

THE HOPKINS HIV REPORT

A bimonthly newsletter for healthcare providers

Antiretroviral Therapy Update From the 44th ICAAC

By Joel E. Gallant, M.D., M.P.H.

There were relatively few studies on antiretroviral therapy and investigational antiretroviral agents presented at the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held in Washington, D.C. earlier this fall. Nevertheless, some of the data presented were important and worthy of commentary.

Antiretroviral Therapy With Approved Agents

Tenofovir + Emtricitabine vs Zidovudine/Lamivudine: GS 934

Brian Gazzard presented preliminary 24-week data from GS934 that expanded on an announcement from Gilead Sciences released shortly before the conference [Abstract H-1137c]. The 934 study is an open-label trial in which over 1,000 treatment-naïve patients were randomized to receive either tenofovir DF (TDF) + emtricitabine (FTC) or coformulated zidovudine (AZT)/lamivudine (3TC), both in combination with efavirenz (EFV). The TDF + FTC arm was associated with superior efficacy by an intent-to-treat (ITT), time to loss of virologic response (TLOVR) analysis, with 73% and 65% of patients achieving a viral load <50 c/mL at 24 weeks, respectively (P=0.038). There was no difference in response by as-treated analysis; the difference in efficacy was explained entirely by the fact that more patients in the AZT/3TC arm dropped out (21%, compared to 11% in the TDF + FTC arm, P=0.01). Discontinuation due to adverse events, especially anemia, was also more common among AZT/3TC recipients (9% vs 3%). The anemia was significant: Among those who discontinued treatment for this reason, the median hematocrit dropped from a baseline value of 40% to a nadir of 22%. Interestingly, patients who failed therapy at 24 weeks frequently had the M184V mutation or EFV resistance, but no patient had thymidine analog mutations (TAMs) or the K65R mutation.

These results are not particularly surprising. Clinicians have long been familiar with the early

side effects and hematologic toxicity associated with AZT. In fact the results from both arms of the study are consistent with what has been observed with TDF- and AZT-containing regimens in other studies. While these early results have clear implications for treatment-naïve patients initiating therapy, they are less relevant to patients currently taking and tolerating AZT/3TC-containing regimens. However, the study is ongoing and is planned to continue through 96 weeks. It will be especially interesting to see longer-term DEXA data from this trial, to determine whether there is a difference in the emergence of lipodystrophy between the two arms.

Concerns about Didanosine + Tenofovir

Several studies presented at ICAAC raised concerns about the NRTI backbone of didanosine (ddI) + TDF, resulting in a “Dear Health Care Provider” letter from Bristol-Myers Squibb, advising clinicians to “use caution when coadministering TDF, ddI EC, and either EFV or NVP in treatment-naïve patients with high baseline viral loads.”

An earlier trial found an unacceptably high rate of virologic failure and emergence of resistance in patients taking the triple-NRTI regimen of TDF, didanosine (ddI) and 3TC [Gemseck J, et al. Abstract 51, 11th CROI, San Francisco, 2004], raising the question of whether TDF + ddI would be an acceptable NRTI backbone if combined with a more potent third agent. At ICAAC Graeme Moyle presented data from a small trial in which 70 patients were randomized to receive initial therapy with EFV plus either ddI + 3TC or ddI + TDF [Abstract H-566]. Virologic failure was more common in the ddI + TDF arm (4/34) than in the ddI + 3TC arm (0/36); all failures occurred among patients with baseline viral loads >100,000 c/mL and CD4 counts <200 cells/mm³. These results echo results from a study involving the same regimen presented by Podzamczar at the XIII International HIV Drug Resistance Workshop earlier this year [Abstract 156].



"Dupont Circle, Washington, D.C." photograph by Joel Meneses

Concerns were also raised about the CD4 response to regimens containing TDF + ddI. Soriano presented data from a retrospective study from Spain comparing patients treated with regimens containing TDF + ddI, TDF alone, ddI alone, or neither agent [Abstract H-1132]. Patients receiving TDF + ddI experienced a decline from baseline in absolute CD4 count. It should be noted that these patients were initially receiving full doses of ddI; when the dose of ddI was subsequently reduced to compensate for the TDF interaction, the CD4 count rose [Negerdo E, et al. Abstract 561]. The potential mechanism is unclear, and the study is limited by the decreasing sample size over time in the ddI + TDF groups. Nevertheless, it provides one more reason to be wary of the combination of ddI and TDF.

