

THE HOPKINS HIV REPORT

A bimonthly newsletter for healthcare providers

3rd IAS Conference on HIV Pathogenesis & Treatment in Rio de Janeiro, Brazil

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3rd IAS Conference: Initial Therapy, Switching, and New Strategies

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

This July, a small group of intrepid Hopkins faculty members courageously left the balmy Baltimore summer behind to brave the infamously harsh winter of Rio, with its 75° temperatures, blue skies, and shivering scantily clad beachgoers, to attend the 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment. Rio is spectacular, of course... undoubtedly one of the most stunning cities on earth. Unfortunately, the meeting itself was held at a dreary conference center far beyond the suburbs. The conference center was deceptively named "RioCentro," which can be translated to mean "downtown Rio," but it was located somewhere near the Uruguayan border...or at least that's how it seemed after 60 to 90 minutes on the bus. Oh well...we wouldn't want our colleagues who stayed behind to be too jealous.

There was appropriate emphasis in Rio on the global epidemic and our response to it. New, clinically relevant presentations were few and far between, but here are a few of the studies pertaining to initial therapy, switching therapy, and new antiretroviral strategies.

Initial Therapy

Perhaps the most important clinical trial of antiretroviral therapy in naïve patients presented in Rio was the GS 934 study, for which 48-week data were presented by Anton Pozniak [Abstract WeOa0202]. This was a large trial in which 511 treatment-naïve patients were randomized to receive efavirenz (EFV) plus either coformulated zidovudine/lamivudine (AZT/3TC) or tenofovir DF (TDF)/emtricitabine (FTC). At 48 weeks, the primary endpoint,

virologic suppression to <400 c/mL by the FDA-mandated TLOVR (Time to Loss of Virologic Failure) analysis was significantly greater in the TDF/FTC arm compared to the AZT/3TC arm. Results were similar for the standard ITT analyses using both the <400 and the <50 cut-off. Excluding patients who were found to have had baseline NNRTI resistance, the TLOVR responses were 80% for the TDF/FTC arm and 70% for the AZT/3TC arm. The differences were primarily driven by the larger number of discontinuations due to adverse events in the AZT/3TC arm (9%) compared to the TDF/FTC arm (4%). This difference was especially notable for anemia, though there was also a suggestion of less nausea, vomiting, fatigue, and leukopenia in the TDF/FTC arm, as well.

Not surprisingly, the presence of baseline NNRTI resistance was associated with a decreased response to therapy with either regimen, emphasizing the importance of baseline resistance testing in treatment-naïve patients. Interestingly, this was not the case with baseline NRTI mutations. The analysis of treatment-emergence resistance from this study was somewhat surprising [McColl DJ, et al. Abstract TuPp0305]. The resistance analysis involved 12 patients in the TDF/FTC group and 23 in the AZT/3TC group whose viral loads exceeded



"Corcovado, Rio de Janeiro"
Photograph by Joel Meneses.

400 c/mL. As expected, NNRTI resistance mutations (K103N and others) were seen frequently, in 73% to 75% of those who failed therapy and underwent resistance testing. What was unexpected was that no patient in either arm developed K65R, which had been observed in 7 patients

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failing TDF/3TC/EFV at the end of the first year of the GS 903 study [[JAMA 2004;292:191-201](#)]. Interestingly, no patient with baseline NNRTI resistance developed K65R. In addition, although not statistically significant, M184V/I was numerically less common in patients on TDF/FTC, which had not been the case in the GS 903 study comparing TDF/3TC and stavudine (d4T)/3TC. Whether this is a real trend, and if so, whether it has to do with the difference in potency or pharmacokinetics of FTC vs 3TC is unclear. Only 1 thymidine analog mutation (TAM) was detected, in the AZT arm.

As in the GS 903 study, there was a significant difference in fasting total cholesterol favoring the TDF/FTC arm; the differences in fasting triglycerides were not significant. DXA scans were performed at 48 weeks in a subset of patients, and although these one-time results indicate that those on TDF/FTC have more limb fat than those on AZT/3TC, we will need to see follow-up data at 96 and 144 weeks before we can conclude that there is progressive lipotrophy with AZT/3TC but not with TDF/FTC.

This study has important implications for the efficacy and tolerability of initial treatment regimens. For patients who are currently on AZT/3TC and doing well, the implications of the 48-week results are less clear. However, if we see continued separation between study groups in lipids and limb fat at 96 and 144 weeks, as was seen in GS 903, then it will provide support for switching therapy despite virologic suppression.

Problems with the combination of TDF and didanosine (ddI) have been raised recently, especially at last year's ICAAC. The TEDDI trial confirmed previous reports of unacceptable rates of virologic failure with the combination of TDF/ddI/EFV; in this study, 25% of patients on that regimen experienced virologic failure by 12 weeks [[van Lunzen J, et al. Abstract TuPp0306](#)]. We also saw follow-up data from the Spanish EFADITE study, in which patients on stable suppressive antiretroviral regimens were randomized to continue their current therapy or to switch to the combination of ddI/TDF/EFV.

While most patients maintained virologic suppression after switch, a significant decline in CD4 cell count was observed in that arm (-25 cells/yr vs +46 in controls) [[Barrios A, et al. Abstract WePe12.3C16](#)]. The decline in CD4 count was associated with the use of higher doses of ddI in this study. It seems clear now that TDF/ddI is an unacceptable dual-NNRTI backbone for patients on initial therapy or who have no TAMs. For experienced patients in whom resistance testing suggest that these are the two most active NRTIs, the combination can be considered, provided the dose of ddI is reduced and the CD4 count is monitored.

