

THE HOPKINS HIV REPORT

A bimonthly newsletter for healthcare providers

Report from ICAAC: New Drugs and Antiretroviral Therapy for Naïve Patients

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

Antiretroviral news was sparse at the 42nd ICAAC, presumably because it followed the International AIDS Conference in Barcelona by only 2 months. Now that we have a yearly international conference once again (the International AIDS Conference alternating with the International AIDS Society Conference), ICAAC may play a less important role as a forum for HIV-related data. Nevertheless, several important studies related to the treatment of naïve patients were presented in San Diego, including studies of both approved and investigational drugs.

Protease Inhibitors

The MaxCmin1 study is a 48-week, open-label, randomized trial comparing two boosted PI regimens: IDV/RTV (800/100 mg bid) and SQV/RTV (1000/100 mg bid) [Gerstoft J, et al. Abstract H-172]. The trial included 306 PI-naïve and experienced patients, of whom 248 completed 48 weeks of therapy. While virologic failure was similar in the two arms (20% and 18%, respectively), switches from randomized treatment were more common among IDV/RTV recipients (42% vs 28%), and were usually due to adverse events, most of which were gastrointestinal. Thus, while the on-treatment analysis showed no significant difference between arms, SQV/RTV was superior in the intent-to-treat (ITT), missing or switch=failure analysis, in which 53% vs 68% achieved HIV RNA <400 c/mL (p=0.014). Lipid profiles were also more favorable in the SQV/RTV group.

The SQV/RTV combination was also compared against EFV in the FOCUS trial, which enrolled 161 treatment-naïve participants [Montaner JSG, et al. Abstract H-167]. In this trial, SQV/RTV was dosed once daily (1600/100 mg qd), and both regimens included two NRTIs. EFV was significantly better tolerated than SQV/RTV, which was associated with more moderate-to-severe nausea (22.2% vs 3.8%) and vomiting (6.2% vs 0%). As a result, EFV was more effective by ITT analysis, with 71% achieving a viral load of <50 c/mL at 48 weeks compared to 51% in the SQV/RTV arm.

The soft-gel formulation of SQV (*Fortovase*) was used in both the MaxCmin1 and the FOCUS trials. There is now growing enthusiasm for reviving the use of the older hard-gel

formulation (*Inivase*), since it achieves equivalent blood levels when boosted with RTV but is associated with fewer gastrointestinal side effects.

Long-term durability data were presented from Abbott's M97-720 trial, in which 100 treatment-naïve patients with HIV RNA >5000 c/mL received LPV/r in combination with d4T and 3TC [Murphy R, et al. Abstract H-165]. At 204 weeks, with data from 71 patients remaining on assigned therapy, 70% had HIV RNA <50 c/mL by ITT, non-completer=failure (NC=F) analysis, and 97% had HIV RNA <50 c/mL by as-treated analysis. CD4 counts continued to rise, with an increase in CD4 count of over 400 cells/mm³ observed at 204 weeks.

Tenofovir

Results of the Gilead 903 study were reported at this year's International AIDS Conference in Barcelona [HHR 2002;14(5):4]. In this large, placebo-controlled trial, 600 patients were randomized to receive either tenofovir disoproxil fumarate (TDF) or d4T, each in combination with efavirenz plus 3TC. The virologic results were presented again, along with an expanded analysis of toxicity data [Gallant JE, et al. Abstract LB-2]. Both regimens were highly effective, with no differences in efficacy between the two arms. By ITT, missing=failure analysis, 82% and 81% achieved an HIV RNA <50 c/mL at 48 weeks (86% and 89% by ITT, missing=excluded analysis). However, TDF was associated with less toxicity than d4T, most notably in terms of lipid elevations. Fasting triglycerides, total and LDL cholesterol were significantly higher in the d4T arm at 48 weeks. In addition, mitochondrial DNA (mtDNA) levels in PBMCs increased from baseline to 48 weeks in the TDF arm, while there was no significant increase above baseline in the d4T arm. mtDNA levels were low at baseline in both groups, as has been reported in other studies of untreated HIV-infected patients, and it has been suggested that while HAART may help to restore normal mtDNA levels, this effect may be

offset by the mitochondrial toxicity of specific NRTIs. A higher proportion of patients in the d4T arm had elevated lactate levels, and investigator-defined peripheral neuropathy was reported less frequently in TDF recipients.

The use of mtDNA assays is controversial, especially when levels are measured in PBMCs. These assays have not been well correlated with clinical adverse events. The Gilead 903 study is designed to continue for 3 years, which may provide an opportunity to help correlate *in vitro* toxicity assays with clinical outcomes.

Other Trials Involving Available Agents

Allavena presented results of the BIKS trial, an open-label, non-randomized multicenter study of lopinavir/ritonavir (LPV/r) plus EFV without NRTIs [Abstract H-169]. LPV/r was given at a dose of 533/100 mg (4 capsules) bid to compensate for the drug interaction with EFV. The trial enrolled 54 treatment-naïve participants and 19 who had failed a single PI but were NNRTI-naïve. At 24 weeks, 89% had an HIV RNA <400 c/mL by on-treatment analysis. The plan is to continue the trial for 48 weeks. Enthusiasm for so-called "NRTI-sparing regimens" has been driven in part by fear of NRTI-associated mitochondrial toxicity. With the availability of NRTIs/NtRTIs such as abacavir and tenofovir DF, which appear to be less toxic to mitochondria, it remains to be seen whether that enthusiasm will be maintained.

Maggiolo presented data from an open-label trial comparing a once daily regimen (ddI + 3TC + EFV) with two twice daily regimens, the "low pill burden regimen" of AZT/3TC + EFV and the "high pill burden regimen" of AZT/3TC + NFV [Abstract H-163]. Each arm included 34 participants. At 12 months, there was no difference between the two EFV-containing arms, but both were superior to the NFV-containing arms in terms of virologic suppression to

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<50 c/mL by ITT analysis. While one might be tempted to conclude that once or twice daily regimens with low pill burdens are superior to twice daily regimens with high pill burdens, the more obvious explanation is simply that EFV is more effective than NFV, which has been demonstrated in other trials.

Atazanavir

Atazanavir (ATV) is an investigational protease inhibitor that does not appear to cause hyperlipidemia and has the advantage of being dosed once daily. A previous trial suggested that it was as potent as nelfinavir, but data on comparisons with “gold standard agents” such as efavirenz and LPV/r have been eagerly awaited to help determine the true potency of this agent. Kathleen Squires presented 48-week data from the BMS-034 trial, a large multi-center, randomized trial of ATV vs efavirenz (EFV) plus AZT/3TC in 805 treatment-naïve patients [Abstract H-1076]. The trial demonstrated equal potency of the two regimens, with 70% of ATV recipients achieving HIV RNA <400 c/mL vs 64% of EFV recipients by ITT, NC=F analysis (95% CI 1.2-11.7% for the difference between arms). Lipid profiles were more favorable in the ATV arm, with changes of +1% vs +18% in LDL cholesterol and -9% and +23% in triglycerides in the ATV and EFV arms, respectively. Five percent of ATV recipients developed jaundice or scleral icterus, a recognized side effect of ATV.

Unfortunately, results using the <50 c/mL HIV RNA assay were less impressive in both arms, and were much lower than what has been reported in other trials of EFV, such as DMP 006, GS 903, and others. Only 32% of ATV recipients and 37% of EFV recipients achieved an HIV RNA <50 c/mL at 48 weeks. A number of explanations have been proposed to explain these discrepant results. This was a multinational study, and there may have been differences in adherence that could have affected virologic response. Virologic response appeared to be lower in areas that enrolled larger numbers of injection drug users. Also, two different viral load assays were used in this study: The Roche *Amplicor* version 1.0 was used in some countries, while the version 1.5 assay was used in parts of the world where non-B sub-clades are more common. The version 1.5 assay is more likely to detect virus in patients who have undetectable viral loads (<50 c/mL) than using the version 1.0 assay. The results of this study have not yet been stratified by viral load assay, an analysis that should allow us to determine the contribution of assay differences toward the virologic response. Finally,

the definition of virologic failure was more stringent than has been used in many other clinical trials. Patients with two consecutive HIV RNA measurements above 50 c/mL were counted as failures. This strict definition of failure has been adopted by the FDA but has been rejected by the AIDS Clinical Trials Group (ACTG) because of variability of viral load assays at low levels of HIV RNA. In addition, patients who discontinued the assigned study drug for any reason were also said to have failed therapy, including those who switched from AZT to another NRTI because of AZT side effects.

