

# THE HOPKINS HIV REPORT

A bimonthly newsletter for healthcare providers

## XVI International AIDS Conference in Toronto, Canada

Complete conference abstracts can be viewed online at <http://www.aids2006.org>

### Antiretroviral News: Initial Therapy

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

The XVI International AIDS Conference was held in Toronto from August 18, 2006. It was an enormous conference: estimates of the number of attendees ranged from 26,000 to 31,000. And, while it's often hard to estimate the impact of a meeting while it's happening, I suspect that this conference will be a pivotal one. At the Vancouver conference in 1996, the world was introduced to the concept of highly active antiretroviral therapy, and HIV infection suddenly became a treatable disease for people living in the developed world. However, the idea of treating patients in resource-limited countries was not on the table; prevention was all we had to offer. By the time of the 2000 conference in Durban, it became impossible to ignore our moral obligation to provide life-saving therapy to people dying of an otherwise fatal illness, no matter where they lived. In the six years since the Durban conference, we've seen steady increases in the number of people on therapy in the developing world, but in many cases prevention efforts have been limited to the "ABC" approach ("Abstinence, Be faithful, and use Condoms") with varying emphasis on the specific components of that approach depending on one's political persuasion.

The Toronto meeting may be remembered for its emphasis on the synthesis of treatment and prevention. On the one hand, we saw impressive results from the DART trial in Uganda, demonstrating 94% 2-year survival rates and a 17-fold drop in overall mortality due to antiretroviral therapy compared to historical controls in the Entebbe cohort [Munderi P, et al. Abstract THLB0208]. On the other hand,



Toronto, Canada by Joel Meneses

Bill Gates, in his speech at the opening session, stated that "treatment without prevention is simply unsustainable." He noted that for every one person started on treatment between 2003 and 2005, ten new people were infected.

*continued on page 2*

### New Data on the Treatment of Antiretroviral-Experienced Patients

By Gregory M. Lucas, M.D., Ph.D.

After a slow start early in the week of the IAC, the Toronto meeting wound up with an 18-abstract, 3-hour, late-breaker extravaganza session. In the mix was a healthy serving of data pertaining to the treatment of antiretroviral-experienced patients. Early data emerged from the Africa-based DART study corroborating the report from the SMART trial earlier this year showing that structured treatment interruptions place patients at increased risk of disease progression. A number of studies addressed the potential role of lopinavir/ritonavir monotherapy [see Gallant J, this issue, *Antiretroviral Therapy: Initial Therapy*], 48-week results of the POWER-1 and -2 studies were presented, and promising data on the use of CCR5 co-receptor inhibitors were presented.

#### Lesson From DART and SMART: Don't Plan to Stop Once You Start

The Development of Antiretroviral Trial in Africa (DART) is a large-scale clinical trial being

*continued on page 12*

### Inside This Issue

Delivering on Women's Health Issues . . . . .	6
Update on Metabolic Complications. . . . .	9
Hepatitis: Limited Data, Lots of Unanswered Questions . . . . .	10
Etravirine: Clinical Pharmacology . . . . .	15



## Antiretroviral News: Initial Therapy

continued from page 1

Gates became uncharacteristically political when he pointed out the weaknesses of the ABC approach to prevention, which ignores a number of harsh realities: that in many parts of the world, women and girls, who must often marry young, do not have the choice to be abstinent, they cannot force their male partners to wear condoms, nor do they have control over whether their husbands are faithful. Gates and his wife Melinda both stressed the importance of putting prevention in the hands of women, through development of vaginal microbicides or even oral agents to be used for pre-exposure prophylaxis. “A woman should never need her partner’s permission to save her own life.” These themes were echoed by many other speakers in Toronto, including Peter Piot from UNAIDS, and former President Bill Clinton.

Understandably, science takes a back seat to these larger global issues at such a conference. Nevertheless, there were a number of important clinical presentations in Toronto, most of them concentrated in a marathon, butt-challenging late-breaker session held on the last day. In this article, I will discuss those studies that dealt with initial therapy.

### Efavirenz: An Old Drug Just Keeps Getting Better

Numerous studies were presented in Toronto that solidified the role of efavirenz-based regimens as the best available therapy for HIV infection. The most important of these studies was the eagerly awaited ACTG 5142, a randomized comparison of efavirenz (EFV), the preferred non-nucleoside reverse transcriptase inhibitor (NNRTI) according to current DHHS guidelines, with lopinavir/ritonavir (LPV/r), the preferred protease inhibitor (PI), both in combination with lamivudine (3TC) and either zidovudine (AZT), extended-release stavudine (d4T XR), or tenofovir DF (TDF) [Riddler, et al. Abstract THLB0204]. A third arm involved LPV/r plus EFV without nucleoside analog reverse transcriptase inhibitor (NRTIs). The study enrolled 753 patients, half of whom had viral loads above 100,000 c/mL, with a median CD4 count of 182 cells/mm<sup>3</sup>.

