to therapy as opposed to assay variation. ■

Disclosure:

Dr. Chernoff is a former employee of Chiron Corporation who currently serves as a consultant to Bayer Diagnostics.

References

1. Mellors JW, Kingsley LA, et al. Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion. *Ann Intern Med* 1995; 122(8):573-9.
2. Mellors JW, Rinaldo CR, et al. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science* 1996; 272(5265):1167-70.
3. Welles SL, Jackson JB, et al. Prognostic value of plasma human immunodeficiency virus type 1 (HIV-1) RNA levels in patients with advanced HIV-1 disease and with little or no prior zidovudine therapy. AIDS Clinical Trials Group Protocol 116A/116B/117 Team. *J Infect Dis* 1996; 174(4):696-703.
4. Katzenstein DA, Hammer SM, et al. The relation of virologic and immunologic markers to clinical outcomes after nucleoside therapy in HIV-infected adults with 200 to 500 CD4 cells per cubic millimeter. AIDS Clinical Trials Group Study 175 Virology Study Team. *N Engl J Med* 1996; 335(15):1091-8.
5. Havlir DV, Richman DD. Viral dynamics of HIV: implications for drug development and therapeutic strategies. *Ann Intern Med* 1996; 124(11):984-94.

6. Fauci AS, Bartlett JG, Goosby EP, Kates J, and the Panel on Clinical Practices for treatment of HIV Infection convened by the Department of Health and Human Services (DHHS) and the Henry J. Kaiser Family Foundation. Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. August 13, 2001. Online at <http://www.hivatis.org/trtgdlns.html>
7. Raboud JM, Montaner JS, et al. Suppression of plasma viral load below 20 copies/mL is required to achieve a long-term response to therapy. *AIDS* 1998; 12(13):1619-1624.
8. Dornadula G, Zhang H, et al. Residual HIV-1 RNA in blood plasma of patients taking suppressive highly active antiretroviral therapy. *JAMA* 1999; 282(17):1627-1632.
9. Gleeves Curt, et al. Multicenter analysis of the VERSANT HIV-1 RNA 3.0 assay analytical and clinical performance. *J Clin Microbiol*. In press.
10. Tanis EA, Hogg RV. *Probability and Statistical Inference*. Macmillan Publishing Co., Inc., 1977.
11. Bayer VERSANT® HIV-1 RNA 3.0 Assay, Bayer Diagnostics, package insert.
12. Roche Amplicor® HIV-1 MONITOR® Test, Roche Molecular Systems, version 1.0, package insert.
13. Bayer VERSANT® HIV-1 RNA 3.0 Assay, Bayer Diagnostics, package insert.
14. Bayer VERSANT® HIV-1 RNA 3.0 Assay, Bayer Diagnostics, package insert.
15. Bayer VERSANT® HIV-1 RNA 3.0 Assay, Bayer Diagnostics, package insert.
16. Roche Amplicor® HIV-1 MONITOR® Test, Roche Molecular Systems, version 1.0, package insert.
17. Roche Amplicor® HIV-1 MONITOR® Test, Roche Molecular Systems, version 1.5, package insert.
18. Roche Amplicor® HIV-1 MONITOR® Test, Roche Molecular Systems, version 1.5, package insert.
19. Murphy DG, Cote L, et al. Multicenter comparison of Roche COBAS AMPLICOR MONITOR version 1.5, Organon Teknika NucliSens QT with extractor, and Bayer Quantiplex version 3.0 for quantification of human immunodeficiency virus type 1 RNA in plasma. *J Clin Microbiol* 2000; 38(11):4034-4041.
20. Erice A, Brambilla D, et al. Performance characteristics of the Quantiplex HIV-1 RNA 3.0 assay for detection and quantitation of human immunodeficiency virus type 1 RNA in plasma. *J Clin Microbiol* 2000; 38(8):2837-2845.
21. Elbeik T, Alvord WG, et al. Comparative analysis of HIV-1 viral load assays on subtype quantification: Bayer Versant HIV-1 RNA 3.0 versus Roche Amplicor HIV-1 Monitor version 1.5. *J AIDS* 2002; 29(4):330-9.
22. Havlir DV, Bassett R, et al. Prevalence and predictive value of intermittent viremia with combination HIV therapy. *JAMA* 2001; 286(2):171-9.
23. Cohen-Stuart J, et al. Mechanisms underlying transient relapses ("blips") of plasma HIV RNA in patients on HAART. 4th International Workshop on HIV Drug Resistance and Treatment Strategies. Stiges, Spain. June 12-16, 2000. (Abstract 137).
24. Moore AL, Youle M, et al. Raised viral load in patients with viral suppression on highly active antiretroviral therapy: transient increase or treatment failure? *AIDS* 2002; 16(4):615-618.
25. Deeks SG, Coleman RL, et al. Variance of plasma human immunodeficiency virus type 1 levels measured by branched DNA within and between days. *J Infect Dis* 1997; 176(2):514-7.