These results are somewhat difficult to interpret because of the relatively poor performance of both ATV and EFV using the <50 c/mL assay. Further analyses of the data should help to determine the degree to which the results can be explained by the various protocol-related factors. In the meantime, it is encouraging that ATV was generally well tolerated, did not cause hyperlipidemia, and appeared to be as effective as EFV in treatment-naïve patients.

Atazanavir levels (AUC and C_{min}) are decreased by approximately 70% when the drug is combined with EFV, and a similar interaction is presumably seen with nevirapine, as well. As with other PIs, ATV levels can be boosted by co-administration with RTV. Agarwala reported on a pharmacokinetics study in which 30 subjects were given ATV 300 mg qd for 10 days, after which they added RTV 100 mg qd [Abstract H-1716]. ATV C_{min} was increased approximately 10-fold above that seen with ATV alone (at the reduced dose of 300 mg qd). These findings may have implications for co-administration of ATV with NNRTIs. Needless to say, boosting of ATV levels with RTV would undermine one of the most significant advantages of ATV—its lack of effect on lipid levels. It is possible that RTV boosting might also increase the risk of indirect hyper-bilirubinemia and jaundice, since C_{min} appears to be the most important factor predicting bilirubin elevation [O'Mara E, et al. Abstract A-1253]. ATV can also be used to boost SQV levels, since it results in a 4- to 7-fold increase in the SQV AUC. Recommendations are that ATV be given at standard dose (400 mg qd) along with 1200 mg of SQV with a high-fat meal.

Fos-amprenavir: The NEAT study

While amprenavir (APV) has a number of attractive features, the current formulation is difficult to take because of the large capsule size, high pill burden, and gastrointestinal side effects. Fos-amprenavir (GW433908, fos-APV) is a pro-drug of APV that is better absorbed and can be

given at a dose of 2 pills twice daily, or 2 pills once daily with low-dose ritonavir. It is better tolerated than APV with fewer gastrointestinal side effects.

In the NEAT study, 251 treatment-naïve patients were randomized in a 2:1 open-label fashion to receive fos-APV (1400 mg bid) or nelfinavir (NFV) in combination with abacavir (ABC) and 3TC [Rodriguez-French A, et al. Abstract H-166]. In a preliminary 24-week analysis, 73% of the fos-APV recipients achieved an HIV RNA of <400 c/mL compared with 54% of those taking NFV (ITT analysis, 95% CI 6%, 31% for the difference between arms). Using the <50 c/mL assay, results were 54% vs 40%. In an as-treated analysis, 87% and 79% achieved an HIV RNA <400 c/mL, respectively. Virologic response was similar between arms among patients with baseline viral loads <100,000 c/mL. However, responses diverged in those with higher viral loads, with 71% vs 35% attaining HIV RNA <400 c/mL (42% vs 11% < 50 c/mL) in the fos-APV and NFV arms, respectively. It should be noted that while the difference between the performance of fos-APV and NFV was striking among patients with high viral loads, there was also a less pronounced difference in virologic response among the fos-APV recipients themselves: 62% with baseline viral loads <100,000 c/mL achieved an HIV RNA <50 c/mL compared to 42% with baseline viral loads >100,000 c/mL. Grade 2-4 diarrhea was observed in 17% of patients randomized to receive NFV and in 5% of those taking fos-APV.

This trial suggests that fos-APV will be an attractive improvement over the current formulation of APV, with excellent tolerability, convenient dosing, and superior performance compared to NFV, especially in patients with high baseline viral loads.

Emtricitabine

Emtricitabine (FTC) is a once daily nucleoside analog reverse transcriptase inhibitor (NRTI) with a toxicity and resistance profile similar to that of 3TC. Saag presented preliminary results from a large trial comparing d4T with FTC, each in combination with ddI EC and efavirenz in 571 treatment-naïve patients [Abstract LB-1]. At 24 weeks, FTC was superior to d4T, with 87% vs 79% of patients achieving HIV RNA <400 c/mL ($p=0.02$), and 81% and 70% achieving HIV RNA <50 c/mL ($p=0.02$). CD4 cell count increase was 156 cells/mm³ among FTC recipients vs 119 among d4T recipients ($p<0.05$). Virologic failure occurred in 4% of those on FTC vs 10% of those randomized to d4T ($p=0.01$), and time to



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virologic failure was longer in the FTC arm, as well ($p=0.0006$). Adverse events were more common in the d4T arm, with more nausea, paresthesias, and hyperlactatemia.

This trial confirms the efficacy and safety of FTC as an NRTI component of HAART regimens. However, the differences in efficacy and tolerability seen in this trial may say more about problems with the combination of ddI and d4T than about FTC itself, and it is possible that the results would have been similar had the study been carried out using 3TC instead of FTC. Nevertheless, FTC will be an attractive new drug, especially if it can be co-formulated with other once daily agents to improve convenience and adherence.

Other Investigational Agents

• **NRTIs:** 3'-fluoro-2'-3'-dideoxyguanosine (FLG) is active against both HIV and HBV, including NRTI-resistant HIV with multiple TAMs or

multi-nucleoside resistant virus with the Q151M complex or the T69 insertion mutations [Zhang H, et al. Abstract H-182]. Related compounds have been associated with significant hepatotoxicity, so safety will be a major concern as this drug is developed.

• **Integrase inhibitors:** Merck has two candidate compounds, L-870812 and L-870810 [Hazuda DJ, et al. Abstract H-1783]. The latter is now in phase I testing. S-1360 is in phase II testing, being developed by Shionogi and GlaxoSmithKline [Kobayashi Y, et al. Abstract H-184].

• **NNRTIs:** TMC 125, from Tibotec-Virco, is a highly potent second generation NNRTI with activity against K103N and double mutants associated with resistance to currently available NNRTIs [Pauwels R, et al. Abstract H-1781]. We were hoping to have heard more by now from this exciting agent, but it is still in development, as is capravirine, another promising second generation NNRTI from Agouron.

• **PIs:** TMC 114 is an investigational PI being developed by Tibotec-Virco that has activity against PI-resistance isolates [Pauwels R, et al. Abstract H-1781]. Tipranavir, from Boehringer-Ingelheim is in more advanced stages of development, and is also active against PI-resistant virus.

• **Entry Inhibitors:** T-20 (enfuvirtide, *Fuzeon*) is a fusion inhibitor now being administered to patients in phase III trials and an expanded access program [see Bartlett, *Treatment of Experienced Patients*, p. 5]. As with any new agent, clinicians using T-20 should be careful not to defer the addition of this drug until after the patient has exhausted all other options. Not surprisingly, in the TORO-1 trial, T-20 had a better and more durable response when it was combined with drugs to which the patient's virus was susceptible [Lalezari JP, et al. Abstract H-1074]. A related

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International HIV Workshop on Management of Treatment-Experienced Patients

By John G. Bartlett, M.D.

This pre-conference workshop, directed by John Mellors and Julio Montagner, took place September 26 and 27 in San Diego. A summary of the presentations addressing the state-of-the-art for treatment experienced patients follows.

HCSUS Experience

Sam Bozette reviewed the experience of the HIV Costs and Services Utilization Study (HCSUS), which is the \$30 million RAND analysis of HIV care in the U.S., and presented the following conclusions:

- In 1995, approximately 200,000 patients in the U.S. were receiving antiretroviral therapy.
- About 94% of patients who had received HIV care had been treated with antiretroviral drugs.
- A major challenge in HIV care is delayed detection of disease. Specifically, 35% of HIV-related deaths in 2000 occurred in patients who

were diagnosed within 6 months of their death. About 50% of those who died had never been treated with antiretroviral drugs. Fifty-six percent of patients with an AIDS-defining diagnosis were "late testers," and 44% developed AIDS while in care.