Antiretroviral Strategies: Monotherapy and Switching

At the 14th International AIDS Conference in Bangkok, we heard preliminary 24-week data on an interesting strategy involving 3TC monotherapy [[Castagna A, et al. Abstract WeOrB1286, XV Int AIDS Conf, 2004](#)]. These data were updated in Rio, with 48 week results [[Castagna A, et al. Abstract WeFo0214](#)]. Eligible patients were those who intended to interrupt therapy and who already had evidence of 3TC resistance. They were randomized to either stop therapy altogether or to continue 3TC alone. Patients in the 3TC monotherapy arm experienced a slower decline in CD4 count and had a lower viral load. They experienced a lower rebound in replication capacity after interruption of HAART and were more likely to maintain pre-existing resistance mutations. However, they did not develop any additional resistance mutations as a result of remaining on 3TC. This approach may be a reasonable alternative to treatment interruption in patients who already have the M184V mutation and in whom interruption is being considered. However, it should be noted that these were not patients on salvage therapy, but were patients with fairly high CD4 counts at the time of interruption. This would presumably not be an acceptable strategy in patients with more advanced disease and more extensive resistance.

Monotherapy strategies are also being explored using boosted PIs. We heard an

update from Jose Arribas on the "OK" trial, which stands for "Only *Kaletra*." In that study, 24 of 28 patients who switched from lopinavir/ritonavir (LPV/r) + 2 NRTIs to LPV/r alone maintained virologic suppression at 48 weeks. As we heard in previous presentations of these data, those who failed LPV/r monotherapy did not develop primary PI resistance mutations and were able to achieve virologic suppression with the addition of NRTIs. The reason for virologic failure in these patients, as well as in patients taking LPV/r monotherapy in other studies, has not been explained. The possibility of incomplete penetration into anatomical or physiologic compartments has been raised, since a handful of patients appear to fail despite good adherence, adequate drug levels, and no evidence of resistance. In a substudy of the OK trial, viral load responses in the two arms were compared using a highly sensitive viral load assay with a lower limit of detection of 3 c/mL [[McKinnon JE, et al. Abstract WeOa0203](#)]. The investigators found no significant differences in viremia at baseline, week 4, or week 8. They also found no statistically significant difference in levels of viremia between those who ultimately experienced virologic failure and those whose viral loads remained suppressed, though virologic failure was typically preceded over several weeks by a rise in viremia using this assay.

An open-label, uncontrolled pilot study of monotherapy with boosted ATV, the ATARITMO trial, is also in progress [[Vernazza P, et al. Abstract WeOa0204](#)]. As of this presentation, 24 patients have reached week 24, 22 of whom have viral loads <50 c/mL. Semen and CSF samples are available in 12 of the 24 subjects at week 24. Two semen and two CSF samples have detectable viral loads, again raising the question of penetration of single drugs into specific anatomic compartments.

Given the concerns about unexplained virologic failure and possible incomplete penetration into compartments with PI monotherapy, this strategy should be reserved for patients in clinical trials, at least for now.



3rd IAS Conference: Initial Therapy, Switching, and New Strategies

The SWAN study was a study in which patients on a stable, suppressive boosted or unboosted PI-based regimen were randomized in a 2:1 fashion to stay on their current regimen or to switch to a once-daily atazanavir (ATV)-based regimen. The baseline regimen was either given twice daily and/or involved at least 3 pills per day. Patients must have been on a first or second HAART regimen and could not have failed a prior PI-based regimen. Of the 278 patients, 25 were also taking TDF and used boosted ATV. Those who switched to ATV were significantly less likely to experience viral rebound to >50 c/mL at week 24 (3% vs 8%), although viral rebound was more common among those who remained on an

unboosted PI than those were on a boosted PI. Patients who switched to ATV also had more favorable lipid profiles, both in terms of total cholesterol and triglyceride levels.

Immune Response to HAART

Data are conflicting on whether there are differences among fully suppressive regimens with respect to immune response to therapy. Several studies were presented in Rio on this subject, and it's fair to say that the data are still conflicting. Six-year follow-up data from the venerable Abbott 720 study of LPV/r + d4T + 3TC demonstrate that the CD4 count has continued to rise over time, with a mean increase of 529 cells/mm³; 81% had an increase of over 500 cells by year 6

[Landay A, et al. Abstract WePe16.7B04]. This large and continuous increase in CD4 count has not been observed in many other trials of antiretroviral therapy, where the CD4 count eventually reaches a plateau. Another study looked at switches to LPV/r in patients on suppressive HAART regimens who were felt to have an inadequate CD4 response to therapy at 6 months [Pittrak D, et al. Abstract WePe16.7B08]. The five patients who switched to LPV/r had a greater increase in CD4 count than the 5 who remained on their original regimens. In contrast, a large observational study found that discordant immune responses, in which

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Despite increasing attention to women with HIV and pregnancy, and growing evidence of the effectiveness of various prophylactic and therapeutic ART regimens in reducing mother-to-child transmission (MTCT) in real-world and low resource settings, there was little new to report at the 3rd IAS Conference. However, there were some important updates from ongoing studies and a few important reminders of some fundamental principles of practice relating to women.