Editor's Note:

The views and opinions expressed herein are those of the author, and do not purport to reflect the official policy or position of the University of California.

Once-daily antiretroviral therapies for HIV infection: Consensus statement of an Advisory Committee of the International Association of Physicians in AIDS Care

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Objective: Adherence is essential to successful virologic outcome of highly active antiretroviral therapy (HAART). Documented factors contributing to poor adherence include toxicity, food requirements, and pill burden. Once-daily antiretroviral therapies for HIV infection offer potential benefit by decreasing pill burden and dosing frequency, which may subsequently improve treatment adherence. This Consensus Statement is intended to offer guidance to physicians actively involved in HIV/AIDS care.

Participants: Eight physicians with expertise in HIV medicine were invited by the International Association of Physicians in AIDS Care (IAPAC) to serve on an ad hoc Advisory Committee.

Consensus process: IAPAC convened the Advisory Committee in June 2002 to develop a draft Consensus Statement. Scientific and clinical research, and other data in published literature and abstracts from scientific conferences were considered by strength of evidence. A Subcommittee updated the Consensus Statement in October 2002 to reflect relevant data presented at the XIV International AIDS Conference and the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy. This document represents consensus agreement of the Advisory Committee.

Conflict of interest disclosure: The International Association of Physicians in AIDS Care sponsored and coordinated the development of this Consensus Statement with an unrestricted educational grant from Bristol-Myers Squibb. The opinions expressed in this Consensus Statement represent only those of the Advisory Committee.

"The somewhat disappointing adherence with simplified twice-daily dosing raises the need to actively investigate once-daily regimens as part of the effort to further improve adherence."¹

– Graeme Moyle, MD, MBBS
Chelsea & Westminster Hospital, London, UK

Key words: antiretroviral, once-daily dosing, pharmacokinetics, twice-daily dosing

Background

Adherence is a key factor in achieving success with antiretroviral therapy, and the complexity of a drug treatment regimen is a barrier to adherence.² Simplifying antiretroviral regimens may improve adherence, and the likelihood of sustained virologic suppression. Once-daily dosing is one means of simplifying therapy that represents a rapidly emerging trend in HIV treatment. It also makes direct observed therapy (DOT) programs

more feasible where they are appropriate. These potential advantages for adherence need to be balanced against the consequences of non-adherence that may not be the same for once-daily compared to twice-daily dosing regimens. Pharmacologic and virologic factors during a long dosing interval may lead to virologic failure of therapy, and the risk of drug resistance may not be equivalent.

There are currently five antiretroviral agents approved for once-daily use (listed here in alphabetical order):

- amprenavir/ritonavir (APV/r)
- didanosine (ddI)
- efavirenz (EFV)
- lamivudine (3TC)
- tenofovir (TFV)

At least four additional antiretroviral agents are under evaluation for once-daily dosing (listed here in alphabetical order):

- atazanavir (ATV)
- emtricitabine (FTC)
- stavudine extended-release (d4T-XR)
- nevirapine (NVP)

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Several ritonavir-boosted protease inhibitor (PI) combinations are also under evaluation (listed here in alphabetical order):

- indinavir/ritonavir (IDV/r)
- lopinavir/ritonavir (LPV/r)
- saquinavir/ritonavir (SQV/r)

The US Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents promote the need for simplification by stating that, “to the extent possible, [highly active antiretroviral therapy] should be simplified by reducing the number of pills and the frequency of therapy...”³ A majority of patients in at least three surveys has also expressed a clear preference for once-daily dosing.⁴⁻⁶ However, comparative trials to demonstrate whether once-daily dosing translates into improved outcomes have yet to be completed.