- Among patients currently in care, 24% had viral loads <50 c/mL, 51% <5,000 c/mL, and 65% <20,000 c/mL.
- Resistance data, which have been summarized previously by Doug Richman, demonstrate that approximately 100,000 of 135,000 (74%) patients on treatment with a viral load >500 c/mL have at least one major resistance mutation.

Bozette concluded that a major challenge for HIV care is to find those who are infected and, in terms of total numbers, this may be substantially more important than dealing with salvage therapy.

Adherence/Physician Experience

Robert Hogg reported his experience at the University of British Columbia with 1,219 patients. He noted that >95% adherence is often cited as the requirement for virologic suppression; however, his analysis concluded that adherence of $\geq 75\%$ of prescribed doses contributes substantially to survival, as reported in his prior study [*AIDS*2002;16:2065]. Low socioeconomic status contributed to reduced survival, but there was no increased risk in a subset analysis restricted to low income patients who were given HAART. The conclusion was that there is a need to establish therapeutic guidelines to insure equitable access. Another major factor emphasized by the author was the role of physician experience, which validates the reports from others [*J Acquir Immune Defic Syndr* 2000;24:106].

Co-morbidity

Amy Justice reported her experience with a three-site study in the VA (VACS-3), which includes 881 adults. Common medical co-morbidities were hepatitis (53%), hypertension (24%), and hyperlipidemia (17%). Also, 46% had significant symptoms of depression (CES-D test), and 21% were at risk for excessive alcohol use (AUDIT test). These co-morbid conditions were considered more important than AIDS for both survival and poor quality of life. In patients with advanced HIV (CD4 count <200 cells/mm³), the major indicators of poor prognosis were increased transaminase, anemia, peripheral neuropathy, renal failure, and pancreatitis. For those with earlier stage HIV infection (CD4 count >200 cells/mm³), the major indicators for decreased survival and quality of life were hypertension, coronary artery disease, and hyperlipidemia. Both AST and hemoglobin showed

an "astonishing interaction" with other factors in survival. The author concluded that non-HIV-related co-morbidities, including general medical and psychiatric diagnoses, are critical factors that must be addressed in the management of HIV infected patients.

Host Immunity

Michael Lederman discussed the possibilities for a therapeutic vaccine. The challenge is enormous: 1) There is no precedent (e.g. no therapeutic vaccine for any disease). 2) HIV is characterized by immune deficiency which obviously hampers this approach to therapy. 3) There is substantial strain variability and mutational escape. 4) There are no good assays for measuring immune response. Despite these obstacles, the author concluded that HIV infection is unique, we now have better vaccines and adjuvants, and that prior tests of this approach to treatment may have been too demanding.

Resistance

Veronica Miller summarized several points, as follows:

- Resistance testing in untreated patients with acute HIV infection has shown at least one major resistance mutation in 6.7-12%, according to studies performed from 1999-2002. Some have reported somewhat sequential results that have not clearly progressed over time, including Little and colleagues, who showed resistant mutations in 3.4% of HIV strains from 264 patients studied in 1995-98, 12% of 113 patients studied in 1999-2000, and 6.7% of 122 patients studied from 2000-2002.
- Clinical implications of baseline resistance in untreated patients seem unclear due to variations in reports. Some show no association between baseline resistance and treatment results [Abstract 167], and others show a significantly greater reduction in the viral load response for those without baseline resistance.
- Measurement of resistance off treatment is problematic because of re-emergence of wild-type virus at 8-11 weeks after treatment is discontinued.

The author concluded that the association between resistance and outcome depends on the method of measuring outcome. The association with viral load is more clear than the association with CD4 cell count changes, and clinical outcome has not been well addressed.

Pharmacokinetics

Courtney Fletcher presented the following possibly important observations as examples of the utility of pharmacology studies:

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International HIV Workshop on Management of Treatment-Experienced Patients

- Concentrations of saquinavir are higher in women.
- There is substantial penetration of EFV into the CNS.
- Both trough levels and AUC seem to correlate with viral suppression.

The author also presented his concept of a “composite concentration index,” which includes intracellular measurements of triphosphate concentrations of nucleosides. His conclusion was that there is a pressing need to merge virology and pharmacology.

One Class Failure

Roy Gulick summarized multiple studies indicating that a first regimen failure can usually be managed successfully with a second regimen, including Merck 035, Merck 039, DuPont 020, ACTG 388, ACTG 364, and Abbott 462. Some studies have shown that failure with PI monotherapy can be managed by simply adding nucleosides; examples included Merck 035, in which AZT/3TC was added to indinavir monotherapy, and ACTG 378, in which amprenavir monotherapy was later supplemented with d4T/3TC. Gulick also emphasized the changing philosophy of managing virologic failure. In 1998, the recommendation was for an entirely new regimen. However, GART and other studies showed that viral breakthrough is usually not associated with resistance to all drugs, making selection based on resistance testing feasible. Nevertheless, he emphasized that a change in therapy should occur early in the course of virologic failure. Gulick concluded by reiterating his strong impression that “failure begets failure” is an erroneous concept when applied to failure following the first regimen.

Two and/or Three Class Failure

Julio Montagner presented his experience with “mega-HAART.” His work has shown that at 24 weeks, 50% achieved a viral load of <400 c/mL and 40% achieved a viral load of <50 c/mL. He cautioned about the complexities of mega-HAART with the following examples: The combination of lopinavir/ritonavir (LPV/r) 3-4 caps bid plus amprenavir (APV) 750 mg bid shows a complex pharmacokinetic interaction; LPV/r 3-4 caps bid plus indinavir (IDV) 600 mg bid requires monitoring for renal toxicity; when prescribing the combination of LPV/r 3-4 caps bid plus saquinavir (SQV) 1,000 mg bid, clinicians should use the *Inivirase* rather than the *Fortovase* formulation of SQV to decrease toxicity. Some of these combinations will require therapeutic drug monitoring due to these complex interactions.

He finished by claiming the availability of new drugs will magnify the options.

Studies of T-20

Joe Eron presented the results of two phase III studies of the new peptide fusion inhibitor, enfuvirtide (T-20). TORO-1 included 491 patients in North America and Brazil who had failed multiple antiretroviral regimens. This group had a median baseline viral load of 5.2 log₁₀ c/mL, a mean of 12 prior antiretroviral agents, and 80% had ≥5 resistance mutations. Results at 24 weeks showed that T-20 recipients had a mean reduction in viral load of 1.7 log₁₀ c/mL compared to 0.76 log₁₀ in the control group. TORO-2 was similar in design and involved 504 patients in Europe and Australia. In this group the mean reduction in viral load at week 24 was 1.3 log₁₀ c/mL in T-20 recipients compared to 0.65 log₁₀ c/mL in control. The most common side effect was reaction at the injection site, but only 3% of participants in both studies discontinued treatment because of adverse reactions.

Resistance Monitoring

James Harrigan presented the following observations regarding resistance testing:

- The latest resistance test underestimates cumulative drug resistance, especially NRTIs.
- Studies in British Columbia in treatment-experienced patients found that NRTI resistance decreased from 1996 to 2002, PI resistance mutations have leveled at 20%, and the rate with NNRTIs is about 50%.
- The most common PI mutations are 90M, 10I and 71V; the most common NRTI mutations are 41L, 215Y and 184V.
- Many mutations are selected that have not been characterized for clinical significance.

Harrigan concluded that interpretation of resistance test results is complex.

Adherence Monitoring

John Urquhart noted that the main problems are under-dosing and intermittent or delayed use. Many patients have good “taking” compliance but poor “timing” compliance.

Viral Load Monitoring

Diane Havlir observed that long-term viral suppression is best predicted by baseline VL and post-treatment nadir. “Blips” do not predict failure, but “bumps” (sustained VL >500 c/mL) do. CD4 count predicts symptoms, so should the goal be VL suppression or CD4 count increase? Switching based on VL is most appropriate at earlier stages of disease, due to the need to preserve options at this stage.

Immunologic Monitoring

Alan Landry noted that virologic failure is associated with or predicted by the following:

- Baseline CD4 <125/mm³ (ACTG 890)
- Increased CD8 activation (ACTG 315)
- Absent lymphocyte proliferation assay response to p24
- Decreased thymic output
- Absent naïve CD4 cell response
- Reduced memory CD4 cell response

Despite the interest in immunologic monitoring, the tests reported here other than a simple CD4 count are generally available only in research labs.