Nevirapine Resistance

There continues to be controversy about the development of nevirapine (NVP) resistance when this drug is used for prevention of MTCT—how often resistance occurs, what it means, and how to prevent it. Recent reports suggest that up to one-half of resistance that develops is not detected by conventional sequence analysis and that resistance can occur even when NVP is used with other ARV agents to prevent HIV transmission. Thus, this topic is a relevant concern, not only in the developing world, where the use of single-dose NVP (sd-NVP) is often the only option for reducing risk of MTCT, but also in resource-rich countries, where NVP may be used in combination with other agents prophylactically during pregnancy and stopped after delivery. Arrive and coworkers performed a meta-analysis of 8 existing studies addressing this issue involving a total of 887 women [Abstract TuPe5.2P15]. Using conventional testing 4-8 weeks after delivery, administration of maternal postpartum antiretrovirals was significantly associated with lower rates of resistance compared to sd-NVP alone (odds ratio 0.08-0.11) in a multivariate analysis. The use of other antepartum/intrapartum agents was not related to risk of resistance after adjustment. This analysis has some potential flaws: conventional resistance testing and aggregate data (some preliminary) were used, there was no information on information on viral subtype, and there was a potpourri of study designs. Nevertheless, the conclusion was supported by an update from the Treatment Options Preservation Study (TOPS) in South Africa, reported by James McIntyre [Abstract TuFo0204]. This study

examines one strategy for preventing the emergence of NVP resistance by giving zidovudine/lamivudine (AZT/3TC) intrapartum and for an additional 4 or 7 days postpartum after sd-NVP. With similar baseline median CD4 counts and viral loads, NVP resistance was detected at 6 weeks in 41/68 (60%) in the NVP-only arm vs 8/67 (12%) in the NVP/AZT/3TC (4 day) group and 7/68 (10%) in the NVP/ AZT/3TC (7 day) group. Furthermore, NVP resistance in infected infants decreased from 6/9 (66.7%) with NVP alone compared to 0 in the NVP/AZT/3TC arms. Viral load has been shown to be an independent variable associated with development of resistance, and in both AZT/3TC arms, the nadir viral load was <500 c/mL compared to 8,300 c/mL in the NVP only arm.

The fact that resistance fades in the absence of drug pressure after a single dose of NVP has been metabolized has led a number of people to question the significance of NVP resistance in this setting. Lallemand presented an update from a study attempting to address this question in terms of maternal response to NNRTI-based ART after exposure to sd-NVP for the prevention of MTCT [Abstract TuFo0205]. After 18 months of follow-up of 191 women exposed to sd-NVP and 44 non-exposed women, there remained a significant difference in those achieving a viral load <50 c/mL (42% of exposed vs 58% non-exposed, $P=0.05$), suggesting that exposure to NVP and development of resistance does make a difference in response to subsequent therapy that contains NVP. On the other hand, in those women with a viral load <50 c/mL at 6 months, there was no significant difference in either immunologic or virologic response at 18 months, suggesting that the disparity in response does not increase over time.

This subject is far from settled, and other randomized trials and observational studies are ongoing or planned that will further explore the significance of NVP resistance in the setting of the prevention of MTCT, as well as strategies to prevent it.

Other Antiretroviral Agents

Concerns have been raised about the use of atazanavir (ATV) in pregnancy, because

of the associated indirect hyperbilirubinemia and uncertainty about whether this may increase risk of kernicterus in the newborn. Morris reported on ATV exposure during pregnancy in 9 women; mothers had good immunologic and virologic response and tolerated therapy well, with total bilirubin at term ranging 0.3-3.5 [Abstract TuPe5.2P01]. Rates of neonatal hyperbilirubinemia were within the range of reported rates in the general population.

Enfuvirtide (T-20, ENF) is being increasingly used as part of salvage regimens. Brennan-Benson described two pregnancies with ENF exposure; in both the drug was well-tolerated and no placental transfer was demonstrated [Abstract TuPe5.2P06]. In pregnant patients who are on salvage therapy with ENF and unable to achieve an undetectable viral load, elective Cesarean delivery should be considered to optimize prevention of perinatal transmission.

An unusual study of the pharmacokinetics of EFV in women who were generally inadvertently treated during pregnancy found that trough levels of the drug were similar during pregnancy to those in nonpregnant adults, with no differences between trimesters of pregnancy [Cassard B, et al. Abstract WePe3.2C012]. Efavirenz is now a FDA category D drug, with documented teratogenicity in pregnancy. However, use after the first trimester, when the risk of birth defects has passed, may be considered when there are no good alternatives.

And Don't Forget...

Despite the enormous strides in prevention of MTCT of HIV, there are still missed opportunities for preventive interventions, which can have devastating effects on the mother, her child and the entire family. D'Ippolito and colleagues reported an impressive 1.2% perinatal transmission rate among 646 infants in Latin America and the Caribbean as part of the NICHD International Site Development Initiative [Abstract TuPe5.1P03]. Five of the eight infected infants illustrated situations where transmission may have been

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prevented, including failure to adequately suppress viral load, use of AZT alone in the presence of high viral load, late start of antiretroviral therapy, and vaginal delivery despite high viral load in late pregnancy.