On most counts, EFV was the winner. Time to virologic failure was significantly shorter for the LPV/r arm than for the EFV arm ( $p=0.006$ ). There was also a trend toward a shorter time to regimen completion with LPV/r than with EFV ( $p=0.02$ , where significance was defined as  $p < 0.016$ ). At 96 weeks, 89% of subjects on the EFV arm had viral loads  $<50$  c/mL compared to 77% on LPV/r ( $p=0.003$ ). Interestingly, the difference could not be explained by side effects, since there was no difference among the arms in time to treatment-limiting toxicity.

The news wasn’t all bad for LPV/r, however. There has been some provocative evidence from prior studies suggesting that the use of LPV/r may lead to better CD4 responses than some other therapies, and this was supported by the results of 5142, in which patients on the LPV/r and EFV + LPV/r arms had significantly better CD4 increases than those on the EFV arm (285, 268, and 241 cells/mm<sup>3</sup>, respectively,  $p=0.01$  for comparisons between EFV and the two LPV/r-containing regimens). In addition, while virologic failure was less common with EFV, the resistance consequences for those who did fail were greater: Of those failing therapy in the EFV + NRTI arm 48% had NNRTI resistance, which appeared to be even more common in the EFV + LPV/r arm (69%). In contrast, PI mutations did not occur in the LPV/r arm. Two-class resistance was also more common among those failing EFV.

Dan Kuritzkes presented data from ACTG 5095 specifically focusing on the 765 patients randomized to the two EFV-containing arms: EFV plus AZT/3TC (*Combivir*) and EFV plus AZT/3TC/abacavir (ABC) (*Trizivir*) [Ribaud H, et al. Abstract THLB0211]. As has been reported previously [Gulick R, et al. *JAMA* 2006;296:769-81], there was no difference in outcome between the two arms. Time to virologic suppression was different, but this difference did not affect the proportion of participants who achieved and maintained suppression, which was the same. What was striking in the presentation at this meeting was that there was no difference in virologic suppression or time to virologic failure among

participants in the various baseline viral load strata, which included the quarter of subjects who entered the trial with viral loads above 300,000 c/mL. CD4 response was also similar, except that those with baseline viral loads above 300,000 c/mL had larger increases, consistent with the greater magnitude of virologic suppression.

Similar results were reported from CPCRA 058, the FIRST Study, in which 1397 treatment-naïve patients were randomized to one of three strategies: a PI-based strategy, an NNRTI-based strategy, and a 3-class strategy, which included a PI, an NNRTI, and 1-2 NRTIs [MacArthur RD, et al. Abstract TUAB0101]. In contrast to ACTG 5142, however, the choice of drugs was left to the clinicians. Only one-quarter of the participants assigned to the PI arm took a ritonavir (RTV)-boosted PI; 61% took nelfinavir. Of the patients randomized to the NNRTI arm, 63% took EFV. Approximately half used AZT/3TC as their NRTI backbone. Median follow-up was 60 months.

In the FIRST study, there was no difference in progression to AIDS, death, or a CD4 count  $<200$  cells/mm<sup>3</sup>. However, both of the NNRTI-containing arms outperformed the PI arm with respect to virologic suppression, and time to virologic failure was faster for the PI arm. As with ACTG 5142, failure of the NNRTI arm was associated with more class-specific mutations than the PI arm. The 3-class strategy was not superior to either of the 2-class approaches, because switching drugs was twice as likely as in the 2-class arms, occurring in 80% of those on triple-class therapy.

Finally, an observational cohort study involving over 900 patients at Johns Hopkins and Vanderbilt Universities found that patients who started therapy with an EFV-based regimen had more durable virologic responses than those who started with a boosted PI [Sterling T, et al. Abstract TUPE0205].

Taken together, these studies provide a ringing endorsement for initial antiretroviral therapy with EFV-based regimens. What was previously a standard of care has now become *the* standard of care. ACTG 5142 and 5095 may finally put to rest the popular but unsupported



## Antiretroviral News: Initial Therapy

myth that patients with advanced disease need PIs. However, these studies also point out some limitations of EFV-based therapy. Aside from the fact that not everyone can take EFV (e.g. women who aren't preventing pregnancy, people with baseline NNRTI resistance, or those intolerant of the neuropsychiatric side effects), it's clear that the consequences of virologic failure are greater for NNRTI-based regimens than for those involving boosted PIs. The long half-life of EFV makes it forgiving of an occasional missed or late dose, but patients who are prone to complete treatment interruptions are at higher risk for resistance with EFV than with boosted PIs. The greater CD4 count increase seen with

LPV/r in ACTG 5142 also suggests that there may be a role for this agent in patients with low CD4 cell counts. While the baseline count probably shouldn't affect the choice of therapy—after all, most people had good CD4 count increases in all three arms—there may be a role for LPV/r, or perhaps for other boosted PIs, in those who fail to experience a significant increase in CD4 count on EFV.