Perhaps the best reason not to use the TDF + ddI backbone (and, by extension, combinations of ABC + ddI or ABC + TDF) in naïve patients is the lack of data from clinical trials, in contrast to the wealth of data supporting the use of 3TC- and FTC-containing combinations. Such combinations may be considered, however, in NRTI-experienced patients when guided by resistance test results,

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especially in patients with TAMs, for whom emergence of K65R is less of a concern.

Quadruple-NRTI Therapy: AZT/3TC/ABC + TDF

While triple-NRTI regimens have fallen out of favor recently, there is still interest in the idea of a “quad regimen” involving coformulated AZT, 3TC, and abacavir (ABC) (*Trizivir*) plus TDF. Moyle presented 48-week results of the TIMS trial, in which 113 treatment-naïve patients were randomized to receive either AZT/3TC + EFV or AZT/3TC/ABC + TDF [Abstract H-1131]. AZT/3TC/ABC was administered twice a day in this study. At 48 weeks, two-thirds of the patients in each arm had a viral load <50 c/mL by ITT analysis. Failure was mostly due to discontinuation of therapy; only one patient, who was randomized to the quad arm, experienced virologic failure. Not surprisingly, fasting cholesterol levels were significantly higher in the EFV arm.

The same 4-drug regimen was studied in an uncontrolled, open-label study in which coformulated AZT/3TC/ABC was given once a day along with TDF to 113 treatment-naïve patients [DeJesus E, et al. Abstract H-564]. At week 24, 54% had a viral loads <50 c/mL by ITT missing=failure analysis. Virologic response was lower among patients with a baseline viral load >100,000 c/mL. Six of the 8 non-responders with genotype data had TAMs with or without M184V at 24 weeks.

This quad-NRTI regimen deserves further study, especially when dosed twice daily based on the results of Moyle’s study. It is relatively simple, spares both NNRTIs and PIs, and is especially attractive in the developing world, since there is no need for refrigeration and no concerns about interactions with rifampin. However, it would be premature to recommend this regimen now. Moyle’s study, while intriguing, was small and not powered to demonstrate non-inferiority. And DeJesus’s study raises questions about the potency of the once daily version of this regimen because of the marked difference in response between patients with high and low baseline viral loads. The relatively large number of patients with TAMs (in contrast to what might be expected in patients failing twice-daily AZT/3TC/ABC alone) also raises questions about whether inclusion of once-daily AZT in this regimen may not increase the risk for drug resistance.

It’s also worth speculating on whether the abacavir component of this four-drug regimen is necessary at all. The one remaining triple-NRTI combination that is still potentially viable but relatively untested is the combination of AZT, TDF, and either 3TC or FTC. This combination has an advantage over AZT/3TC/ABC because the M184V mutation has beneficial effects on susceptibility to both AZT and TDF. There is certainly no reason to consider using such a combination in the developed world now. But the patent on AZT will be expiring soon, which will lead to growing interest in how to use low-cost generic AZT in simple, class-sparing regimens.

Efavirenz vs Boosted Indinavir in Patients With Advanced Disease

It is a commonly accepted dogma that patients with advanced HIV disease (i.e., those with high viral loads or low CD4 cell counts) “need” a PI, though there have never been strong data to support this assertion. José Miró presented data from a study in which 34 treatment-naïve patients with baseline CD4 counts <100 cells/mm³ (median 40 cells/mm³) were randomized to receive AZT/3TC plus either EFV or ritonavir-boosted indinavir (IDV/RTV 800/200 mg bid) [Abstract H-574]. At 38 weeks, virologic and CD4 response appeared to favor the EFV arm, though the differences did not achieve statistical significance in this small study. These results suggest that EFV was at least as effective as IDV/RTV, and that it can be considered a reliable option in patients with low CD4 counts. The more definitive study will be the large ongoing ACTG trial in which patients are randomized to receive two NRTIs plus either LPV/r or EFV.