Finally, studies from Brazil [Friedman R, et al. Abstract TuPe5.5P26] and Italy [Compostella S, et al. Abstract TuPe5.5P14] reported surveys of HIV-infected women's desire to become pregnant. Of 173 Brazilian women, 18.5% expressed a desire to conceive within the previous 6 months; of 122 Italian women with a mean age of 40, 77% expressed some desire to become pregnant. Although this desire was significantly attenuated with consideration of their HIV status, with primary concerns about health of a child, the availability of HAART appeared to encourage consideration of pregnancy. These studies and others confirm the need to include assessment of pregnancy plans and preconception counseling as part of the primary care for HIV infected women of childbearing age.

Summary

There continues to be controversy about the development of NVP resistance when this drug is used for prevention of mother-to-child transmission. Despite presentations on the subject at this and other meetings, the subject is far from settled, and randomized trials and observational studies are ongoing or planned that will further explore this critical issue.

Despite concerns about indirect hyperbilirubinemia with ATV, one study showed that rates of neonatal hyperbilirubinemia were within the range of reported rates in the general population. A report of two pregnant patients on ENF indicate good tolerability and no transmission; however, elective C-section may be recommended in patients on ENF who do not achieve an undetectable viral load. A study of pregnant women inadvertently given EFV suggests trough levels similar to women who were not pregnant.

Finally, additional studies remind providers of the need to be vigilant regarding missed opportunities to prevent HIV transmission and to include discussions of pregnancy plans as part of primary care. ▲

3rd IAS Conference: Prevention Highlights

By John G. Bartlett, M.D.

There was substantial emphasis on prevention at the 3rd Annual IAS meeting in Rio de Janeiro, with multiple featured presentations, oral abstracts and posters; but there was far more smoke than fire. The statistics continue to be staggering. In 2004 were 39.4 million persons living with HIV infection, 4.9 million new infections, and 3.1 million deaths [Piot P, Abstract WeSI01]. These figures are 50% higher than the 1991 projections from the World Health Organization.

One of the most striking new observations regarding transmission was the explosive epidemic of HIV in Eurasia, as reported by Chris Beyrer [Abstract MoPI02]. This is largely a result of the "heroin highway" from Afghanistan to neighboring areas in Asia and Russia. In Russia, the number of reported cases increased from about 2,000 in 1997 to 200,000 in 2002. Longitudinal data showed that the epidemic of heroin addiction came first, followed by hepatitis C and then HIV. Most infected individuals are young men who are sexually active, leading to an increase in heterosexual transmission. An important observation by Dr. Beyrer is the fact that Afghanistan has increased its production capacity to an astonishing 430 metric tons of heroin per year. A second important observation is the lack of any federal or state programs to deal with substance abuse; the usual mechanisms (provision of clean needles, methadone or buprenorphine detoxification or maintenance programs, and other harm reduction approaches) are either nonexistent or illegal.

That said, Dr. Karium noted that 86% of HIV transmissions in the world occur as result of heterosexual contact, so sex must remain the central focus of global prevention plans [Abstract TuPI02]. The obvious solution is the promotion of condom use, but this seems to have been spectacularly unsuccessful, as group after group described repeated disappointing experiences, including less than 5% condom use in Sri Lanka, 7% among female sex workers in Nigeria, and even low use of condoms among medical students in Brazil.

Particularly challenging is the observation of "secondary" transmission occurring as a result of high-level viremia associated with acute or early infection, which had previously been reported by Ron Gray of Hopkins from his discordant couple study in Rakai. These findings were reiterated at the conference [Gray R, Abstract MoFo0101]. The high viral load noted in the first several weeks after transmission accounted for approximately 40% of all transmissions in the Rakai cohort, with an efficiency that was approximately ten-fold higher than during the chronic infection phase. Patients in this early stage of infection are notoriously difficult to identify. Susan Allen from Emory reported on a similar discordant couple survey from Rwanda and Zambia [Abstract MoOa0107] and again noted relatively high rates of seroconversion (26/115 or 23%) in the first three months after initial transmission as indicated by a positive P24 antigen test combined with negative serology. Early detection is critical, but remains a major challenge.

A relatively recent observation that has now gained substantial validity is the potential role of male circumcision in preventing female-to-male infection. This was previously reported by Dr. Gray from observational data, but was the subject of an enormous study by Auvert and colleagues, who presented results of a randomized trial of circumcision in 3,273 men ages 18 to 24 who underwent serologic testing at 3, 12 and 21 months [Abstract TuOa0402]. Circumcision was associated with a 65% reduction in the rate of HIV seroconversion. There was also a surprising report on female circumcision by Stallings and Karugendo [Abstract TuOA0401]. Despite multiple reasons why this procedure might increase risk, their observational data found an unanticipated 50% reduction in transmissions among circumcised women. This observation remained unexplained, but statistically significant.

A potentially important presentation on prevention was a report by A. Telenti from

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Targeting HIV Reservoirs With Valproic Acid

By Janet M. Siliciano, Ph.D. and Robert F. Siliciano, M.D., Ph.D.