### **KLEAN: Fosamprenavir Battles Lopinavir**

Joseph Eron presented the 48-week results of KLEAN, a comparison of boosted fosamprenavir (FPV/r) and LPV/r, combined with ABC/3TC (*Epzicom*) in treatment-naïve studies [Abstract

THLB0205]. This large study (n=888) was remarkable for the fact that it essentially showed *no difference* between the two agents by any measure examined. Virologic suppression to <400 c/mL was approximately 72% by time to loss of virologic response (TLOVR) analysis and 97% by on treatment analysis in both arms. Over half the patients enrolled had baseline viral loads above 100,000 c/mL, but there were no differences between arms by viral load or CD4 strata, and CD4 response was the same. Five percent discontinued in each arm due to adverse

*continued on page 4*

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## Antiretroviral News: Initial Therapy

continued from page 3

events. PI resistance was uncommon in either arm, and the mutations seen were felt to be minor ones, although it is worth noting that one patient in the FPV arm developed an I54I/L mutation known to decrease susceptibility to amprenavir/fosamprenavir. The tolerability of the two regimens was comparable, as were the lipid profiles [see Todd Brown, this issue, *Update on Metabolic Complications*].

So is there a winner in this apparent draw? Some might argue that there are two losers: LPV/r, stinging from its defeat at the hands of EFV in ACTG 5142, now has a harder time holding on to its title as the champion among boosted PIs. On the other hand, all we can say about FPV/r is that it's as good and as tolerable

as the older, less tolerable gel cap formulation of LPV/r, which, by extrapolation, might suggest that it's less tolerable than the new tablet formulation of LPV/r. KLEAN helps us to feel more confident in the efficacy of FPV/r when we use it, but it doesn't give us a clear reason to choose FPV/r over other boosted PIs.

### GS934: More Differences Emerge at 96 Weeks

The 48-week results of GS934 found that the combination of TDF, emtricitabine (FTC), and EFV was superior to AZT/3TC and EFV, primarily because of greater discontinuation due to toxicity in the AZT/3TC arm [Gallant JE, et al. *N Engl J Med* 2006; 354:251-60]. The 96-week results (of a planned 144-week comparative study) were presented in Toronto, showing a similar difference in efficacy, as well as some emerging differences with respect to toxicity and resistance [Gallant JE, et al. Abstract TUPE0064]. At 96 weeks, 75% of patients on TDF/FTC had viral loads <400 c/mL by time-to-loss of virologic response analysis (TLOVR) compared to 62% on AZT/3TC ( $p=0.004$ ). Using a <50 c/mL analysis, the results were 67% vs. 62%, respectively, a difference that is no longer significant ( $p=0.19$ ). The reason for the loss of significance between year 1 and 2 has to do with the TLOVR analysis and its intolerance of blips. In fact, most of the patients who failed to meet the <50 c/mL TLOVR criteria were not experiencing virologic failure, but had viral loads below 50 c/mL at 120 weeks. Once again, the proportion of patients who discontinued therapy due to adverse events was higher in the AZT/3TC arm than in the TDF/FTC arm (12% vs. 5%,  $p=0.007$ ), but there was also significantly more virologic rebound in the AZT/3TC arm (5% vs. 1%,  $p=0.007$ ). Patients on TDF/FTC experienced a greater CD4 increase than those on AZT/3TC at 96 weeks (270 vs. 237 cells/mm<sup>3</sup>,  $p=0.036$ ).

At the end of the first year of the study, there was a hint of greater lipoatrophy in the AZT/3TC arm, as 48-week DEXA data found significantly lower limb fat among AZT-treated patients. The 96-week data now demonstrate

that patients in the AZT/3TC arm have significantly less limb fat than they did at 48 weeks, and the difference in limb fat between the two arms (2.3 kg) is now greater ( $p<0.0001$ ). The demonstration of progressive loss in limb fat is consistent with other studies, though it should be noted that these findings differ from those of ACTG 384, in which patients on AZT/3TC/EFV did not appear to lose limb fat [Komarow L, et al. Abstract WEPE0167].