Investigational Antiretroviral Agents

Tipranavir: The RESIST-1 Trial

Charles Hicks from Duke University presented 24-week data from the ongoing RESIST-1 trial, a randomized, open-label trial in which over 600 patients with 3-class experience treated with at least 2 PI-containing regimens were randomized to receive either ritonavir-boosted tipranavir (TPV/RTV 500/200 mg bid) or a comparator boosted PI (CPI) along with an optimized background regimen [Abstract H-1137a]. Entry criteria required that patients have at least 1 primary PI mutation but no more than

2 mutations at codons 30, 82, 84, and 90. The median baseline viral load was 4.8 log₁₀ c/mL, and the median baseline CD4 count was 123 cells/mm³. At 24 weeks, 41.5% of TPV/r-treated patients achieved a viral load reduction of ≥1 log compared with 22.3% in the CPI arm by ITT analysis (P<0.001). Viral load reduction to <400 c/mL was achieved by 34.7% and 16.5%, respectively, (25.1% vs 10.0% for <50 c/mL, P<0.01 for both comparisons). Enfuvirtide (ENF) was included in the optimized background regimen in 36% of participants, and not surprisingly, use of ENF improved virologic response in both groups. For example, virologic suppression to <400 c/mL was achieved in 47.1% of TPV/r recipients who also took ENF compared to 34.7% overall, and in 21.9% of those in the CPI arm compared to 16.5% overall. Patients on TPV/r were more likely to have elevations in transaminases and lipids than those in the CPI arm, perhaps because of the higher dose of ritonavir.

These data support the efficacy of TPV in patients with PI experience and resistance, and also emphasize the importance of including more than one active agent in a salvage regimen. Availability of this drug and other “second-generation” agents through clinical trials and expanded access programs will probably also increase the use of ENF, which many clinicians have been reluctant to use in highly experienced patients because for many such patients there were no other effective drugs available to combine it with.

Similar results were seen in the RESIST-2 study, which were presented recently by Pedro Cahn in Glasgow at the 7th International Congress on Drug Therapy in HIV Infection (November 14-18, Abstract PL14.3).

D-d4FC (Reverset) in NRTI-Experienced Patients

Robert Murphy presented data from a 10-day monotherapy study in which 8 patients added varying doses of D-d4FC to a failing regimen [Abstract H-1130]. The mean viral load reduction among those receiving D-d4FC was -0.8 log₁₀ c/mL at day 10, although the response was somewhat lower among the 4 patients with 3-4 TAMs at baseline. A larger phase IIB trial in antiretroviral-experienced patients is ongoing, and should help to determine the role of this agent in patients with multiple TAMs.



Antiretroviral Therapy Update From the 44th ICAAC

CCR5 Antagonists

A number of coreceptor antagonists are now in clinical development; those furthest along inhibit binding to the CCR5 coreceptor, thus preventing entry of HIV into the CD4 cell (See Shepherd J and Quinn T, *HHR* 2004;16(4):1-4). Lalezari presented data from a 10-day dose-ranging study of 873140, a CCR5 inhibitor from GlaxoSmithKline [Abstract H-1137b]. There was a clear dose-response relationship, with subjects who received the highest dose (600 mg bid) experiencing a decline in viral load of over 1.6 log₁₀ c/mL. The peak virologic effect occurred at day 12, 2 days after discontinuation of the drug, an effect that was attributed to prolonged receptor occupancy. The drug was well tolerated; the most common side

effects were mild and transient gastrointestinal problems.

One concern with use of CCR5 inhibitors is the potential for selection of pre-existing X4- or R5/X4-tropic virus, which could result in more rapid progression of HIV disease. A study by Moyle and colleagues demonstrated a higher prevalence of X4- or dual-tropic virus among patients with CD4 counts <100 cells/mm³ [Abstract H-1135], and Demarest presented data showing that while R5-tropic virus was most common among all groups of patients, the prevalence of X4- or dual-tropic virus was higher among treatment-experienced patients than among treatment-naïve patients [Abstract H-1136]. Two patients treated with 10 days of monotherapy with the Pfizer CCR5 antagonist,

UK-427,857 developed dual-tropic virus during the course of the study, which appeared to emerge as a result of low-level pre-existing dual-tropic virus that had not been detected by the screening tropism assay, which has a detection threshold of approximately 10% [Lewis ME, et al. Abstract H-584b]. Phylogenetic analysis revealed that in one patient, dual-tropic virus was replaced by R5-tropic virus at day 40, one month after discontinuation of the study drug. However, the second patient continued to have significant levels of dual-tropic virus one year after completion of the study.