The demonstration that HAART could lower plasma virus levels to below the limit of the detection raised hopes that eradication could be achieved with prolonged therapy [Perelson AS, et al. *Nature* 1997;387:188]. However in recent years, there has been little discussion of a cure for HIV infection. Shortly after the advent of HAART, several groups showed that the virus could persist in a latent form in resting memory CD4 cells even in patients who had no detectable viremia for prolonged periods of time as a result of HAART [Finzi D, et al. *Science* 1997;278:1295; Chun TW, et al. *Proc Natl Acad Sci U.S.A.* 1997;94:13193; Wong JK, et al. *Science* 1997;278:1291]. These latently infected cells arise when activated CD4 cells are infected. They then survive long enough to revert back to a resting state as long lived memory cells. In these cells, virus production ceases, and HIV persists in a latent form as a double-stranded viral DNA genome stably integrated into host cell DNA. In addition to this latent reservoir, there are also small numbers of free virus particles in the blood of patients on HAART. In patients with clinically undetectable viral loads, this low level viremia can be detected with special assays [Dornadula G, et al. *JAMA* 1999;282:1627; Hermankova M, et al. *JAMA* 2001;286:196; Nettles RE, et al. *JAMA* 2005;293:817]. Residual low-level viremia is indicative of continued virus production despite effective HAART, perhaps reflecting release of virus from stable reservoirs such as that in resting CD4 cells. These findings have led most investigators in the field to conclude that eradication of the infection will not be possible without novel approaches that eliminate viral reservoirs.

Despite the prevailing pessimism, several groups have been directly attacking the problem of viral reservoirs, and a recent report in *Lancet* goes so far as to raise the possibility of a cure [Lehrman G, et al. *Lancet* 2005;366:549]. This study involved the use valproic acid to activate latent HIV in resting CD4 cells. Valproic acid is an

antiepileptic drug also used in the treatment of bipolar illness and migraine. Its mechanism of action is not entirely clear but may involve effects on concentrations of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA). However, valproic acid also inhibits histone deacetylase (HDAC), an enzyme involved in chromatin remodeling and the repression of gene expression in various systems. Some studies have suggested that HIV latency involves changes in chromatin structure that make the latent provirus inaccessible [Jordan A, et al. *EMBO J* 2003;22:1868], and a previous in vitro study had suggested that inhibition of HDAC could stimulate release of virus from latently infected cells [Ylisastigui L, et al. *AIDS* 2004;18:1101]. The authors therefore carried out a small proof of concept study to determine whether valproic acid could reduce the size of the resting CD4 cell reservoir *in vivo*. The underlying assumption of the study was that activation of latent HIV in a patient on HAART would lead to death of the infected cells without further spread of the virus.

In this study, 4 patients with prolonged suppression of viremia to <50 c/mL on HAART intensified their therapy by adding enfuvirtide for 4 to 6 weeks. Valproic acid was then added for 12 weeks. At the end of this time, 3 of 4 patients showed a reduction in the size of the latent reservoir. The mean reduction in the three responders was 75%. The authors conclude with the optimistic statement that “new approaches will allow the cure of HIV infection in the future.”

Because few investigators have been willing to speculate on the possibility of a cure in recent years, this report received a great deal of attention in the lay press and stimulated many inquiries from curious patients. It is important, therefore, to put this work in perspective. While the search for ways to eliminate viral reservoirs is clearly essential to finding a cure, there are several reasons why speculation about a cure is premature.

First, it is not entirely clear that the results will hold up in a larger study carried

out over a longer time frame. Measurements of the size of the latent reservoir are notoriously difficult because of the scarcity of latently infected cells. Assays for latently infected cells, originally developed at Johns Hopkins [Chun T-W, et al. *Nature* 1997;387:183], involve the purification of resting CD4 cells from peripheral blood, the stimulation of these cells *in vitro* with mitogens, and the subsequent amplification of virus released by the activation of latently infected cells. After 2-3 weeks, virus growth is detected by an ELISA assay. By carrying out the cultures in a limiting dilution format, it is possible to estimate the frequency of latently infected cells. Typically, the frequencies are less than 1 per million. The error inherent in frequency measurements of rare cells is substantial, typically on the order to $\pm 0.7 \log_{10}$ c/mL. Thus, changes of less than $1.0 \log_{10}$ c/mL may not be statistically significant. It is therefore important that the provocative results of Lehrman and colleagues be confirmed in a larger study with longer follow-up.

A second major issue involves the underlying rationale for using HDAC inhibitors. In principle, such an approach might be useful if latency were exclusively due to changes in chromatin structure that prevent expression of viral genes. However, the molecular mechanism of HIV latency, although not entirely clear, is likely to be multifactorial (for a review, see Lassen K, et al. *Trends Mol Med* 2004;10:525). A recent study shows that in resting CD4 cells, HIV DNA is usually integrated into introns of cellular genes that are actively being transcribed [Han Y, et al. *J Virol* 2004;78:6122]. This result suggests that the lack of HIV gene expression in latently infected cells is not an accessibility issue. Rather, the transcription of HIV genes may be reduced by interference from the surrounding host gene and by the absence in resting cells of activation-dependent host factors needed for efficient transcriptional initiation and elongation [Nabel G, et al. *Nature* 1987;326:711; Tong-Starksen SE, et al. *Proc*



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Natl Acad Sci U.S.A. 1987;84:6845; Herrmann CH, et al. *J Virol* 1998;72:9881]. In addition, there are post-transcriptional mechanisms that may prevent virus production even if some transcription of HIV genes occurs [Seshamma T, et al. *Proc Natl Acad Sci U.S.A.* 1992;89:10663]. Thus, latency is complex, and it is not clear that inhibition of HDAC alone will overcome other blocks to HIV production in resting CD4 cells.