Once-daily therapies as a viable treatment option, their efficacy compared to therapies requiring more frequent dosing, and their suitability for use in different patient populations are summarized in this Consensus Statement.

Virologic impact of once-daily antiretrovirals

Drugs pharmacologically selected to be dosed once daily form the basis for once-daily regimens. They may provide more “forgiveness” for non-adherence than some more frequently dosed regimens. Based on non-randomized cohort studies, data suggest some once-daily drugs and some once-daily regimens have equivalent anti-HIV activity compared to drugs that require twice-daily or more frequent dosing.

The Advisory Committee emphasizes that this section is based on studies of variable size and power, and that the list of studies is not exhaustive. Some of the conclusions should be put into context given these limitations.

Nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs)

Didanosine (ddI) enteric-coated – BMS 152: Enteric-coated didanosine capsules given once daily in combination with d4T and NFV provided antiretroviral activity similar to that produced by a triple combination regimen of zidovudine (ZDV) + 3TC + NFV.⁷ Didanosine given once daily significantly improved adherence ($p=0.03$) and plasma viral load response ($p=0.05$), compared to didanosine given twice daily.⁸

Lamivudine (3TC): Once-daily and twice-daily dosing of 3TC between two groups of patients have been compared in two open label trials:

- COLA 4005: High levels of sustained virologic suppression were shown at 24 weeks in this

prospective trial of once-daily 3TC (300 mg), compared to continued standard twice-daily 3TC (150 mg). In the once-daily group, 95 percent of patients maintained <400 copies/mL, compared to 90 percent in the twice-daily group (intent-to-treat, or ITT analysis).⁹

- Bruno, et al: Pharmacokinetic analysis showed equivalency between once-daily (300 mg) and twice-daily (150 mg) dosing of 3TC with respect to mean values of half-life and serum levels with comparable daily systemic exposure (area under the drug concentration time curve, or AUC).¹⁰

Tenofovir (TFV): Respective reductions from pre-treatment baseline viral load of 0.4 log, 0.6 log, and 0.7 log occurred with TFV, when given in daily doses of 75 mg, 150 mg, and 300 mg in NRTI-experienced patients. A greater impact of about 1.6 log was seen when given as a single agent to antiretroviral-naïve patients.^{11,12}

Stavudine extended-release (d4T-XR) [investigational]: The combination of d4T-XR + 3TC + EFV demonstrated reduction in viral load comparable to d4T-IR (immediate release formulation) + 3TC + EFV at 48 weeks.¹³

- <400 copies/mL: 80 percent versus 75 percent of patients (ITT analysis)
- <50 copies/mL: 59 percent versus 57 percent of patients (ITT analysis)

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Efavirenz (EFV) – DPC-006: A greater reduction in viral load to <50 copies/mL (ITT analysis) occurred for EFV + ZDV + 3TC (52 percent), compared to IDV + ZDV + 3TC (30 percent) ($p\leq 0.05$) at 144 weeks.¹⁴

Nevirapine (NVP) [investigational]: Three separate studies showed a once-daily 400 mg dose of NVP to be as safe and effective as the standard twice-daily dose of NVP when given in combination with stavudine (d4T) twice daily, and didanosine (ddI) once daily.¹⁵⁻¹⁷

Protease inhibitor (PI)

Atazanavir (ATV) [investigational]: At 48 weeks, viral suppression occurred in more patients taking regimens containing ATV 400 mg once daily or 600 mg once daily, compared to those taking nelfinavir (NFV) 1,250 mg twice daily. Following is the percent of patients <400 copies/mL (ITT analysis) at 48 weeks.¹⁸

- 74 percent - ATV 400 mg once daily + 3TC + d4T
- 75 percent - ATV 600 mg once daily + 3TC + d4T
- 53 percent - NFV 1,250 mg twice daily + 3TC + d4T