The most promising use of these agents, therefore, would be as a component of initial

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The Hopkins HIV Report is published six times per year by The Johns Hopkins University AIDS Service, Division of Infectious Diseases. Publication of this newsletter is underwritten by a generous grant from GlaxoSmithKline; we gratefully acknowledge their support.

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Update from the 6th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV

By Todd Brown, M.D. and Joseph Cofrancesco, Jr., M.D., M.P.H.

Researchers from around the world gathered in Washington, D.C. in October for the 6th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV. This article will focus on the research with clinical relevance.

Effects of Specific Medications

The impact of specific antiretroviral medication on insulin resistance was further clarified. In healthy volunteers, a single high dose of 800 mg of ritonavir was found to induce insulin resistance [Lee, GA, et al. Abstract 7]. Indinavir/ritonavir also induced insulin resistance, but atazanavir/ritonavir did not.

[Droan DA, et al. Abstract 6]. Although insulin resistance is thought to be a class effect, there are clearly differences among protease inhibitors (PIs). Low-dose ritonavir and atazanavir do not appear to affect insulin sensitivity, whereas indinavir and high-dose ritonavir do.

There are increasing data suggesting that the choice of the nucleoside analogs is also important in the development of insulin resistance. In an analysis of 1,288 participants in the Multicenter AIDS Cohort Study (MACS), insulin resistance was independently associated with cumulative PI use as well as cumulative NRTI use, with the strongest effect on insulin resistance seen with cumulative stavudine exposure [Brown TT, et al. Abstract 10].

Subjects in the SOLO study who completed at least 48 weeks of once daily fosamprenavir 1400mg + ritonavir 200 mg were followed to week 120. The nucleoside backbone was abacavir (ABC) + lamivudine (3TC) in 83% of subjects. The 174 subjects demonstrated increases in HDL cholesterol (+13 mg/dL by week 120), and the proportion of subjects with a TC:HDL ratio >6.5 did not increase and was quite low (9%) at week 120 [Flamm J, et al. Abstract 99]. Altogether, 18% of subjects reported fat accumulation and 5% reported fat loss; these changes did not increase from week 48 to 120 [Walmsley S, et al. Abstract 50]. Taken together, the data suggest that fosamprenavir, even when boosted by low-dose ritonavir, has only a modest impact on lipids. The lack of fat loss no doubt stems from the fact that ABC/3TC was used as the nucleoside backbone. We do need to remember that LDL cholesterol and DEXA data were not presented, and only those successful at week 48 were followed until week 120.

Finally, there are increasing data that switching to tenofovir DF (TDF) can help to prevent or reverse some NRTI-associated complications. In one small study, 11 male and 6 female subjects changed from varying NRTI backbone drugs to TDF-containing regimens for a variety of reasons (e.g. failure, side effects). These subjects experienced no change in body mass, weight or bone density, but had increased total, limb and trunk fat by DEXA as well as decreases in cholesterol levels [Tsekes G, et al. Abstract 46]. Similarly, Gilmore and colleagues

presented 48-week data demonstrating that a switch from d4T to TDF led to a more favorable lipid profile [Gilmore J, et al. Abstract 102]

Treatment for Fat Accumulation

Previous trials have demonstrated reductions in central and dorsocervical fat with the use of Growth Hormone (GH), but at the expense of significant side effects, including insulin resistance, high cost, and loss of subcutaneous fat. Grinspoon and colleagues presented a multicenter, randomized trial of a GH releasing factor (GHRF) [Abstract 2]. Sixty-one subjects with central adiposity were randomized to receive daily subcutaneous injections of placebo, 1.0 mg, or 2.0 mg of TH9507 (Theratechnologies, Montreal). At 12 weeks, there was a 16% decrease in visceral fat and an increase in limb muscle mass as measured by CT in the 2.0 mg group and no significant change in the placebo group. Although IGF-1 levels increased in the 1 mg dose, changes in body composition did not reach significance at this dose. Importantly, there were no significant changes in limb fat, glycemic control, or markers of insulin resistance. This proof-of-concept study suggests GHRF analogs may be safe and effective to reduce visceral fat without the risk insulin resistance or lipoatrophy, but larger trials of longer duration are needed.