A third problem is that partial reductions in the size of the latent reservoir are not clinically useful. Latently infected cells are rare, and the occasional reactivation of these cells contributes only a very small amount of the virus produced in an untreated patient. Thus the reservoir does not present a problem unless cure is the goal of treatment. In this case, partial reductions are clinically insignificant, because when therapy is stopped, viral replication increases rapidly and exponentially until the previous set point is reached [Davey RT, et al. *Proc Natl Acad Sci U.S.A.* 1999;96:15109]. This exponential growth means that in principle, even a single latently infected could rekindle the infection. Because of the exponential nature of the viral rebound, reductions in the latent pool should be viewed on a log scale. If the size of the reservoir is 10⁶ cells [Chun T-W, et al. *Nature* 1997;387:183], a 75% reduction still leaves 2.5 x 10⁵ cells. Eradication would require a >99.9999% reduction in the reservoir. In previous studies in which immune activation by interleukin-2 was used to affect a dramatic reduction in the size of the latent reservoir, treatment interruption led to a very rapid rebound in viremia [Davey RT, et al. *Proc Natl Acad Sci U.S.A.* 1999;96:15109].

A final caveat is that there may be other cellular and anatomic reservoirs for HIV [Blankson JN, et al. *Annu Rev Med* 2002;53:557]. These reservoirs may involve different mechanisms of persistence not affected by HDAC inhibition.

The problem of viral persistence in latent reservoirs is a truly daunting one, and in the view of these authors, talk of a cure is premature. Research on strategies for

eliminating viral reservoirs is clearly essential. Even if a cure cannot be achieved, understanding viral reservoirs can contribute to the management of HIV infection. One critical issue is the ability of the latent reservoir in resting CD4 cells to store drug-resistant virus [Persaud D, et al. *J Clin Invest* 2000;105:995; Ruff CT, et al. *J Virol* 2002;76:9481]. Any viral species that has circulated at high levels for a significant amount of time (weeks) has the potential to become archived in the reservoir, thereby permanently limiting treatment options. Another example involves the low level viremia that continues in patients on HAART who have undetectable viral loads. Recent studies of this low level viremia suggest that it represents release of virus from stable reservoirs without further replication or evolution [Kieffer TL, et al. *J Infect Dis* 2004;189:1452]. This is true even in patients who experience “blips” [Nettles RE, et al. *JAMA* 2005;293:817]. Thus, even if approaches for eliminating the reservoir cannot be developed in the near future, some comfort can be taken from the fact that HAART appears capable of fully arresting viral evolution in adherent patients. With optimal treatment, patients should be able to expect a normal life span. ▲

3rd IAS Conference: Prevention Highlights

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Switzerland who studied a cohort of sex workers in Kenya. Participants had repeated HIV exposure through unprotected sex over a period of ten years, but never seroconverted [Abstract TuP102]. The presentation included some family trees that demonstrated a genetic pattern of non-susceptibility. On the basis of these observations, Dr. Telenti is now developing a “genetic propensity index” in the hopes of defining the components of the immune system that appeared to be protective.

Summary

The presentations on prevention at the 3rd IAS Conferences highlighted the following:

- An explosive epidemic of HIV associated with injection drug use in Russia, with no clear national plan for how to deal with it.
- A disappointing record for condom use in multiple resource-limited countries.
- Male circumcision is now added to the list of interventions with verified benefit.
- Further studies show that prevention programs need to deal with the high rates of transmission that occur during acute infection, preceding seroconversion.
- Not surprisingly, the risk of HIV appears to be related to genetic susceptibility. ▲

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3rd IAS Conference: Metabolic and Fat Metabolism Issues

By Joseph Cofrancesco, Jr., M.D., M.P.H.

The most eventful aspect of the 3rd IAS Conference in Rio de Janeiro for me was a missed connection and lost luggage for three days. However, we did deepen our understanding of fat and metabolic issues. And, of course, the weather and the Brazilians were beautiful.

Bone Loss

Bongiovanni evaluated potential predictors of bone demineralization in HIV-infected patients [Abstract TuPe2.2B08]. Questionnaires, blood and urine samples, and blinded bone DEXA scans were performed on 161 consecutive HIV-infected outpatients aged 30 to 50 years. Of these, 48 were ART naïve and 113 were taking HAART; males were equally represented in each group (60% and 65% respectively). Using WHO criteria, approximately half had an abnormal DEXA: 65 had osteopenia (46% of naïve, 51% on HAART), but only 15 had frank osteoporosis (10% naïve, 9% HAART). Low bone density was associated with traditional risk factors: female gender, older age, and low body mass index. In addition, there was also a greater risk in patients with higher viral loads. HAART use was not associated with markers of bone metabolism. There was no comment on the specific HAART regimens used, cigarette smoking (another known risk factor) or protective factors such as exercise, calcium and vitamin use.

Similarly, a small cohort of 200 French patients (74% male, median age 43 years), selected from HIV-infected patients followed in the Bordeaux University Hospital, underwent DEXA between November and December 2004 [Dutronec H, et al. Abstract TuPe2.2B19]. Using WHO criteria, 80 patients (40%) had osteopenia while 21 patients (11%) had osteoporosis. Both studies show a relatively high prevalence of osteoporosis at approximately 10%, and even higher prevalence of osteopenia. Traditional risk factors are implicated. HIV seems to be playing a role, but neither study was

powered nor designed to determine the effects of specific medications. Clinicians should be aware that osteoporosis will likely be an issue for some patients, particularly those with other risk factors. Fortunately, a higher risk for fractures, the only thing that really matters in the end, has not been yet demonstrated.