Conclusions

The workshop provided a good review of HIV treatment failure with relatively sparse information that could be used by experienced care providers in their clinics the next Monday. However, there were some points worth emphasizing:

- The biggest challenge is to find people with HIV infection who haven't been diagnosed.
- HIV-infected patients under treatment have complex psychiatric and general medical conditions that require multidisciplinary non-ID resources.
- Adherence is accepted as a critical factor in outcome, but the “95% rule” may oversimplify the issue since lower levels of adherence may still lead to clinical benefit, and timing is an under-appreciated determinant.
- Rescue treatment after one regimen failure is often easy. It gets tougher with subsequent treatment failure.
- Therapeutic drug monitoring is topical, but specific recommendations that result in better clinical outcomes have not been established.
- Genomics are presumably important, but we don't have any useful applications yet.
- Resistance testing is now the standard of care for virologic failure, but it seems best for defining which drugs shouldn't be used. Old tests and drug history are critical, and the previous rule stressing the need to change all drugs is obsolete.
- Immunologic monitoring includes multiple studies that measure CMI response and competency of new CD4 cells, but the only test available to most clinicians is a CD4 cell count.
- Virologic control is the goal, but CD4 counts predict morbidity, and “failing” therapy still benefits patients who have no other options.
- The most important rule for achieving virologic success is to change early in the course of failure.
- There are several new drugs in development, but the most exciting, most potent, most expensive, and most near to FDA approval is T-20. ▲



HIV Notes from the 40th Annual Meeting of the Infectious Diseases Society of America

By Emily J. Erbelding, M.D., M.P.H., Gregory M. Lucas, M.D., and Rajesh T. Gandhi, M.D.

While IDSA is generally not the venue for breaking HIV treatment data, there was some new information regarding laboratory monitoring strategies for resource-poor countries, rising HIV risk behaviors, adherence, complications of therapy, and vaccines presented at this year's conference in Chicago.

Immune Status Monitoring in Resource-Poor Countries

Developing surrogate measures predictive of immunocompromise that are inexpensive and feasible for use in resource-poor settings will be critical to the success of AIDS treatment in Africa. Spacek and colleagues presented an analysis comparing strategies for identifying patients who would benefit clinically from initiation of HAART in settings where flow cytometry is not consistently available [Abstract 27]. Within the Johns Hopkins HIV cohort database, a CD4 count of 200 cells/mm³ was correlated with a total lymphocyte count (TLC) of 1200, adding validity to the recent WHO recommendations for initiation of HAART [http://www.who.int/HIV_AIDS/CARE/Scaling_UP_ENG_021002.pdf]. Adding a second criterion of hemoglobin ≤ 12 g/dL improved the predictive value of TLC alone for both men and women. When the TLC value was "intermediate," using hemoglobin increased the sensitivity of detecting a CD4 count ≤ 200 cells/mm³, suggesting that this might be a useful low-cost staging strategy in resource-poor settings where HAART will be initiated.

STDs and HIV Transmission Risk

- **Syphilis and HIV:** Syphilis may be mounting a resurgence among those with HIV infection, particularly among men who report same sex contact as an HIV transmission risk. Wong and colleagues reported estimates of syphilis incidence in San Francisco among HIV-infected men [Abstract 665]. Health department surveillance data indicated that syphilis incidence among men with HIV infection was approximately 525/100,000. A second estimate was calculated from additional serologic testing for syphilis performed on specimens sent for HIV viral load testing from 10 HIV primary care sites. The latter method indicated a primary/secondary syphilis rate of 1864 cases/100,000 (The current rate for the U.S. population as a whole is 2.2 cases/100,000). The authors concluded that syphilis rates among HIV-infected men were extraordinarily high in their community and that effective prevention programs targeting those with HIV infection, particularly men who have sex with men, are urgently needed.

- **Reducing STD risk in those with HIV infection:** Preventing those with known HIV infection from continuing to expose others to HIV is a critical component of the U.S. HIV prevention strategy. Data on high risk sexual and drug use behaviors in women admitted to the inpatient HIV service at Jackson Memorial Hospital in Miami, Florida suggest that the hospital setting might provide opportunities to address transmission behaviors intensively [Brewer TH, et al. Abstract 543]. Among 73 hospitalized women, 80% had symptomatic AIDS, but only 27% were prescribed HAART. Twenty-nine percent reported ≥ 4 sex partners in the past year, with 14% reporting recent exchange of sex for money or drugs. Inconsistent attendance at primary care visits was also common, with fewer than 25% keeping 2 or more scheduled primary care visits over the past year. Overall, the findings demonstrate that hospitalized patients may benefit from aggressive case management to improve individual health outcomes, but also that the hospital setting may provide a unique opportunity to improve community health outcomes through more aggressive STD screening and risk reduction interventions.

Adherence

- **HAART "Dry Run":** Mock trials using candy have been advocated as a way to familiarize patients with the rigors of taking antiretroviral therapy and potentially to improve adherence when actual therapy is initiated (<http://www.hivatis.org>). However, like many commonly cited adherence interventions, this strategy is untested. Eggleston and co-workers randomized 60 patients initiating HAART to a 2-week mock trial of methylcellulose capsules (designed to approximate the planned antiretroviral regimen) or no intervention [Abstract 488]. In an intent-to-treat analysis, 65% of patients in the mock trial arm achieved HIV RNA < 400 c/mL compared to 59% in the control group (P=NS), indicating no benefit from routine use of mock ART trials.
- **Adherence and Resistance:** Non-adherence is widely believed to be the most important determinant of viral suppression and development of drug resistance. However, evidence increasingly suggests that the relationship between adherence and resistance is not linear. Howard and colleagues monitored antiretroviral adherence with MEMS caps in 114 HIV-infected patients on methadone maintenance in New York [Abstract 460]. Adherence was strongly associated with viral load suppression. A subset of 30 patients with virologic failure during the study (HIV RNA $> 1,000$ c/mL)

had genotype resistance assays performed. Among this viremic subgroup, the mean number of resistance mutations was 1.3 in patients with low adherence and 4.8 among those with high adherence (P=0.009). A recently published study of IDV concentrations in hair samples of HIV-infected patients taking this drug also suggested a parabolic relationship between adherence and development of antiretroviral resistance [Bernard L, et al. *Ann Intern Med* 2002;137:656]. In this study, patients with viral suppression had the highest mean IDV concentration, viremic patients who had developed PI resistance mutations had an intermediate mean IDV concentration, and viremic patients without detectable PI resistance had the lowest mean IDV concentration. The hypothesis is that, in the absence of viral suppression, higher levels of adherence exert greater selective pressure on HIV, and create circumstances most favorable to progressive development of resistance.

- **Directly observed therapy (DOT):** Interest in DOT for HIV continues to grow, particularly now that novel once daily HAART regimens can be fashioned [Singh K, et al. Abstract 485]. Lucas and colleagues reported that HAART DOT in a methadone maintenance clinic was associated with a trend toward a greater likelihood of achieving HIV RNA < 400 c/mL compared to a matched, but non-randomized, comparison group receiving standard care (76% vs 54%, P=0.08) [Abstract 489]. Dieckhaus monitored adherence with electronic bottle caps in HIV-infected prisoners taking self-administered therapy (SAT) and as part of a DOT program [Abstract 484]. Mean adherence was 89% for SAT and 75% for DOT (P=NS). The author suggested that currently existing DOT programs in prisons should not be assumed to improve adherence compared to SAT, particularly if understaffed or associated with stigmatization. Randomized controlled trials of HAART DOT are now needed.

Complications and Opportunistic Infections

- **Coronary Artery Disease (CAD):** It is clear that ART is associated with insulin resistance, hyperlipidemia, and centripetal obesity, all factors strongly associated with CAD. Major questions at this time include: 1) Are HIV-infected individuals at higher risk for CAD than matched patients in the general population? 2) Does HIV infection itself impart increased CAD risk? 3) Are specific antiretroviral agents associated with increased CAD risk? 4) If so, do drugs increase risk independently of identifiable effects on glucose and lipid metabolism?