NRTIs and Mitochondrial Toxicity

It is generally accepted that NRTIs, by damaging mitochondrial DNA, are linked to a number of complications, including fat loss and lactic acidosis. Data implicating the thymidine analogs (stavudine [d4T] and zidovudine [AZT]) were presented at this meeting. A study of healthy volunteers receiving d4T/3TC or AZT/3TC for six weeks demonstrated inhibition of mitochondrial RNA transcription in adipocytes [Mallon PWG, et al. Abstract 15]. Similarly, in a study of 87 HIV-infected patients, both AZT and d4T were associated with mitochondrial depletion in adipocytes, with a larger effect seen with d4T. In contrast, exposure to non-thymidine analog-containing regimens was not associated with effects on mitochondria [Hammond E, et al. Abstract 16]. Although these data are from cell lines, there is growing

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Please note: The HHR is published every *other* month— January, March, May, July, September, and November.



Update from the 6th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV

evidence from clinical studies as well that the thymidine analogs are toxic to mitochondria, with d4T being the worst offender. Providers need to be aware of these issues when selecting a nucleoside backbone or when assessing a patient with evidence of early nucleoside toxicity.

There is continuing interest in the potential utility of uridine, a pyrimidine precursor, to protect mitochondria. A group in Germany was able to block a number of markers of mitochondrial damage in cell culture by pre-treating with uridine [Walker UA, et al. Abstract 14]. It is premature to recommend this product for patients, but human studies are underway.

Treatment for Lipoatrophy

Many small studies suggest a restorative benefit from various face- or body-filling compounds [Mest DR, et al. Abstract 59; Casavates LC, et al. Abstract 60; Guaraldi G, et al. Abstract 87]. Guaraldi presented data from a prospective, 24-week, partially randomized trial using three different face fillers [Abstract 12]. Patients with “adequate fat” received autologous fat transplants. Those without adequate fat were randomized 1:1 to receive poly(lactic acid) (PLA), a reabsorbable compound now FDA-approved as *Sculptra*, or polyacrylamide (PCA I), a non-reabsorbable compound. Ultrasound measurement suggested that all three compounds appeared to restore facial volume to a similar degree, with no differences between groups. Interestingly, fat transplant subjects were less satisfied. No serious adverse events were reported. However, 4/24 (16%) of the fat transplant patients developed what is now being referred to as “hamster syndrome,” that is, fat hypertrophy of the cheeks accompanying fat re-accumulation at the donor site. For that reason, it was suggested that the dorsocervical area should not be used as the fat donor site. Nine of the 24 patients required a “retouch” for aesthetic reasons, and 12/24 reported mild edema. Forty percent (8/20) of the PLA patients had non-absorption nodules in cheeks. It should be noted that those receiving fat were not randomized and may well be different in the physiology of their fat cells and in etiology of their fat gain. Other subjects were excluded if the treating physicians did not believe subjects “would benefit.” Moreover, the study was only 24 weeks in duration. Much longer follow-up will be

required to determine the relative merits of specific compounds. Patients and clinicians will continue to have difficult times determining which compound is best, as most trials are small, uncontrolled or non-randomized, and of relatively short duration.

Treatment Interruption

Structured treatment interruption (STI) continues to be a promising method in selected patients to prevent or reverse complications of therapy. Patients enrolled in an STI protocol involving four cycles (two months on/one month off) followed by permanent discontinuation of ART, showed rapid improvements in lipid profiles and abnormal fat distribution, which were persistent at one year [Milinkovic A, et al. Abstract 81]. All subjects had been on d4T/3TC and a PI (indinavir-10, nelfinavir-3). Another STI protocol that was designed to assess the impact of interleukin-2 (IL-2) on viral parameters showed that triglycerides and LDL and total cholesterol all improved within the first 4 weeks of interruption, and improvements were maintained at week 48. There was no change in insulin resistance. IL-2 had no effect on these changes [Tebas P, et al. Abstract 20]. Unfortunately, many patients are not appropriate candidates for treatment interruptions due to low CD4 nadirs, high baseline viral loads, or a history of OIs; and treatment interruption may increase the risk of drug resistance. However, for those who can afford an interruption, it is helpful to know that metabolic parameters improve quickly and that fat accumulation or lipoatrophy may slowly improve.