Intriguing differences in resistance are also emerging in this study. After two years, there are still no cases of K65R in either group, in contrast to the results of GS903, in which 8 patients had developed K65R in the TDF/3TC arm by this time point. There are also significantly more M184V mutations among participants failing AZT/3TC in the 934 study (9 vs. 2,  $p=0.037$ ). These data are consistent with those of other studies, such as Abbott 418 trial, in which there has been no emergence of K65R among 190 patients treated with TDF, FTC, and LPV/r, and less M184V than had been observed in studies using either AZT/3TC or TDF/3TC. The reason for the difference is unclear but may have to do with the longer intracellular half-life of FTC compared to 3TC. The comparison of GS934 with GS903 certainly suggests that at least with TDF, there are good reasons to use FTC as opposed to 3TC beyond the convenience of coformulation.

There has been no evidence of renal toxicity in GS 934. The median calculated creatinine clearance by the Cockcroft-Gault equation remains unchanged in both groups over 96 weeks with no differences between groups. However, the median glomerular filtration rate (GFR) calculated by the MDRD equation is significantly lower on the TDF/FTC arm (100 vs. 108 mL/min/1.73m<sup>2</sup>,  $p=0.006$ ). This difference is of doubtful clinical significance, however, since the GFR increased immediately in the AZT/3TC arm and then remained stable, whereas the GFR has remained essentially unchanged from baseline in the TDF/FTC arm.

Taking together the results of GS934, ACTG 5142, ACTG 5095, and the FIRST study, discussed above, one can anticipate that

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## Antiretroviral News: Initial Therapy

the combination of TDF, FTC, and EFV, now coformulated as *Atripla*, will become the “default regimen” for initial therapy: the one you use unless you have a reason not to. Reasons not to use EFV have already been discussed. The best reasons to avoid TDF/FTC would be pre-existing renal dysfunction, especially when progressive, or baseline resistance affecting either TDF or FTC.

### Boosted PI Monotherapy Studies

Multiple studies were presented studying monotherapy with boosted PIs, mostly LPV/r. In MO3-613, treatment-naïve patients were randomized to receive either AZT/3TC and EFV or AZT/3TC and LPV/r [Cameron DW, et al. Abstract THLB0201]. Those on the LPV/r arm switched to LPV/r monotherapy if their viral load remained <50 c/mL for 3 consecutive months. The time to first viral load >50 c/mL was significantly shorter in patients on LPV/r monotherapy ( $p < 0.001$ ). Most virologic failures were at low levels, between 50 and 400 c/mL. Three of 15 patients tested in the LPV/r arm developed PI mutations.

The MONARK study randomized 138 treatment-naïve patients in a 2:1 fashion to receive either LPV/r monotherapy or LPV/r plus AZT/3TC [Delfraissy JF, et al. Abstract THLB0202]. At week 48, 75% of those on LPV/r plus NRTIs had a viral load <50 c/mL by ITT analysis compared to 71% on LPV/r monotherapy. As in MO3-613, more patients taking LPV/r monotherapy had viral loads in the 50-400 c/mL range throughout the 48 week study period.

In the Spanish OK04 study, 198 patients whose viral loads had been suppressed to <50 c/mL on LPV/r plus 2 NRTIs for at least 6 months were randomized to continue the current regimen or to drop the NRTIs [Arribas J, et al. Abstract THLB0203]. Time to virologic failure was not significantly different between the arms, but 4 patients in the monotherapy arm required intensification with NRTIs due to virologic rebound to >500 c/mL. When those 4 patients were classified as failures, the proportion without failure was 89.8% in the LPV/r + NRTIs

arm and 85% in the LPV/r monotherapy arm. Three primary PI mutations were observed, 2 in the monotherapy arm and 1 in the control arm, although it is not clear whether these were mutations that truly emerged on treatment.

The Brazilian KALMO study randomized 60 patients whose viral loads were suppressed on HAART for at least 6 months to continue their current HAART regimen or to switch to LPV/r monotherapy [Nunes EP, et al. Abstract THAB0102]. One virologic failure occurred in each arm, with no emergence of PI mutations. The patient who failed in the monotherapy arm experienced virologic resuppression with the addition of NRTIs.

Finally, there was a report on ATARITMO study, a pilot trial in which 30 patients whose viral loads were suppressed on HAART took monotherapy with boosted atazanavir (ATV/r) [Vernazza P, et al. Abstract WEPE0073]. Two patients experienced virologic failure at week 24, and five had blips. At week 24, 3 of 20 (15%) patients tested had CSF viral loads >100 c/mL and 2 of 15 (13%) had detectable viral load in semen.