No adequately powered comparative trials of once-daily and twice-daily regimens have been conducted. These

trials are warranted. However, promising results have been observed in small cohort studies using once-daily regimens.

ddl + 3TC + EFV: This combination administered once daily has been evaluated in two trials: 1) a prospective, clinically based study of ddl (300 mg) + 3TC (300 mg) + EFV (600 mg) taken once daily by 75 antiretroviral-naïve patients by Maggiolo, et al.; and 2) a multicenter pilot study of ddl (400/200 mg) + 3TC (300 mg) + EFV (600 mg) taken once daily by 40 HIV-1-infected patients by Landman, et al.

- Maggiolo, et al: At 48 weeks, 78.3 percent of patients had <50 copies/mL (ITT analysis).¹⁹
- Landman, et al: At 15 months, 92 percent of patients had <500 copies/mL and 69 percent achieved <50 copies/mL (as-treated, or AT analysis).²⁰

FTC + ddl + EFV: This once-daily combination was evaluated in the ANRS 091 pilot study of FTC (200 mg) + ddl (400 mg if ≥60 kg; 250 mg if <60 kg) + EFV (600 mg) taken once daily by 40 antiretroviral-naïve patients by Molina, et al. A 64-week follow-up of this cohort showed sustained virologic suppression in patients taking this combination.²¹

- At 24 weeks, 98 percent of patients maintained plasma HIV RNA <400 copies/mL, while 93 percent achieved <50 copies/mL (ITT analysis).
- At 48 weeks, 95 percent of patients maintained plasma HIV RNA <500 copies/mL (ITT analysis).
- At 64 weeks, 90 percent of patients maintained plasma HIV RNA <400 copies/mL (ITT analysis).

Pharmacokinetics of once-daily antiretrovirals

Compared to twice-daily drugs (and those requiring higher frequency dosing), once-daily antiretrovirals feature prolonged intracellular half-life that enables them to sustain

adequate inhibitory concentrations over the full 24-hour dosing period. For example, the half-life of some of the once-daily drugs ranges from 40 to 55 hours (EFV), 25 to 40 hours (ddl), 30 hours (TFV), and 16 hours (3TC).²²⁻²⁵

Higher serum levels and more prolonged half-life of some antiretroviral drugs can also be achieved by exploiting drug/drug interactions. For example, protease inhibitor boosting with RTV is an effective strategy (currently used in the twice-daily regimen LPV/r) under investigation for once-daily application. Through the inhibition of metabolic enzymes, primarily cytochrome P450 CYP3A4, in the gut mucosa and liver, RTV increases the plasma concentrations of APV, IDV, LPV, and SQV.²⁶ In several pharmacokinetic studies, co-administration of RTV with the protease inhibitor of interest results in serum levels of the protease inhibitor that significantly exceeds the IC₅₀ for at least 24 hours (24-hour C_{min} exceeds the IC₅₀).²⁷⁻³⁰

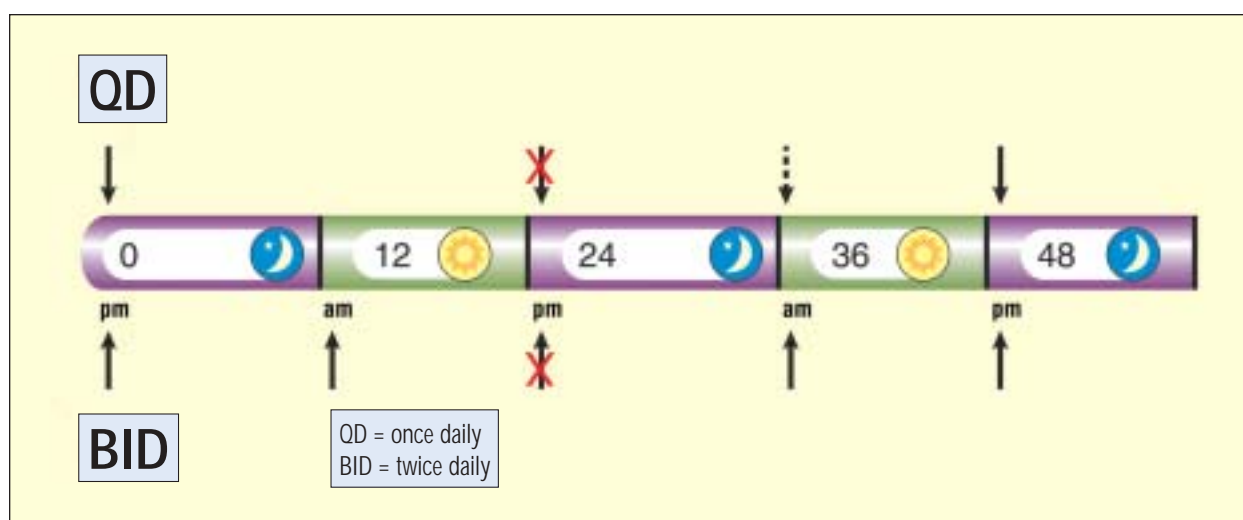
Once-daily dosing and the “forgiveness” factor