Cardiovascular Disease

Several abstracts confirmed an increased cardiovascular risk in HIV-infected patients. Parenti presented data on HIV-infected men receiving over 24 months of PI-containing HAART who had no cardiac symptoms [Abstract 116]. Among these subjects 60% had increased coronary artery calcification, a marker of atherosclerosis. However, Mangili demonstrated a similar prevalence of coronary calcium but found no association with HAART [Abstract 119]. Finally, an important finding from Boccara was that the presentation of the acute coronary syndrome may be different in HIV-infected patients [Abstract 121]. In a case-

control study of 50 HIV-infected and 50 seronegative patients undergoing percutaneous coronary intervention, HIV-infected patients were less likely to have an ST-elevation on EKG and were more likely to have a late diagnosis. Fortunately, re-stenosis rates after 1 year of follow-up did not differ.

The data on cardiovascular disease in HIV is evolving, but these data, along with the D:A:D study [Friis-Moller N, et al. *N Engl J Med* 2003;349:1993-2003] suggest that clinicians need to have a high level of suspicion for coronary disease in HIV-infected patients.

Adverse Effects of Drugs used to treat Metabolic Abnormalities

HMG CoA-reductase inhibitors (“statins”) lower LDL cholesterol, but their effect on other HIV parameters is unknown. Iloejo conducted a cohort study of 272 HIV-infected patients, half of whom were exposed to statins, and found that statin exposure was associated with a blunting of the CD4 response to antiretrovirals (12% increase in cases vs 32% in controls) [Abstract 69]. In another small study using cells cultured with ddI, d4T or ddC taken from patients receiving a statin or fibrate, there was a suggestion of additive toxicity when the statin was combined with a nucleoside analog [Susan-Resiga D, et al. Abstract 32]. These were not randomized studies, and the clinical significance is unclear, but it does give us pause, as we increasingly add these medications to our patients’ complex drug regimens. We are learning of a number of effects that statins may have in HIV-negative individuals, and there is growing evidence that they are anti-inflammatory. This may be one of the reasons statins impact CD4 counts and viral load measurements in HIV positive individuals, though intra-cellular interactions are only beginning to be explored.

Resource Poor nations

This year, there was a large presence of investigators from developing countries, where complications of HAART have not been as well studied. In a cohort of antiretroviral-naïve patients in South India assessed after 6 months of therapy, both efavirenz and nevirapine

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The DHHS Adult ART Guidelines Are Revised

By John G. Bartlett, M.D.

On October 29, 2004, the DHHS released the most recent version of the federal guidelines for use of antiretroviral agents in HIV-infected adults and adolescents. **Guidelines for use of anti-retroviral agents in HIV-1-infected adults and adolescents [Panel on Clinical Practices for Treatment of HIV Infection, Department of Health and Human Services (DHHS)]**: This is a draft version posted on the AIDSInfo web site, <http://AIDSinfo.nih.gov>, with a request for comments, which should be sent to aidsinfowebmaster@aidsinfo.nih.gov. This document has been entirely rewritten. The most important changes are summarized in the "Indications to Treat" table on this page.

When to Start Therapy

Minor changes in this section include a more precise definition of symptomatic HIV infection as an indication for therapy regardless of CD4 cell count or viral load. Additionally, the threshold viral load for considering therapy in asymptomatic patients with a CD4 count above 350 cells/mm³ has been increased to 100,000 c/mL. The specific recommendations for initiating antiretroviral therapy are summarized in the following table.

Table. Recommended Regimens

Preferred
EFV + (3TC or FTC) + (AZT or TDF)
LPV/r + (3TC or FTC) + AZT
Alternative
EFV + (3TC or FTC) + (ABC or ddl or d4T)
NVP + (3TC or FTC) + (AZT or d4T or ddl or ABC or TDF)
ATV + (3TC or FTC) + (AZT or d4T or ABC or ddl) or (TDF + RTV 100 mg/d)
FPV + (3TC or FTC) + (AZT or d4T or ABC or TDF or ddl)
FPV + RTV + (3TC or FTC) + (AZT or d4T or ABC or TDF or ddl)
IDV + RTV + (3TC or FTC) + (AZT or d4T or ABC or TDF or ddl)
LPV/r + (3TC or FTC) + (d4T or ABC or TDF or ddl)
NFV + (3TC or FTC) + (AZT or d4T or ABC or TDF or ddl)
SQV (sgc or hcg) + RTV + (3TC or FTC) + (AZT or d4T or ABC or TDF or ddl)
Triple NRTI *
AZT + 3TC + ABC