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In a symposium (S78), Judith Currier reviewed available evidence on the risk of CAD in HIV-infected patients. To date, the data from large cohorts are mixed. A report from Kaiser Permanente, including 14,823 and 189,628 person-years of follow-up in HIV-positive and HIV-negative men, respectively, suggests that CAD rates are significantly higher in the former rather than the latter group, regardless of treatment status in the former [Klein D, et al. *J Acquir Immune Defic Syndr* 2002;30:471]. In contrast, CAD rates were similar in HIV-infected, untreated men and age-matched men in the general population in a French study with 36,907 person-years of follow-up [Mary-Krause, et al. 8th CROI, Abstract 657]. Both the Kaiser study above and a U.S. Veterans Health Administration study [Bozzette, et al. 9th CROI, Abstract LB9] found no evidence that PIs are associated with a higher risk of CAD. The latter study, involving 121,936 person-years of follow-up, reported slightly decreasing rates of admission for cardio- or cerebrovascular events in HIV-infected patients from 1993 to 2001 (1.6 to 0.9 events/100 person-years), despite dramatic increases in the use of PIs and steep declines in overall mortality (18 to 5 deaths/100 person-years). In contrast, a small study from Frankfurt noted a significantly increased risk of CAD with HAART use [Rickerts V, et al. *Eur J Med Res* 2000;18:329]. Similarly, the French study found a dose-response relationship, with longer duration of PI use associated with increased rates of CAD events [Mary-Krause, et al. 8th CROI, Abstract 657]. Undoubtedly the picture will be clearer in upcoming years. HAART has only been in widespread use for 5 years, and substantial lag time would be expected between use of new therapies and CAD events, particularly in age groups at low baseline risk for CAD.

• **Gynecomastia and EFV:** There have been case reports of gynecomastia in patients on efavirenz-containing regimens [Caso JA, et al. *AIDS* 2001;15:1447]. In a retrospective case control study, Rahim and colleagues found that EFV-containing regimens were strongly associated with the development of gynecomastia (OR 20, 95% CI 4.86-88.94) [Abstract 472]. No other antiretroviral agent was associated with this finding. Prolactin levels were normal in seven cases in which it was measured. Prospective studies in which patients are randomized to regimens that do or do not contain EFV, such as ACTG 384, may help clarify the timing and strength of the association between gynecomastia and EFV-containing regimens.

• **HHV-8:** M. Gandhi from UCSF presented a study on the rate of HHV-8 shedding in HIV

infected women in the WIHS cohort [Abstract 826]. In a study of 66 women, the rate of HHV-8 shedding in saliva was higher in women whose CD4 count was >350 cells/mm³ and whose CD4 cell count nadir was never <200 /mm³. One possible explanation for this finding is that CD4 cells promote HHV-8 replication in other cell types, such as B cells. Orogenital or oral-oral transmission of HHV-8 may account for the continued high prevalence of this infection in men who have sex with men during a time period that HIV-1 prevalence has fallen [Osmond DH, et al. *JAMA* 2002; 287:221].

Vaccines

Two presentations focused on reviewing the current status of HIV vaccine development. Feinberg from Emory discussed recent studies of a number of vaccine candidates that result in control of viral replication in animals but do not induce sterilizing immunity [Symposium 17]. If such approaches work in humans, control of viral replication may delay progression to clinical disease and slow transmission. Feinberg pointed out that widespread smallpox vaccination, if adopted to counter bioterrorism threats, may interfere with one promising strategy for boosting HIV immune responses, the viral vector modified vaccinia Ankara, which is related to the smallpox vaccine. Graham from the NIH reviewed the HIV vaccine pipeline [Symposium 79]. Graham reported that canarypox vaccination will not go forward in U.S. phase III trials since the rate of CTL response induced was only about 15-20%. DNA vaccines and recombinant adenovirus vectors are going forward in human trials. Of note, these strategies are also being tested as therapeutic vaccines for individuals who already have HIV.

Addo from Bruce Walker's group presented data on CD8⁺ cytotoxic T lymphocyte (CTL) responses in 50 HIV-1 controllers (i.e. subjects with VL <1000 c/mL) [Abstract 30]. The CD8 immune responses in these individuals were most commonly directed against regions of HIV gag, pol and nef, but every HIV gene product can be targeted in infected individuals. Importantly, there was no difference in either the magnitude or breadth of the CD8 response between HIV-1 controllers and 29 untreated HIV⁺ individuals who were not controllers. There may be other immunologic explanations for viral control, such as the maturity of CD8 cells or the level of HIV-specific CD4 helper responses. This study suggests that in evaluating HIV vaccine strategies, we will need to assess the functional characteristics of the immune response in addition to the magnitude and breadth.

Conclusions

This year's IDSA included a smattering of new data across a broad range of HIV topics. In resource-poor areas, total lymphocyte count and hemoglobin may provide a cost-effective surrogate to CD4 cell count monitoring. Skyrocketing rates of syphilis in MSM in San Francisco make the case that risk reduction strategies are urgently needed. Use of DOT for ART continues to attract attention as once daily regimens become more available. HAART seems likely to increase CAD risk in some, but observational studies to date have produced mixed results. Finally, while vaccine progress is being made, new insights into the complex interplay between HIV and the immune system continues to underscore the challenges of this endeavor. ▲

New Drugs and Antiretroviral Therapy for Naïve Patients

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compound, T-1249, is being investigated in phase I/II clinical trials [Gulick R, et al. Abstract H-1075]. Unlike T-20, it can be dosed once a day and is active against T-20-resistant isolates. The most common adverse reactions with both agents are injection site reactions. Other entry inhibitors include co-receptor antagonists, such as SCH-C, which interferes with viral binding to the CCR5 co-receptor [Doms RW, Abstract H-1782]. BMS-806 inhibits viral entry by blocking the interaction between gp120 and the CD4 receptor [Lin P, et al. Abstract H-181].

Conclusions

Perhaps the most important data pertaining to the treatment of antiretroviral-naïve patients were the NEAT study, comparing fosamprenavir with nelfinavir, and, despite its somewhat confusing findings, the BMS-034 trial, comparing atazanavir with efavirenz. The NEAT trial also provided promising data on fosamprenavir. In addition, studies such as GS 903 continue to suggest that there are real differences between agents with respect to their potential for causing long-term toxicity. Emerging data and development of new antiretroviral agents offer clinicians and patients a greater variety of options to choose from, and allow for easier dosing, better tolerability, and possibly less long-term toxicity. Indeed, optimists might argue that long-term toxicity may not be an inevitable outcome of antiretroviral therapy, though longer-term data will be needed to support their optimism. ▲



Report on Adherence From the XIV International AIDS Conference in Barcelona

By Beulah Perdue Sabundayo, Pharm.D., M.P.H.

Investigators and clinicians continue to be interested in predicting, measuring, and improving adherence to highly active antiretroviral therapy (HAART). However, new information was sparse at the International AIDS conference in Barcelona in July, despite the presentation of over 60 abstracts on the subject. Many definitions of adherence were used, without clear agreement, as evidenced by definitions based upon number of doses missed within a specified time period, appointments missed, self-report, caregiver reports, pill counts, electronic monitoring devices, and pharmacy refill records.

Can We Predict Adherence?

Several groups looked at illicit drug and alcohol use as a predictor of adherence with conflicting results. Sharpe and colleagues interviewed 1655 African American women who attended health department clinics in Georgia between July 1997 and December 2000 [Abstract 5817]. They found that women who used crack or other illicit substances were less likely to take medications as prescribed (OR 0.37 and 0.47, respectively) than non-users. Ekstrand and associates interviewed 200 people (90% men, 54% Caucasian, 28% African American, 12% Latino) who were on antiretroviral therapy, had detectable viral loads, and admitted to some recent use of alcohol or illicit drugs [Abstract 5841]. In a multivariate analysis, those who were non-adherent to prescribed regimens had more reasons for missing doses, were depressed, had less structure to their daily lives, felt more helpless/overwhelmed, and felt less able to manage side effects. In contrast to Sharpe's study, adherence was not associated with alcohol or illicit drug use. Hinkin and colleagues also evaluated the impact of alcohol, illicit drug use, and neuro-psychiatric factors on non-adherence [Abstract 5828]. Medication Event Monitoring System (MEMS) caps were used for 1 month in 142 patients. Patients >50 years of age were 4.6 times more likely to be good adherers (>90% adherence). Those who had neuropsychological impairment or neuropsychiatric dysfunction were more likely to be non-adherent (2.5 times and 4 times more likely, respectively). Current drug use, but not alcohol abuse, was strongly associated with non-adherence.