The Advisory Committee notes that this section represents a discussion of a theoretical factor, and that data are needed to understand how the “forgiveness” factor may translate into treatment outcomes.

The prolonged intracellular and serum half-life of once-daily drugs means that an inhibitory concentration is more likely to be sustained beyond the dosing period. Some argue this may provide “insurance” in the case of missed or delayed doses.

A subject of theoretical debate remains whether once-daily or twice-daily dosing is better suited to safeguard against virologic escape in the case of missed or delayed doses. Compared to twice-daily dosing, once-

Figure 1. Impact of missed twice-daily evening dose



daily dosing may leave patients open to risk of virologic escape without adequate drug levels for a 24-hour period. However, based upon the longer half-life of the once-daily formulations, there may be greater opportunity to make up a missed dose on a once-daily schedule. On the other hand, if a dose of a drug with a long half-life is delayed or missed, low drug levels may allow for an increase in virus replication and the selection of resistant virus. Indirect evidence of this possibility is commonly seen drug resistance in patients with low-level viral load rebounds who receive efavirenz, lamivudine, or nevirapine—drugs with long half-life and a low genetic barrier to resistance.

In balance, the once-daily dosing pharmacokinetic profile permits dosing every 24 hours, while twice-daily pharmacokinetics necessitate dosing every 12 hours. A patient who misses a dose while taking the once-daily regimen has more opportunity to address the problem before drug concentration levels fall below effective levels. This becomes significant for missed evening doses. The once-daily regimen allows the patient to make up the dose the next morning (halfway through the dosing schedule), while the patient on a twice-daily regimen wakes up having missed the entire dosing period.

It is critically important that each component of the regimen must be evaluated individually to determine its degree of “forgiveness.” Furthermore, “forgiveness” issues between once-daily versus twice-daily dosing will only be resolved by the availability of sufficient pharmacokinetic data and in comparative clinical trials.

Patients likely to benefit from once-daily therapies

It is agreed that a majority of patients should benefit from the ease-of-use of once-daily therapy, but clinical validation of adherence and virologic benefit is still needed.

Any patient can theoretically benefit from a simplified medication schedule, so it follows that once-daily dosing may benefit all patients. Once-daily dosing may be particularly beneficial for patients experiencing adherence difficulties with their current twice-daily schedules. It may also be beneficial for patients who forget to take their medication in the absence of a daily routine. Consistent with this observation, a recent retrospective analysis of a large claims database identified a tendency for younger patients to have suboptimal adherence, and more likely to discontinue therapy over time than their older counterparts.³¹ Finally, once-daily dosing is particularly well adapted for the convenience of staff administration of directly observed therapy to patients in methadone clinics and in correctional institutions.³²

Switching to once-daily therapies

Although doctors may be reluctant to switch patients from established successful therapy, they may consider switching to once-daily therapy to deal with experienced or anticipated adherence difficulties.

Conclusion

Optimal use of highly active antiretroviral therapy (HAART) is an important strategy to improve clinical outcomes of HIV-infected patients. Complex treatment regimens complicate implementation of HAART because of challenges related to adherence. Simplified once-daily regimens may improve adherence and treatment success. In fact, the majority of surveyed patients has stated a preference for once-daily antiretroviral drugs.