What conclusions can we draw from these studies? It seems clear that most people do well on boosted PI monotherapy, but in most of these studies there are patients who fail to maintain suppression to <50 c/mL, which seems to be more common than with standard therapy in the controlled trials. There is also concern that monotherapy may not allow penetration into all anatomical sites, including the central nervous system and genital secretions. Finally, it's worth noting that none of these studies is large enough to be definitive. It's fair to say that we've now seen enough small trials of PI monotherapy. Each trial suggests that there's a reason to study this approach further in a larger trial, but none provides a reason to embrace the strategy in clinical practice.

Some might argue that there's really no rationale for PI/r monotherapy, even if it's shown to be successful. They would point out that current standards of care for first-line therapy in the developed world are even simpler and better tolerated than PI monotherapy. However, in resource-limited countries, most patients who

receive therapy take a combination of an NNRTI, 3TC, and a thymidine analog without viral load monitoring. In such settings, failure of first-line therapy is likely to be associated with high-level NRTI and NNRTI resistance, leaving no effective second-line NRTIs. It's important to find out whether boosted PI monotherapy could provide adequate rescue therapy for PI-naïve patients with no options among the reverse transcriptase inhibitors. A large clinical trial looking at boosted PI monotherapy for second-line therapy in resource limited settings would be of great interest.

### Initial Therapy Using New Agents

Until the end of the late-breaker session, it was looking like nothing could beat efavirenz for initial therapy...then along came MK-0518. Markowitz presented data from a trial in which 203 treatment-naïve patients were randomized to receive EFV or one of 4 doses of Merck's new integrase inhibitor in combination with TDF and 3TC [Abstract THLB0214]. By 24 weeks, most participants had a viral load below 50 c/mL, but those on MK-0518 reached that target much faster than those on EFV: the majority within 4 weeks. MK-0518 was also better tolerated, primarily because of the lack of neuropsychiatric side effects. It's unclear whether the long-term outcome will be any different with MK-0518 than with EFV, but the extremely rapid rates of virologic suppression, together with the dramatic declines in viral load observed in earlier 10-day monotherapy studies, speak to the potency of this agent, and its short-term tolerability is highly encouraging.

### Conclusion

The clinical data at the Toronto conference confirmed just how good our options are for initial therapy. The treatment guidelines of the International AIDS Society-USA were updated and announced at this conference, and published in the “AIDS issue” of *JAMA* [Hammer SM, et al. *JAMA* 2006;296:827-43]. The new

*continued on page 15*



## Delivering on Women's Health Issues

By Jean R. Anderson, M.D. and Barbara Wilgus-Wegweiser, C.R.N.P.

The XVI International AIDS Conference will be remembered as the first to provide a strong focus on HIV infection in women. Although there were relatively few new data presented scientifically in terms of issues specifically related to women with HIV, the feminization of the HIV/AIDS epidemic, and the gender inequities that continue to drive it were acknowledged, discussed and debated in (conservatively) some 400 abstracts, 1 plenary session, 2 symposia, 1 special session, 7 skills building sessions and 13 satellite sessions, not to mention by most of the speakers in the opening ceremony. Almost 3000 abstracts contained the words women or gender.

The following summary represents a selection of these presentations that were chosen by the reviewers for their relevance to clinical care and scientific interest.

### HIV Prevention

Measures to prevent the spread of HIV infection were a key focus of the conference and continue to be a challenge. The controversy of so-called "ABC" (Abstinence, Be faithful, use Condoms) behavioral interventions continues to be an issue, with many presentations alluding to the failure of this measure in stemming the spread of HIV. Pulerwitz presented information regarding one such program in Kenya, where questionnaires given to 1300 adults and youth ages 13 to 19 asked for specific definitions of each ABC category [Abstract MOAX0503]. The investigators found limited awareness of what the ABC terms mean: 39% of adults and 46% of youth were able to correctly define abstinence, 35% of adults and 23% of youth correctly defined being faithful, and only 17% of adults and 13% of youth correctly defined preventive condom use. The questionnaire also asked participants to identify their primary source of health care information, which in the case of this cohort was the radio, though most respondents expressed a preference for health care information to come from health care providers.

Vaginal microbicides and their potential as a prevention measure for women were a topic of

excitement at this conference and were discussed in several sessions. The key research goals at this time are to match vaginal microbicides to transmission mechanisms, blocking viral attachment with barrier, chemical, and even antiretroviral measures. Clinical effectiveness data are still forthcoming, however, with the first large-scale clinical trial data expected in 2007 and at this conference information was limited to development data [Shattock R, Abstract WEAA0501].