Durvasula and others looked at gender differences between 130 men and 32 women [Abstract 5823]. Mean adherence scores by MEMS caps did not differ by gender (79.6% for men versus 71.6% for women); however, the reasons for non-adherence were different.

Barriers to adherence for men were mainly cognitive, such as higher levels of efficacy and intent to follow medication recommendations, while women tended to have more practical reasons for non-adherence (care-giving duties and fewer economic resources).

Research on HAART adherence in adolescents has been limited. Hosek and colleagues interviewed 25 males and 17 females, ages 16-25 years [Abstract 5826]. No gender differences were found, but depression/anxiety and age of first marijuana use were found to be predictors of non-adherence. The most important predictors of adherence included their belief in whether the drugs would work, side effects, number of pills, and number of doses. The most frequent reasons for missing doses were forgetting, sleeping through the dosing time, and not having medications at the time of the prescribed dose.

We continue to explore the relationship between clinician and patient and whether we, as healthcare providers, can successfully predict who will be adherent. Mannheim and colleagues compared provider-estimated adherence to patient self-report [Abstract 5845]. Agreement between the two was low (Kappa=0.11). They did find that clinicians' estimates of non-adherence were primarily influenced by laboratory markers (viral load, CD4 cell count) and that patients associated non-adherence with depression and a history of psychiatric illness. Spire and colleagues also investigated the clinician-patient relationship and found a similar level of agreement (Kappa=0.25) [Abstract 5827]. When adherence was estimated to be low by either self-report or by the physician, blood levels of protease inhibitors were undetectable in 32% and 31% of patients, respectively. Similarly, for those who were deemed to be highly adherent by self-report or by physician, viral loads were undetectable in 75% of patients in both groups.

What's In a Regimen?

With so many different regimens now available, particularly for naïve or minimally experienced patients, there is a movement toward once daily regimens that are well tolerated and effective.

Roca and colleagues compared adherence of patients taking ddI (chewable buffered tabs) twice daily to adherence in the same patients after switching to the enteric coated (EC) formulation given once daily. [Abstract 5815]. Patients were considered adherent if they kept their

appointments, reported taking >80% of doses, and their HIV RNA levels were at least 1.5 log₁₀ c/mL below baseline. Data from visits taking place during twice daily dosing (-6, -3, and 0 months) were pooled and compared to pooled once daily visits (+3, +6, and +9 months). Pooled data showed significant improvement in adherence after switch to once daily therapy compared to adherence on twice daily therapy. HIV RNA was also lower with once daily therapy. No difference was observed in CD4 cell counts.

Fumaz and a group from Spain evaluated quality of life (QOL) and adherence when HAART was switched to a once daily regimen of nevirapine/ddI/tenofovir [Abstract 5834]. In this prospective study of 58 patients with baseline viral suppression, 30 were changed to the once daily regimen and 28 remained on their previous combinations. QOL measured by MOS-HIV and adherence measured by self-report were evaluated at baseline and week 12. By week 12, QOL was better in the once daily versus the twice daily group; however, adherence did not differ significantly between groups.

Knobel and colleagues looked at the impact of simplification of therapy by switching to AZT/3TC/ABC (*Trizivir*) in patients who were previously deemed severely non-adherent by self-report (<50% of doses taken in the previous 3 months or complete withdrawal from therapy) and who had viral loads in excess of 5000 c/mL [Abstract 5829]. In an intention-to-treat analysis, 44% of patients achieved a viral load of <500 c/mL (66.5% by on treatment analysis). The mean viral load change was -1.6 log₁₀ c/mL, mean CD4 count change was +124 cells/mm³, mortality was 6%, and 40% were lost to follow-up. At the end of the year of follow-up, 50% of patients reported >90% adherence to the simplified regimen of one pill twice a day.

Goelz and colleagues performed a retrospective analysis, comparing durability of 3 categories of regimens for initial therapy: 2 NRTIs + 1-2 PIs, 2 NRTIs + 1 NNRTI, and 3 NRTIs (99% of which were AZT/3TC/ABC) [Abstract 5838]. After 52 weeks, 71% of those on 3 NRTIs, 50% on NNRTI-based regimens, and 21% of those on PI-based regimens were still taking their initial regimen. Non-adherence caused a treatment change in 12% of those on PIs, 6% on NNRTIs, and 2% on NRTIs.

Antinori and colleagues reported the findings of an inter-cohort analysis of 2 Italian observational adherence studies comparing NNRTI regimens to PI-based regimens [Abstract 5852]. Non-adherence was defined as having



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missed >1 dose in the last week or having an interruption of drug supply by self-report. In a multivariate analysis, those receiving an NNRTI regimen had decreased odds of non-adherence (OR 0.56), and those who were <35 years of age or injection drug users had increased odds of non-adherence (OR 1.53 and 2.99, respectively). For treatment-naïve patients, only efavirenz-based regimens decreased the risk of non-adherence (OR 0.20).

Two groups looked at the durability of regimens as a function of adherence. Dezii and colleagues evaluated mean adherence rates to NRTIs over 3 years, based on California Medicaid pharmacy claims for 2369 patients initiating therapy between July 1994 and June 2000 [Abstract 5842]. Their data suggested that those who were poor adherers (<60%) at the start of therapy did not change their degree of adherence over time. However, for those who initially had better adherence (>60%), it waned over the 3 year period: a mean adherence of 70% in year one declined to 59% by year 3, and those who started with 91% adherence experienced a decline to 74% by year 3. Spire and associates reported on the dynamics of adherence, also over a 3-year period, for 360 patients who took part in the French APROCO cohort and who started a PI-containing regimen [Abstract 2137]. Initial adherence was measured at month 4 and over the course of month 12 through month 36. Those who were considered highly adherent (100% of doses taken) decreased over time (59.2% at month 4 versus 54.2% at month 36). Being highly adherent versus moderately adherent versus non-adherent at month 4 was significantly associated with virologic success (64.8%, 42.2%, and 35.3%, respectively), defined as an undetectable viral load at months 28 and 36 (the undetectable level was not defined) and immunologic success (60.1%, 55.2%, 38.7%, respectively), defined as a >200 cell increase in CD4 count at month 36.

Multiple Disciplines Come Together

Szabo and colleagues reported findings from a 5-stage, multi-disciplinary intensive adherence program (IAP) [Abstract 5810]. Stage I consisted of a readiness assessment performed by a social worker, intended to identify potential barriers to adherence. In Stage II the IAP team formulated a plan, and the pharmacist reviewed an intensive medication plan with the patient. Stage III involved initiation of HAART. In Stage IV, patients received phone calls and adherence visits with the pharmacist during the first 2 weeks of therapy, along with a visit with their care provider

at week 4. Stage V involved the chronic maintenance phase of follow-up, consisting of phone calls, pharmacist and care provider visits, and questionnaires. Between December 1999 and September 2001, 23 patients (14 antiretroviral-naïve) were screened for IAP. Multiple barriers were identified in 57% of patients. At 6 months, 53.8% of patients achieved a viral load of <50 c/mL. After a mean of 10.2 months on therapy, there was a mean increase of 76 CD4 cells and viral load decreased from a mean of 244,000 c/mL to 8800 c/mL. Only 38.5% of patients had viral loads <50 c/mL (61.5% were <400 c/mL).

Carmona reported a subgroup analysis of a prospective, multicenter study on improved adherence in severely non-adherent patients (defined as <70% adherence by self-report) who received ongoing individualized counseling with a treatment adherence counselor (TAC) [Abstract 1365]. TAC sessions were performed at baseline and at 3, 6, and 12 months after starting therapy by either a nurse or pharmacist, in addition to adherence counseling by a physician (standard of care). At month 12, adherence was improved to >90% in 76% of those who received TAC as opposed to 56% of those who received standard of care. For those who received TAC, 45% had a viral load <500 c/mL vs 33% of those who received standard of care.