Once-daily dosing may be useful for all patients, and may be particularly useful in patient populations with identifiable adherence difficulties. In open-label trials, the use of once-daily antiretroviral drugs in HIV combination therapy appears to promise equivalent viral suppression, compared to other studies that evaluate the use of drugs requiring more frequent dosing.

The Advisory Committee believes data support the importance of once-daily dosed antiretroviral therapies. The Advisory Committee also recognizes the importance of conducting adequately powered, prospective randomized trials to demonstrate the equivalence of once-daily dosing to twice-daily regimens. Until such time as these trials are complete, the Advisory Committee considers once-daily antiretroviral therapies, and regimens containing all once-daily medications, an important consideration in the management of HIV-infected patients. ■

References

1. Moyle G. The once-a-day era is upon us. *AIDS Reader* 2002; 12(2):56-58.
2. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med* 2000;133(1):21-30.
3. US DHHS Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. February 4, 2002. Online at www.hivatis.org
4. AWARE Treatment Lifestyle Survey, December 2001.
5. Bristol-Myers Squibb Virology Survey of *POZ* Magazine Readers. *POZ Magazine*, December 2001.
6. Jordan J, Carranza Rosenweig J, Pathak D, et al. Perceived influence of regimen characteristics on adherence. 5th International Congress on Drug Therapy in HIV Infection. Glasgow, Scotland. October 22-26, 2000. (Abstract P121).
7. Badaro R, Gathe J, Grimwood A, et al. Evaluation of a triple combination regimen containing enteric-coated didanosine administered once daily. 1st IAS Conference on HIV Pathogenesis and Treatment. Buenos Aires, Argentina. July 8-11, 2001. (Abstract 57).
8. Roca B, et al. Adherence and efficacy of HAART with bid or qd didanosine. 14th International AIDS Conference. Barcelona, Spain. July 7-12, 2002. (Abstract WePeB5815).
9. Sension M, Bellos N, Johnson J, et al. Efficacy and safety of switch to 3TC 300 mg QD vs. continued 3TC 150 mg BID in subjects