Finally, HSV suppressive therapy as a means of decreasing genital HIV RNA shedding has been studied in several small clinical trials. Mayaud presented data from the ANRS 1285 trials in Burkina Faso [Abstract TUAC0501]. These are randomized controlled trials studying the effect of valacyclovir (VCV) 500 mg bid versus placebo with (ANRS 1285B) or without (ANRS 1285A) HAART on genital HIV RNA, genital HSV-2 DNA, and plasma HIV RNA among HIV/HSV-coinfected women. Over a 75-day pre-treatment period, 140 women in 1285A and 60 women in 1285B underwent biweekly virologic measurements and were then randomized to treatment versus placebo for up to 165 days. In the 1285A group not on HAART, both the frequency and quantity of genital HIV RNA shedding were significantly reduced by VCV, with a 20% decrease in quantitative genital HIV RNA from one biweekly measurement to the next ( $p < 0.01$ ). The 1285B group on HAART, however, did not show a significant reduction in detectable genital HIV RNA (36.7% vs 40.0%,  $p = 0.79$ ) beyond levels achieved by HAART. Both 1285A and 1285B are limited by a small sample size. Further investigation with larger clinical trials is warranted to determine whether HSV suppressive therapy will be effective as a prevention method.

### HIV in Pregnancy

**HIV Acquisition in Pregnancy.** Recent published studies suggest that pregnancy may be a time of unique vulnerability to HIV acquisition, even when controlling for sexual

behavior [Gray RH, et al. *Lancet* 2005;366:1182]. Two large studies appear to contradict this conclusion. Urassa and coworkers utilized demographic surveys and village HIV testing in Tanzanian women of childbearing age from 1994-2005. Analyzing 17,928 person-years of observation and 5755 pregnancies, the investigators found that successful pregnancy was associated with lower HIV incidence (relative risk 0.3, CI 0.2-0.4) [Abstract MOPE0324]. Although it was not possible to determine whether seroconversion actually coincided with pregnancy, the strength and consistency of the findings, even after adjustment for possible confounders, supports the conclusion that pregnancy is associated with decreased HIV incidence. Similarly, a prospective study conducted in Uganda and Zimbabwe involving 4,439 women 18-35 years and 31,369 follow-up visits, found that neither pregnancy nor lactation placed women at increased risk of HIV seroconversion [Morrison C, et al. Abstract MOPE0346].

**HAART in Pregnancy.** The use of effective combination antiretroviral therapy regimens in pregnancy has become the standard of care and the mainstay in preventing mother-to-child transmission in resource rich countries. However, concerns remain about potential toxicity or adverse effects of these regimens, particularly among women who do not yet require ART for treatment of their own HIV infection.

Using comprehensive population-based surveillance in the UK and Ireland from 1990-2005, Townsend and coworkers studied the effect of antiretroviral therapy on preterm delivery [Abstract MOPE0532]. Analyzing approximately 5,000 pregnancies, the authors found that the risk of preterm delivery (<37 weeks) was increased 1.5-fold with exposure to HAART compared to mono- or dual-therapy exposure, after adjustment for age, ethnicity, clinical status and IDU risk factor (adjusted OR 1.5, 95% CI 1.2-1.9,  $p = 0.001$ ). This association was found with both PI- and NNRTI-based HAART. This confirms previous reports from Europe, but, as the authors note, must be



## Delivering on Women's Health Issues

balanced against the substantial benefits of HAART in reducing perinatal transmission.

There has been equivocal evidence concerning *in utero* NRTI exposure and mitochondrial toxicity in HIV-uninfected infants. A retrospective review of 1,020 HIV-uninfected infants born to HIV-infected mothers in PACTG protocols identified 20 possible cases of mitochondrial dysfunction using standardized criteria. There was no significant association between *in utero* NRTI exposure any time in gestation and clinically evident mitochondrial toxicity [Brogly S, et al. Abstract THAB0103].

An ongoing concern about the use of HAART for perinatal prophylaxis is the risk of antiretroviral drug resistance development, potentially affecting response to future regimens used for treatment. Duran and colleagues analyzed the occurrence of primary resistance mutations in a prospective cohort of 198 women in Latin America and the Caribbean who were newly diagnosed with HIV and first exposed to antiretroviral drugs during pregnancy [Abstract WEAB0103]. Genotypic resistance testing was performed at baseline and at 6-12 weeks postpartum. At baseline 98% of women were asymptomatic and 62% had viral loads <1,000 c/mL. When taking into account the inability to amplify samples (generally due to very low viral load), primary resistance mutations were detected in 9/76 (12%) at enrollment and 12/97 (12%) at 6-12 weeks postpartum. Detection of resistance was not associated with plasma viral load, CD4 cell count, CDC disease stage, timing of antiretroviral drug exposure, or the complexity or number of regimens. The occurrence of resistance was not associated with perinatal transmission nor with the short-term use of HAART for prophylaxis, and the rate of resistance mutations was similar to that reported among other newly HIV-diagnosed individuals in the region. These findings reinforce the recent change in USPHS Perinatal Guidelines recommending resistance testing prior to initiation of therapy or prophylaxis in pregnancy. The most common PI used in HAART regimens during pregnancy in the US, and listed as a preferred PI in the USPHS guidelines, is