Caprio and colleagues described the impact of a multi-disciplinary adherence team (ACT) on improving adherence among indigent women in Houston [Abstract 5857]. ACT consisted of a nurse, pharmacist, HIV-infected peer counselor, and a social worker/drug use specialist. Antiretroviral-experienced patients (57%) had a mean baseline adherence rate of 67%, which improved to 90% and 92% at weeks 4 and 8, respectively. Antiretroviral-naïve patients had 98% and 100% adherence at weeks 4 and 8, respectively. After 8 weeks, 73% of patients had >1.5 log₁₀ decline in viral load.

Bentz and colleagues evaluated the effect of counseling by a trained adherence nurse [Abstract 5867]. This prospective, randomized controlled trial compared 123 people in the intervention group to 121 in a control group. Patients in the intervention group received 3 counseling sessions with a nurse. Adherence was significantly higher in the intervention group (75% vs 61%) at 6 months. In addition, there was a significant difference in the mean decrease in viral load in the intervention group versus the control group.

Ashraf and associates described an educational pilot project, "Project Adherence,"

which included a team of educators (a nurse, pharmacist, and social worker), all experienced in the care of HIV-infected patients [Abstract 5873]. The 134 patients enrolled in this program had previously failed treatment and had a history of poor compliance to clinic appointments. After 6 weeks of adherence education, 71% had an improvement in virologic suppression, 35% had viral loads <400 c/mL, and 10% had >1 log₁₀ decline in viral load.

Myers and colleagues reported their experience with a short-term directly observed therapy (DOT) intervention for patients with refractory non-adherence [Abstract 5868]. Patients were referred to the "Success Through Anti-Retroviral Therapy" (START) DOT program for a 4-6 week admission to a skilled nursing facility in which volunteers, social workers, and medical staff supervised therapy. HIV education and support groups were also utilized during the stay. After discharge, 85 patients were followed for a mean of 24 months and 75% maintained adherence to therapy by self-report and care providers. At 24 months, 48% maintained a viral load of <1000 c/mL and 19% sustained a viral load of <50 c/mL.

Comparing Electronics

Bova and colleagues questioned whether electronic monitoring devices (EMD) should be considered the reference standard for measurement of adherence [Abstract 5821]. They described an exploratory study of EMD in 172 patients who were enrolled in a 15-month randomized controlled trial and who were treated with 3 or more drugs. Interviews were conducted throughout the study period and a structured questionnaire was administered at month 12. Thirty-six percent of patients admitted to not using the EMD consistently; 41% took out more than 1 dose at a time; 26% reported opening the bottle but not taking the medication; 29% said use of a pillbox was a major barrier to EMD use; and social problems accounted for 11% of all reported problems with EMD use.

In contrast, Deschamps and colleagues compared electronic event monitoring (EEM), which they referred to as the "gold standard," to patient self-report and physician assessment of adherence [Abstract 2136]. When asked about the effect EEM had on their pill-taking habits, 26% felt EEM had a positive effect, 14% reported a negative effect, and 60% felt it had no effect. Many patients (84%) complained about

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Women's Health Issues: News from the XIV International AIDS Conference in Barcelona

By Jean Keller, P.A.C., Judy Lee, M.D., and Jean Anderson M.D.

Attention to HIV's devastating effect on the lives of women around the globe continues to grow, and women's issues were well represented at the XIV International AIDS Conference. This article presents highlights from the conference (complete coverage can be found on the Johns Hopkins AIDS Service website, <http://hopkins-aids.edu>).

Prevention of Mother to Child Transmission (MTCT)

- **Developed Countries:** Observational data on the use of HAART in pregnancy from the U.S. [Morris, Abstract 5917], Italy [Melzi, Abstract 3682], Brazil [Nogueira, Abstract 5912], and Argentina [Coll, Abstract 6269] continue to show the lowest rates of MTCT with these regimens. Out of a total of 414 women on HAART in these uncontrolled series (data on mode of delivery and viral load was not consistently reported), there was a transmission rate of 0.5%.

This would seem to be a good omen for the ultimate eradication of perinatal HIV/AIDS in areas where HAART is available and accessible. However, a report from the Pediatric Spectrum of HIV Disease cohort in the U.S. demonstrated that many opportunities for perinatal HIV prevention are still missed [Peters VB, et al. Abstract 1429]. In an examination of HIV-exposed infants between 1996 and 2001, a missed opportunity for prevention of MTCT was identified in 56% of cases. Of these, 18% of mothers had no prenatal care, 29% had prenatal care but were not tested for HIV infection, and 9% were known or found to be HIV-infected but did not receive antiretroviral prophylaxis. Illicit drug use was a significant predictor of lack of prenatal care. These findings support current recommendations by the American Medical Association, the Institute of Medicine, the CDC, and the American College of Obstetricians and Gynecologists that HIV testing be made a routine part of antenatal care for all women.

- **Developing Countries:** Prevention of MTCT continues to garner major attention as the gulf between the developing world, where over 95% of new infant infections occur, and the developed world, where availability of HAART has led to near eradication of pediatric AIDS, continues to widen. In low-resource settings where HAART is not yet available, clinical trials have demonstrated that short courses of AZT, AZT/3TC, or nevirapine (NVP) are all associated with reductions in MTCT in both breastfeeding and non-breastfeeding

populations. These may have relevance for settings in developed countries when HIV infected women present late in pregnancy or in labor without having had prior treatment.

The success of NVP in reducing MTCT has prompted further study of regimens combining AZT and NVP given to the mother and/or newborn to determine whether these regimens might reduce MTCT further. In a late breaker session, Lallemand and colleagues reported preliminary results of a randomized, double-blind, placebo-controlled clinical trial in Thailand comparing (1) AZT beginning at 28 weeks and continuing through labor plus 1 week of AZT given to the newborn (reference regimen), (2) the reference regimen plus NVP given to the mother in labor and to the newborn, and (3) the reference regimen plus intrapartum NVP only [Abstract LB22]. At the first interim analysis the reference arm of AZT alone was discontinued because it was associated with a significantly higher transmission rate than the NVP intrapartum/neonatal arm ($p < 0.001$). Enrollment continues in the two NVP arms. It should be emphasized that in the setting of a developed country, where most women receive HAART and where elective C-section is commonly employed, the addition of the intrapartum/newborn NVP regimen to existing HAART regimens did not offer additional benefit [Cunningham CK, et al. *J Infect Dis* 2002;186:181].

Two studies examined the use of AZT and NVP for post-exposure prophylaxis with newborn-only administration. This is an important topic to explore, since in many areas of the world, and especially in low resource settings, women of unknown HIV status may present in labor and may deliver before HIV status can be determined or before antiretroviral prophylaxis can be administered to the mother. Furthermore, the effectiveness of post exposure prophylaxis given to the newborn alone would eliminate the risk of precipitating antiretroviral resistance in mothers (although similar concerns would remain about resistance in the infant). In an open label, randomized clinical trial in Malawi, a single dose of NVP plus one week of AZT provided significantly more protection than a single dose of NVP alone [Taha TE, et al. Abstract 1427]. However, in a trial from South Africa, HIV-exposed infants randomized to NVP vs 6 weeks of AZT had statistically similar transmission rates at 6 weeks [Gray, Abstract LB13].

Antiretroviral Resistance in Prevention of MTCT

The feasibility of NVP monotherapy for prevention of MTCT has been tempered by concerns about resistance, since NNRTI resistance was detected in 19% of women in HIVNET 012 at 6 weeks postpartum. In a late breaker poster session, Sullivan and colleagues reported on selection of resistance mutations in women and infants enrolled in the SAINT trial, in which pregnant women were randomized to receive two doses of NVP plus single dose NVP to the infant at 72 hours after birth, vs AZT/3TC in labor and for one week after delivery for mother and infant [Abstract LB9024]. NVP resistance mutations were detected at 6 weeks post-partum in 74 of 111 (67%) women who received NVP, but no AZT/3TC resistance was detected in the 37 women receiving this therapy. At 9 to 12 months, 78% of 36 evaluable women with initial NVP resistance had reversion to wild-type virus. Of 40 infected infants exposed to NVP, 53% had NVP resistance mutations at 4 to 6 weeks of life.