- with virologic suppression on stable 3TC/d4T/PI therapy (COLA 4005): Final 24-week results. 8th Conference on Retroviruses and Opportunistic Infections. Chicago, IL. February 4-8, 2001. (Abstract 317).
10. Bruno R, Ciappina V, Villani P, et al. Comparison of the plasma pharmacokinetics of lamivudine during twice and once daily dosing in HIV-1 infected individuals. 1st IAS Conference on HIV Pathogenesis and Treatment. Buenos Aires, Argentina. July 8-11, 2001. (Abstract 342).
 11. Schooley R, Myers R, Ruane P, et al. Tenofovir disoproxil fumarate (TDF) for the treatment of antiretroviral-experienced patients: a double blind placebo-controlled study. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Canada. September 17-20, 2000. (Abstract 692).
 12. Louie M, Hogan C, Hurley A, et al. Determining the relative efficacy of Tenofovir DF using frequent measurements of HIV-1 RNA during a short course of monotherapy in antiretroviral drug naive individuals. 9th Conference on Retroviruses and Opportunistic Infections. Seattle, WA. February 24-28, 2002. (Abstract 3).
 13. Pollard RB, et al. Stavudine extended/prolonged release (XR/PRC) vs stavudine immediate release (IR) in combination with lamivudine and efavirenz: 48 week efficacy and safety. 14th International AIDS Conference. Barcelona, Spain. July 7-12, 2002. (Abstract LbPeB9014).
 14. Arribas J, Staszewski M, Nelson M. Three-year durability of response with an efavirenz (EFV)-containing regimen: 144-week follow-up of study 006. 11th European Congress of Clinical Microbiology and Infectious Diseases. Istanbul, Turkey. April 1-4, 2001.
 15. Raffi F, Reliquet V, Ferre V, et al. d4T + qd ddI + nevirapine (bid or qd) in antiretroviral-naïve HIV-1-infected patients: 1-year results of the VIRGO study. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy. San Francisco, CA. September 26-29, 1999. (Abstract 1978).
 16. Murphy RL, Katlama C, Johnson V, et al. The Atlantic Study: a randomized, open-label trial comparing two protease inhibitor (PI)-sparing antiretroviral strategies versus a standard PI-containing regimen, 48-week data. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy. San Francisco, CA. September 26-29, 1999. (Abstract LB-22).
 17. Felipe G, Hernando K, Antonia SM, et al. An open randomized study comparing d4T + ddI + nevirapine (QD) vs d4T + ddI + nevirapine (BID) in antiretroviral-naïve, chronic HIV-infected patients in very early stage: Spanish scan study – Final results. XIII International AIDS Conference. Durban, South Africa. July 9-14, 2000. (Abstract 1156).
 18. Sanne I, Cahn P, Percival L, et al. Comparative results (phase II, 48-week): BMS232632, stavudine, lamivudine as HAART for treatment-naïve HIV(+) patients (A1424-008). 41st Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, IL. December 16-19, 2001. (Abstract 1-667).
 19. Maggiolo F, Migliorino M, Maserati R, et al. Once-a-day treatment for HIV infection: Final 48-week results. 8th Conference on Retroviruses and Opportunistic Infections. Chicago, IL. February 4-8, 2001. (Abstract 320).
 20. Landman R, Thiam S, et al. Long-term evaluation (15 months) of ddI, 3TC and efavirenz once-daily regimen in naïve patients in Senegal: ANRS 12-04 study/IMEA 011 study. 9th Conference on Retroviruses and Opportunistic Infections. Seattle, WA. February 24-28, 2002. (Abstract 458-W).
 21. Molina JM, Perusat S, Ferchal F, et al. Once-daily combination therapy with emtricitabine, didanosine and efavirenz in treatment naïve HIV-infected adults: 64-week follow-up of the ANRS 091 trial. 8th Conference on Retroviruses and Opportunistic Infections. Chicago, IL. February 4-8, 2001. (Abstract 321).
 22. Sustiva, full prescribing information, Bristol-Myers Squibb Company, 2002.
 23. Videx EC, full prescribing information, Bristol-Myers Squibb Company, 2001.
 24. Viread, full prescribing information, Gilead Sciences Inc., 2001.
 25. Epivir, full prescribing information, GlaxoSmithKline, 2001.
 26. Norvir, full prescribing information, Abbott Laboratories, 2001.
 27. Rosenbach KA, Allison R, Nadler JP. Daily dosing of highly active antiretroviral therapy. *Clin Infect Dis* 2002;34(5):686-92.
 28. Suleiman J, Rhodes R, Campo R, et al. Preliminary results from indinavir (IDV), and ritonavir (RTV) in a once daily regimen (Merck 103/104). 8th Conference on Retroviruses and Opportunistic Infections. Chicago, IL. February 4-8, 2001. (Abstract 336).
 29. Saah A, Winchell G, Seniuk M, et al. Multiple-dose pharmacokinetics (PK) and tolerability of indinavir (IDV) and ritonavir (RTV) combinations in a once-daily regimen in healthy volunteers (Merck 089). 39th Interscience Conference on Antimicrobial Agents and Chemotherapy. San Francisco, CA. September 26-29, 1999. (Abstract 329).
 30. Hsyu PH, Lewis R, Tran J, et al. Pharmacokinetics (PK) of nelfinavir (NFV) after once-daily dosing in combination with mini-doses of ritonavir (RTV) in healthy subjects. XIII International AIDS Conference. Durban, South Africa. July 9-14, 2000. (Abstract 7049).
 31. Becker S, Hodder S, Burtcel B, et al. Antiretroviral therapy adherence as measured by prescription refill behavior: A large claims database study. 8th European Conference on Clinical Aspects and Treatment of HIV Infection. Athens, Greece. October 28-31, 2001. (Abstract 80).
 32. Fischl M, Castro J, Monroig R, et al. Impact of DOT on long-term outcomes in HIV clinical trials. 8th Conference on Retroviruses and Opportunistic Infections. Chicago, IL. February 4-8, 2001. (Abstract 528).

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