* Only for use when other preferred or alternative regimens cannot be used
ABC = abacavir, ATV = atazanavir, AZT = zidovudine, ddl = didanosine, EFV = efavirenz, FPV = fosamprenavir, IDV = indinavir, LPV/r = lopinavir/ritonavir, NFV = nelfinavir, NVP = nevirapine, RTV = ritonavir, SQV = saquinavir

Table. Indications to Treat

Category	CD4 cells/mm ³	VL (c/mL)	Recommendation
AIDS/Severe symptoms*	Any	Any	Treat
Asymptomatic	<200	Any	Treat
Asymptomatic	200-350	Any	Offer treatment
Asymptomatic	>350	>100,000	Consider
Asymptomatic	>350	<100,000	Defer

* Unexplained fever or diarrhea >2-4 weeks, thrush or >10% unexplained weight loss.

Recommended Regimens

This section has been entirely revised to reflect: 1) availability of emtricitabine (FTC), 2) concern about the long term toxicity of stavudine (d4T), and 3) endorsement of tenofovir (TDF) plus lamivudine (3TC) or FTC as a recommended NRTI backbone. The regimen recommendations are summarized below.

Resistance Tests

In previous versions of the guidelines, it was stated that resistance testing in the setting of virologic failure must be performed while the patient is on therapy. This has now been changed to allow testing during administration or up to four weeks after discontinuation of therapy. This change is based on the results of multiple studies

indicating that replacement by wild-type HIV occurs at least four weeks or later after discontinuation. Baseline resistance testing in chronically infected, treatment-naïve patients was not felt to be indicated in previous guidelines, but is now considered "an option." This change is based on studies showing that resistance mutations in transmitted strains may persist for prolonged periods, although this is quite variable.

Planned Treatment Interruption

This is a new section of the guidelines that states that all antiretroviral agents should be stopped simultaneously when discontinuing therapy. The possible exception is in nevirapine- or efavirenz-containing regimens. Since serum concentrations of these drugs may persist for 21 days or longer, simultaneous discontinuation may result in a prolonged period of monotherapy. No specific strategy has been adequately studied to allow for a specific recommendation, but some authorities recommend discontinuation of the NNRTI before discontinuation of the nucleoside analogs, while others substitute a PI for 2-4 weeks prior to interruption to deal with this potential complication.

A second concern with respect to discontinuation is the possibility of a flare of HBV with the discontinuation of emtricitabine, lamivudine or tenofovir. The current recommendation in such cases is to carefully monitor such patients or to give adefovir.

A review of published studies on planned treatment interruption was conducted to establish recommendations in various clinical settings. Available data indicate that planned interruption cannot be recommended in patients experiencing virologic failure with resistance to multiple drugs in order to allow re-emergence of wild-type HIV. Treatment interruption is also not indicated in patients with acute HIV infection who have achieved virologic suppression in an attempt



The DHHS Adult ART Guidelines Are Revised

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establish a better virologic set-point. However, discontinuation “may be offered” to patients who have experienced immune reconstitution (the “CD4-guided” treatment interruption strategy), although participation in a controlled trial would be preferred.

Special Populations

There are now sections dealing with HIV infection and antiretroviral therapy in adolescents, injection drug users, patients coinfecting with hepatitis B or C, and patients with TB co-infection.

New Tables

The latest version of the guidelines includes 29 tables. New tables include a tabulation of published clinical trials with 48 week outcome results and a comprehensive table dealing with adverse reactions. In addition, all of the previous tables have been extensively revised and updated.

Treatment Failure

The guidelines now define virologic failure as failure to achieve a viral load <400 c/mL at 24 weeks, failure to achieve a viral load <50 c/mL at 48 weeks, or a confirmed virologic rebound after virologic suppression. Immunologic failure is defined as the failure of the CD4 count to increase by 25-50 cells/mm³ over baseline during the first year, and clinical progression is defined as occurrence of an HIV-related event after at least three months of HAART. For practical purposes, recommendations for changing antiretroviral therapy are based on exclusively on virologic failure.