NRTIs And Toxicity

In a late breaker, Fisac reported on 71 treatment naïve subjects who were randomized in the open-label ABCDE study to take abacavir (ABC) vs stavudine (d4T) combined with efavirenz (EFV) and lamivudine (3TC) [Abstract TuPeLB-2.2B02]. Baseline characteristics were similar in the 2 groups. At month 24, median insulin levels and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) (a measure of insulin resistance) increased significantly only in the d4T arm (+27% and +38%, respectively). Patients with “lipodystrophy” and increased waist-to-hip ratios had the highest increases. These results are consistent with a growing body of literature suggesting that the choice of NRTIs is important not only with respect to the risk of lipodystrophy but for glucose metabolism as well. As with other studies, d4T, but not ABC, is implicated as having negative metabolic effects.

Switching medications continues to be a strategy used to help reverse undesirable metabolic and fat changes associated with HIV treatment. Calza and colleagues evaluated 130 NNRTI-naïve patients who were stable on their first HAART regimen, but had hyperlipidemia [Abstract TuFo0105]. Subjects were randomized to: switch from a protease inhibitor (PI) to nevirapine (NVP) (arm 1), switch from a protease inhibitor (PI) to efavirenz (EFV) (arm 2), or to remain on PI and add pravastatin (arm 3), or bezafibrate (arm 4). This open-label, 12-month study suggested that lipid-lowering medications were more effective than switching ART. Triglyceride levels (TG) were reduced 25%, 9%, 41% and 47% in arms 1-4, respectively, compared

to baseline; there was a statistically significant difference between arms A-B and C-D. Comparable results were seen for LDL-cholesterol levels. As expected, switching to NVP resulted in greater reductions in TG than switching to EFV. Unfortunately, there were no data presented on the NRTI backbone or baseline PIs, and the sample size was relatively small, so comparison between individual arms could not be made.

It is not surprising that use of lipid-lowering agents would have a greater impact than treatment switches, since switches, at best, can only return lipid levels to pre-treatment baselines, whereas lipid-lowering agents can go further. Many patients have high lipid levels at baseline. However, for many patients, switching therapy will result in satisfactory reductions in lipid levels without the need for additional medications, with their cost and potential for toxicity and drug interactions. It should also be noted that when drug therapy is required for the treatment of hyperlipidemia, the choice of a statin vs a fibrate should not be made by coin-toss, as in this study, but should be based on the characteristics of the lipid profile. Statins are preferred for elevations in LDL cholesterol; fibrates are preferred for hypertriglyceridemia.

A series of studies reinforced the benefit of switching from d4T to tenofovir DF (TDF). GS 903e is an extension study of the large GS 903 trial comparing d4T versus TDF with 3TC/EFV in naïve subjects) [Madruga JVR, et al. Abstract TuPe2.2B12]. Both lipid levels and lipodystrophy improved in 85 subjects who had been on d4T but switched to TDF. The mean time on d4T before the switch was 152 weeks. At 48 weeks after switch, total cholesterol decreased by a mean of 38 mg/dL; triglycerides decreased by 72 mg/dL and LDL cholesterol by 16 mg/dL. There were no significant changes in HDL cholesterol or DEXA bone densities. There was a mean increase of 0.42kg in limb fat, also measurement by DEXA, at week 48.

Similarly, Palacios reported 48-week data on 237 patients, identified from a



multicenter, prospective cohort of 1286 patients, who switched from d4T to TDF for lipatrophy. [Abstract TuPe2.3C15]. No patient withdrew for virologic failure. There were no significant changes in blood pressure, smoking (approximately 53% in each group), or diabetes between the two arms. However, the 10-year overall cardiovascular risk decreased from 7.2% to 6.8%, accompanied by a decrease in total cholesterol and LDL cholesterol.

In a late breaker, Benn and colleagues reported the 3-D surface laser measurements for facial lipatrophy performed at baseline and week 48 on 47 subjects (24 on ABC and 23 on TDF) from the larger RAVE study involving switches from a thymidine analog to ABC or TDF [Abstract TuPeLB2.3C02]. They found no difference between treatment arms, with the mean volume over the cheek at week 48 similar to what would be expected for collagen injections. Sixty-nine percent of the subjects reported no change or improvement in facial appearance. There were no differences between study arms in baseline limb fat and both showed similar improvements (+0.36 kg). The amount of limb fat by DEXA correlated significantly with cheek volume. Although not surprising, taken together these studies demonstrate the value of eliminating thymidine analogs, especially d4T, for lipatrophy and metabolic toxicities. The RAVE study suggests that ABC and TDF are equally non-toxic and may lead to a slow reversal of some of the fat changes. It should also be noted that investigators were looking for improvement or lack of progression, which is not the same thing as total reversal or normalization. Clinicians need to remain vigilant to notice early lipid or fat changes early, and to make the appropriate switches.

PIs and Toxicity

Not all switch studies involve a switch to an NNRTI, and not all PIs have the same lipid or glucose metabolism issues. Moebius reported the results of a very small prospective, open-label, 24-week cohort study of 33 antiretroviral-experienced patients with hyperlipidemia [Abstract

TuPe2.4C20]. Switching to atazanavir (ATV) lead to a rapid 45% decrease in TG levels and an 18% decrease in total cholesterol. HDL and LDL cholesterol did not change. There were no data presented on baseline regimens, the reason for switch, virologic outcomes, or whether the ATV was boosted. As with most studies, data on diet and exercise were also not provided. Nonetheless, these data are consistent with previously published data suggesting that ATV does not have a negative impact on lipids or TG and that switching to ATV can reverse previously induced changes.