nelfinavir (NFV), because of its safety profile, tolerability and availability of PK data. However, studies in non-pregnant adults have demonstrated that NFV is inferior virologically to more potent ritonavir (RTV)-boosted PIs such as lopinavir/ritonavir. The question remains whether NFV can be used without detriment in women who need treatment only for prevention of mother-to-child-transmission (PMTCT), with plans to discontinue therapy after delivery. Kakehasi presented the first data trying to address this issue [Abstract WEAB0105]. New NFV-associated mutations developed in 5/19 (26.1%) women exposed to NFV for prophylaxis only, 2 of which were major. There was no association with HIV subtype (70% were subtype B). Although this study provides useful and potentially concerning information, it is limited by small numbers and lack of information with respect to dosing/formulation, adherence, pharmacokinetics and associated nutritional intake. Further study is clearly needed.

Continued analysis by the Antiretroviral Pregnancy Registry, now updated through July 2005 with 5,169 live births, found 1,980 first trimester exposures to ARV drugs with a total of 59 (3.0%) birth defects, which is not different from the general US prevalence (3.1/100 live births) based from CDC surveillance statistics [Beckerman K, et al. Abstract MOPE0515].

**Prevention of Postpartum Infectious Complications.** The use of prophylactic intrapartum antibiotics is routine for Cesarean deliveries in HIV-infected women to prevent postpartum infections. Sebitloane and colleagues conducted a double-blind randomized clinical trial of a single 2 gm dose of cefoxitin for prevention of septic complications in 675 HIV-infected women in whom delivery was anticipated [Abstract WEPE0241]. Overall, septic complications were reduced from 40.6% to 18.9% by use of antibiotics in women with CD4 counts <200 cells/mm<sup>3</sup> (p=.005); in the study sample infections were reduced by 22%, although this was not statistically significant. Most infections were diagnosed by 1 week after delivery and were associated with episiotomies.

**Missed Opportunities.** Availability of effective

combination ARV therapy in pregnancy and safe and affordable alternatives to breastfeeding have resulted in perinatal transmission rates of less than 2% in developed countries. "Opt-out" HIV testing, in which patients are tested routinely unless they refuse testing, has been recommended in pregnant women in the US for some time in order to take advantage of these interventions, although this approach is still not universally applied and is not legal in Maryland given current statutory restrictions. The American College of Obstetrics and Gynecology also recommends repeat HIV testing in the third trimester in selected high risk women. Two studies confirm that women who seroconvert during pregnancy are responsible for a significant proportion of the remaining perinatal transmissions occurring in the US. In an analysis of 2144 HIV seropositive birth events, Birkhead and colleagues found that only 1.4% represented seroconversions (tested HIV-negative early in pregnancy), yet these accounted for 23.4% of all MTCT in 2002-2004 [Abstract WEPE0271]. Similarly, the CDC analyzed data from women who were initially HIV-negative in pregnancy and either tested positive within 3 months of delivery or had an infant who tested positive at delivery or by two years of age if not breastfed [Sansom S, et al. Abstract WEPE0269]. The authors found that among 4,006 deliveries by HIV-infected women, 1.4% had seroconverted during pregnancy; these accounted for 8.2% of all transmissions in this group, with a significantly higher rate of transmission (29.3%) than in those who had not seroconverted (4.8%).

**Pregnancy in Low Resource Settings.** Over the past 6 years there has been a new commitment to HIV interventions, most prominently PMTCT in low resource settings where the majority of infections continue to occur. Although overall goals have not been met, it is clear that there is much to celebrate. Spensley reported on the experience of the Elizabeth Glaser Pediatric AIDS Foundation in 11 countries with HIV prevalence of at least 6%,

*continued on page 8*



## Delivering on Women's Health Issues

*continued from page 7*

where PMTCT programs have expanded and reached over 1.3 million women [Abstract TUPE0338]. In the DREAM cohort in Mozambique, in which HIV-infected women were offered HAART irrespective of CD4 count beginning at 25 weeks gestation through 6 months postpartum and all women breastfed, the MTCT rate was 1.2% at 1 month of age in 171 mother-infant pairs [Marazzi MC, et al. Abstract WEPE0545].