Virologic Failure

The guidelines contain a rewritten section on virologic failure that is too complicated to summarize. However, the key principles are 1) to assess adherence, intolerance and pharmacokinetic issues that may account for failure; 2) to use results of all current and prior resistance tests as well as drug treatment history in selecting a new regimen; 3) to employ at least three active agents; and 4) to use new agents, including drugs from new classes such as HIV entry inhibitors, when necessary.

Expertise: The panel recommends that HIV care should be provided by a clinician who has a patient load of at least 25 active HIV-infected patients. ▲

Antiretroviral Therapy Update From the 44th ICAAC

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therapy, perhaps initiated at earlier stages of disease than is currently the practice. However, the competition for a role in initial therapy is fierce, given the convenience and tolerability of currently used agents.

The Significance of Blips

Richard Nettles from Johns Hopkins University presented a study in which 10 patients on HAART with virologic suppression were intensively monitored to help characterize the phenomenon of “blips,” or transient episodes of low-level viremia [Abstract H-1134]. Viral loads were measured in two different laboratories three times a week over a 3-month study period. Nine of the 10 participants experienced at least one blip. The median duration of the blips was 60 hours, and the median magnitude was 79 c/mL. Interestingly, of the 18 blips observed during this study, only one was detected by both laboratories, suggesting that many blips may represent normal assay variation rather than true viremia. This possibility is further supported by the observation that no new mutations were detectable before, during, or after blips. The apparent lack of viral evolution is in contrast to data published by the same group demonstrating that emergence of resistance does occur in patients with low-level but persistent viremia [Nettles RE, et al. *Clin Infect Dis* 2004;39:1030-7], a finding that has now been observed in a number of studies, including one presented at ICAAC this year [Edwards D, et al. Abstract H-176]. These data are reassuring, since blips are commonly seen in clinical practice. The challenge for clinicians is to know whether a detectable viral load represents an inconsequential blip or the beginning of virologic failure, an important distinction, given that viral loads in clinical practice are typically drawn every 3 months rather than 3 times per week.

Conclusions

The handful of studies on antiretroviral therapy that were presented at ICAAC this year helped us to learn more about the growing number of options for initial therapy and shed light on several promising investigational agents. We can expect to learn much more at the upcoming Conference on Retroviruses and Opportunistic Infections, to be held in February, 2005 in Boston, which will be extensively covered in *The Hopkins HIV Report*. ▲

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Update from the 6th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV

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treatment was associated with increased fasting glucose values, but only efavirenz-treated subjects showed increases in body fat or LDL and HDL cholesterol [Saghayam S, et al. Abstract 62]. In HIV-infected Thai patients, the prevalence of metabolic and morphologic abnormalities was similar to those seen in Western populations and was associated with PI-based or d4T-containing regimens [Homasant M, Abstract 61]. These issues are increasingly challenging in resource-limited nations. HAART options are limited to generic formulations and often selected by governmental agencies. Options for switching medications may not be available. Treating HIV and preventing disease progression remain paramount; however, providers will need to be aware of complications as they are likely to become prevalent. Health officials may wish to consider the cost of long-term complications when selecting antiretroviral medications for their nation.

Summary

The complexity of HIV-associated complications is apparent. This workshop shed further light on the role of specific antiretroviral agents or classes of agents in the emergence of these complications. Although insulin resistance is often thought of as a complication associated with protease inhibitors, there are clear differences among the PIs, and nucleoside analogs may also play a role. Ritonavir-boosted fosamprenavir or atazanavir appear to have only minimal effects on insulin resistance and lipid elevations. The data continue to implicate thymidine analogs, particularly stavudine, in causing mitochondrial damage and resulting clinical syndromes. Switching from another NRTI to tenofovir or abacavir may help with these complications. There were encouraging data on treatment of fat accumulation with growth hormone releasing factor and lipodystrophy

using “filling” compounds or fat transplants, but long-term benefit needs to be established. Studies continue to show an increased risk of cardiovascular disease with HIV infection, and in some cases with HAART, and one study suggested that HIV-infected patients may have an altered presentation of acute coronary syndrome compared to uninfected patients. Taken together, it is clear that the selection of HAART is important not only to control the virus, but to limit long-term toxicities. However, patient and disease factors cannot be ignored. This workshop provided important basic science and clinical data that will help us better understand the long-term complications of HIV therapy.

NOTE: All accepted abstracts from the 6th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV will be published in the journal, Antiviral Therapy ▲

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