Finally, more data were presented from the large, multicenter D:A:D study group [Sabin C, et al. Abstract TuPe2.2B28]. Using standard definitions, after adjustment for other factors PI exposure was a significant independent risk factor for diabetes mellitus (RR 1.06 per year). However, once TG levels were entered into the model, the PI effect disappeared. Traditional risk factors were significantly associated with the development of diabetes including older age, male sex, increased BMI and black race. As with other cardiovascular risk factors in this cohort, earlier calendar year was also a risk, which presumably reflects the use of more toxic medications available in prior years. The study suggests that diabetes and hypertriglyceridemia are related in many patients, and that some PIs are associated with hypertriglyceridemia and/or diabetes risk. This study does not specify the PI or the NRTI backbone used. As we are learning, not all agents within classes have the same degree of have class toxicities.

Vascular Disease

Kaplan and colleagues found an increased prevalence of subclinical carotid artery lesions in HIV-infected women in the Women's Interagency HIV Study [Abstract TuPe2.3C12]. Using B-mode ultrasound, carotid artery intima-media lesions were more common among HIV-infected (10%) than among HIV-negative women (2%), regardless of HAART exposure. Compared to HIV-negative women, HIV-infected women had a 4.18-fold higher risk of lesions

after adjustment for age, race, BMI, and smoking. The clinical significance of these subclinical lesions is unclear, but the data supports the view that left unchecked both metabolic abnormalities and HIV infection contribute to vascular disease.

Reimbursement Issues

Lastly, in an intriguing study of the potential impact of government and insurance companies' policies, Manfredi and colleagues evaluated recent changes in the Italian government's reimbursement for lipid-lowering drugs [Abstract TuPe2.4C03]. Free access to or reimbursement for statins, fibrates, and omega-3 fatty acids is now restricted to patients who need secondary prophylaxis because they have already had a vascular event, those with a genetically-proven familial dyslipidemia, or those with a 10-year risk of a primary cardiovascular event >20% as calculated by software developed for the general population. The authors noted that <5% of the HIV infected Italian cohort of >1,000 would meet these criteria for reimbursement. The authors conclude that the increased life expectancy achieved by HAART may be threatened by untreated lipid abnormalities. The impact of formulary restrictions, payment cutbacks with increased co-payments, and increased paperwork is not surprising to an American audience. Time will tell how these changes will affect our patients' long-term health.

Summary

For bone loss, traditional risk factors continue to be implicated. HIV seems to be playing a role, but none of the studies was powered nor designed to determine whether a specific medication was implicated, or whether medication may be protective by controlling the contribution of inflammation caused by HIV. Providers need to be aware that osteoporosis is likely to be an issue for some patients. However, it is worth noting that a higher risk for fractures, which is what really matters, has not been demonstrated.

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patients experienced virologic suppression without a corresponding immune response to HAART, were no more common among patients taking NNRTIs compared to PIs [Sullivan AK, et al. Abstract WePe12.2C02].

Kimberly Smith reported results from ACTG 5174, in which 60 patients who were doing well on HAART for over 1 year were randomized to receive continued HAART vs HAART plus human growth hormone (hGH), given at a dose of 1.5 mg sq qd [Abstract TuOa0203]. After 24 weeks, those on the HAART alone arm then added hGH at a dose of 3.0 mg sq qd. In this trial, hGH was associated with a dose-dependent increase in both naïve and total CD4 cells. These results are similar to those of a smaller pilot trial with longer-term follow-up data, in which hGH was also found to increase thymic mass [Napolitano LA, et al. Abstract MoPpLB0104]. The clinical implications are completely unclear, especially since hGH is extremely expensive and not without side effects.

In short, we still don't know what to do with the patient whose viral load is suppressed but who has a lackluster CD4 response, but there are at least some data to

suggest that there may be interventions available, short of interleukin-2 injections, that will improve the CD4 response. The harder question is whether these interventions will make a meaningful difference in outcome. Two large clinical trials of interleukin-2 have had a hard time demonstrating a clinical benefit, presumably because people with undetectable viral loads tend to do well regardless of their CD4 counts.

Conclusion

The profusion of HIV conferences dilutes the quality of the data and keeps us from our day jobs. Next year's XVI International AIDS Conference will be held in Toronto (which is only a *little* farther from Baltimore by plane than the Brazilian conference center was from Rio by bus!). In between, we'll have ICAAC, IDSA, EACS, and CROI, not to mention smaller meetings devoted to lipodystrophy, resistance, and pharmacology, just to name a few. Still, it's encouraging to look back over a year's worth of data, as spread out as it is, and realize that steady progress is being made in the management of HIV infection. ▲

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Additional evidence was presented indicating that NRTI selection is important not only for fat changes but also glucose metabolism. As with other studies, d4T is implicated as having negative effects, but not ABC or TDF. Methods to avert metabolic complications include switching anti-retrovirals. Data were presented showing the small lipid benefit of switching from PI to EFV or NVP compared to the addition of a lipid lowering agent. Despite this, practicality may lead to switching anti-retrovirals as opposed to adding additional medications. A number of studies reported reduction in lipid and metabolic complications with a switch to TDF from other NRTIs, while another study suggested that ATV may be a reasonable PI option for those with significant lipid or glucose issues. Finally, a report from the Women's Interagency HIV Study suggests that HIV infection may increase the risk of vascular disease independent of HAART exposure. ▲

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