More reassuring was a report from Thailand which found NVP resistance in only 5% of mothers at 1 month post-partum when single-dose NVP was combined with short course AZT from 34 to 36 weeks to labor, intrapartum, and 4 weeks to the infant, [Leelawiat W, et al. Abstract 3124]. Three infants were infected and one had NVP resistance mutations. No AZT resistance was detected in mothers or infected infants. These data suggest that the risk of developing resistance with preventive therapy for MTCT may be reduced by using combination nucleoside therapy or adding a nucleoside to NVP, compared with NVP monotherapy. These studies confirm the need for further efforts to minimize both MTCT and the development of antiretroviral resistance in resource-poor settings.

Antiretroviral Therapy and Birth Defects

Both health care providers and pregnant women frequently raise concerns about drug-related birth defects associated with the use of antiretroviral therapy. A report from the Antiretroviral Pregnancy Registry should be reassuring. A review of birth defects in infants exposed to antiretroviral agents in the first trimester through January 2002 found a rate of 24 per 952 live births, which is not an increase over the general population-based prevalence. Rates were similar with exposure to regimens with and without protease inhibitors [Garcia PM, et al. Abstract 5955]. These data and others



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[Tuomala RE, et al. *N Engl J Med* 2002;346:1863] suggest that the risk of birth defects and adverse pregnancy outcomes using currently available antiretroviral agents is minimal, the notable exception being efavirenz. However, ongoing surveillance is paramount, as the aggregate experience with antiretroviral therapy is still limited.

MTCT from Breastfeeding

In a meta-analysis of 9 clinical trials evaluating the role of late post-natal transmission of HIV via breastfeeding (defined as infant infection diagnosed after 4 weeks of age with prior negative test[s]), 1509 children were evaluated, with a mean duration of follow-up of 12.2 months and mean duration of breastfeeding 6.8 months [Read JS, et al. Abstract 1177]. Overall transmission rate was 25% (378/1509). Of the infected children, timing of infection could be categorized in 179, and 36% of these infections were due to breastfeeding, reinforcing the significance of this mode of transmission between mother and infant.

HCV Vertical Transmission

In a prospective multi-center study from France involving women with hepatitis C infection, co-infection with HIV was a significant predictor of hepatitis C transmission to the infant [Barjoan, et al. Abstract 1379]. In 144 mother-infant pairs, the HCV transmission rate was 1% (1/107) in HIV-negative women, but 16% (6/37) in HIV-infected women ($P < 0.001$). No infants were HIV-infected. Four of the six HCV-infected children born to HIV infected women were delivered by elective C-section prior to rupture of membranes, suggesting that vertical transmission of hepatitis C occurs prior to the time of delivery and that C-section is not protective. Women co-infected with HIV and HCV who become pregnant or are contemplating pregnancy should receive counseling about this issue and its potential implications.

Lower Genital Tract Dysplasia

There has been much interest in the effect of HAART on progression, recurrence and regression of human papilloma virus (HPV)-related disease; several studies presented in Barcelona fueled existing controversies. A prospective study of 154 HIV-infected women on different ART regimens and with negative PAP smears but high-risk HPV (HR-HPV) present at baseline, found that immune reconstitution with antiretroviral treatment was not associated with a decrease in HR-HPV

persistence or a decreased incidence of cytologic/histologic dysplasia over a mean of 2.8 years [Lillo F, et al. Abstract 6047]. Similarly, 40 women with positive vaginal HPV were followed for at least 3 months after starting HAART and had no change in vaginal HPV viral load between two consecutive visits before and after starting HAART, even among those with successful virologic suppression [Conley LJ, et al. Abstract 7309].

In contrast, the Canadian Women's HIV study followed 132 women who had cervical dysplasia (18% of the cohort) [Hankins C, et al. Abstract 5969]. Data were available for 99 women, and 10.5% were on HAART. Overall, progression of cervical lesions was seen at a rate of 3.4/100 patient years, with persistence in 34.7/100 patient years; none of the women on HAART had progression or persistence of cervical lesions at follow-up. Women with regression of cervical lesions were also more likely to be on HAART. In a retrospective cohort of 56 women who underwent excisional treatment for high-grade cervical dysplasia, predictors of recurrence included higher mean viral load ($p=0.01$), detectable viral load >400 c/mL ($p=0.002$), lower mean CD4 count ($p=0.035$), positive margins ($p=0.05$), and no antiretroviral therapy ($p=0.019$) [Keller J, et al. Abstract 2096]. Those women who were taking antiretroviral therapy at the time of follow-up were significantly less likely to have recurrence of cervical disease after excisional treatment ($p=0.02$). In summary, data about the effect of HAART on HPV and cervical dysplasia remain mixed, and guidelines for screening and management of cervical disease are unchanged in women on HAART.

Questions also remain about the predictive value of pap smear in HIV-infected women. Anderson and colleagues evaluated a subgroup from the HERS cohort, including 189 HIV-infected women (1200 patient visits) and 95 HIV-uninfected but high risk women (602 visits) with pap smear, HPV-DNA testing, colposcopy, and biopsy if indicated, at planned 6 month intervals [Abstract 7399]. HIV-infected women were significantly more likely to have abnormal biopsy results with normal pap smears, as compared with HIV-uninfected women. Risk factors for abnormal biopsy with normal pap included presence of HPV and CD4 <500 cells/mm³. However, 17 of the 19 HIV infected women with normal pap and dysplasia on biopsy were found to have an abnormal pap within one year of the discordant results. These data do not support the need for routine colposcopy in women with HIV but underscore the need for regular cytologic screening.

Conclusions

In summary, data continue to accumulate which suggest that the use of HAART and achievement of optimal viral load suppression is associated with the greatest reduction of MTCT, although there is increasing concern about resistance with single dose NVP for both mother and child. The identification of HIV infection in pregnant women is the biggest hurdle in reducing MTCT, which underscores the importance of current recommendations that routine testing be made a part of antenatal care for all women. Lastly, the effect of HAART on the natural history of cervical dysplasia remains unclear and recommendations for evaluation and careful follow-up are unchanged. ▲

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Report on Adherence From the XIV International AIDS Conference in Barcelona

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the practicality of using EEM. Comparing rates of adherence according to the 3 measures, non-adherence was observed in 40% by EEM, 5% by self-report, and 28% by physician assessment. When compared to EEM, self-report had an accuracy of 60%, and physicians were accurate 56% of the time.

Safren and colleagues randomized 44 patients who were <90% adherent by MEMS caps in the 2 weeks prior to randomization to compare continuation of MEMS alone versus the addition of reminder interventions via pager (*MediMOM*) over a 12-week period [Abstract 5864]. Patients in the *MediMOM* group showed greater improvement in adherence by MEMS caps (55% at baseline versus 64% at week 12) than those who only continued with MEMS caps alone (57% versus 52%, respectively).

Conclusions

Research efforts continue to explore methods to improve adherence, through multi-disciplinary programs, readiness assessments, and simplification of regimens (either through decreased pill burden, less frequent dosing, or better tolerability). Our ability to predict adherence remains poor. Patients who abuse drugs or alcohol appear more likely to be non-adherent in many, but not in all studies, and other baseline characteristics appear to have little predictive value. Perhaps the best way to improve adherence is with the use of multi-disciplinary programs that provide continuous reminders from multiple members of the healthcare team. The interventions should be maintained throughout the course of therapy, not just during

the initial period, as numerous studies demonstrate that adherence is improved as long as an intervention is in place, but that it wanes over time. Additional tools may be helpful to enhance adherence, such as pillboxes or electronic devices that remind patients when a dose is due. The use of electronic monitoring devices to measure or improve adherence remains controversial, as they may underestimate adherence, and they may interfere with other behavioral interventions, such as the use of pillboxes. The data suggest that more than one method of adherence measurement should be used when evaluating how well patients take their medications. ▲

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