Because nevirapine (NVP)-based HAART or use of single-dose NVP is generally the standard for pregnant women in low resource settings, there are serious concerns about the development of NVP resistance, particularly among women who are treated prophylactically and do not continue effective therapy after delivery. There is a particular concern with NVP both because of its long half-life and its low genetic barrier to resistance. Two studies addressed this issue. Jourdain and colleagues studied 24-month outcomes of NVP-based HAART in postpartum women who had participated in perinatal HIV prevention trials utilizing single-dose (SD)-NVP [Abstract WEAB0102]. A total of 286 women with a median CD4 count of 154 cells/mm<sup>3</sup> initiated HAART a median of 7.7 months after delivery. In an intent-to-treat analysis (switch=failure) at 2 years, 55% had a viral load <400 c/mL. Although the same group had demonstrated that exposure to SD-NVP reduced the likelihood of maximal viral load suppression at 6 months after initiating HAART, this was not seen at 24 months, although the power to detect a significant difference at this time period was low. Chi reported on a study of 6100 women in Zambia who initiated NVP-based HAART, of whom 679 had been exposed to SD-NVP in pregnancy (median 16.1 months prior to initiation) [Abstract WEAB0104]. Looking at CD4 response and clinical outcomes but not viral load suppression, there was no difference in CD4 response at 6 and 12 months and mortality trends were similar. Of significance, those women unexposed to SD-NVP were older and had more advanced disease at baseline. Both of these studies may be considered mildly reassuring but are still far from definitive. This is an issue of considerable

importance, and more studies with longer follow-up, larger sample sizes, and more sensitive measures of virologic failure are urgently needed.

There are also continued cautions about the use of ongoing NVP-based regimens due to hepatic toxicity. In Mozambique, mild-moderate and severe hepatic toxicity was reported in 29% and 3% respectively of 254 pregnant women on NVP-containing regimens; the rate of severe hepatic toxicity was doubled in women with CD4 counts 250-350 cells/mm<sup>3</sup> [Jamisse L, et al. WEPE0173]. In Malawi 3 serious rashes and one case of clinical hepatitis were seen among 39 postpartum women (all with CD4 counts >200 cells/mm<sup>3</sup>) exposed to 28 days of ZDV/3TC/NVP as a PMTCT intervention during breastfeeding [Bramson B, et al. Abstract WEPE0082]. No similar complications were seen in women exposed to NFV-based regimens or to no therapy.

### Fertility Intentions in HIV Positive Women and Men

Several studies assessed fertility intentions in both HIV seropositive women and men. Hoffman and coworkers enrolled 227 Malawian women in a longitudinal cohort at the time of first HIV-positive test and assessed pregnancy status, fertility intention, and contraceptive use quarterly for 1 year [Abstract WEAC0103]. While the desire to have another child decreased significantly over the first year after HIV diagnosis (35% to 13%,  $p < 0.0001$ ), neither use of contraceptives (38% to 49%) nor use of condoms (4% to 5%) changed significantly, indicating a serious disconnect between desire for pregnancy and actions toward preventing pregnancy. Sixteen women became pregnant in the first 6 months of the study and an additional 13 in months 6-12 for an overall incidence of 15.5/100 person-years; pregnancy incidence was 12.8/100 person-years among women who did not want pregnancy versus 32.0/100 person-years in those who expressed a desire for pregnancy ( $p < 0.02$ ). Paiva and associates assessed the fertility intentions of 729 HIV-infected women and 250 HIV-infected bisexual or heterosexual men in Brazil using both a

questionnaire and face-to-face interview [Abstract TUAD0105]. Of the respondents 89% were on antiretroviral therapy and 28% expressed a desire to have more children. When analyzed by sex, the proportion of men desiring children was 50% compared to 19% of the women; this was the most significant variable. However, men had significantly less knowledge about MTCT than women. In Brooklyn, New York, 30 HIV-infected men were questioned regarding fertility intentions in a pilot study conducted from October 2003 to January 2004 [Weinberg A, et al. Abstract TUAD0101]. Regardless of fertility intentions, 87% of respondents reported that they had not discussed family planning with their health care provider at any visit, and 50% said they wished to discuss this issue. This pilot study did not include female respondents for comparison. These studies emphasize the need to address fertility intentions in both HIV+ women and men and to improve male involvement in reproductive health care.

### HPV and Cervical Dysplasia

Cervical dysplasia and cervical cancer remain a significant factor in morbidity and mortality in HIV-infected women worldwide. There is limited screening and treatment for cervical dysplasia in developing countries, which has been extensively noted in the literature, but HPV type specific testing adds new considerations for potential clinical management. Parham and collaborators evaluated prevalence and predictors of cervical cytological abnormalities among 150 HIV-positive women in Zambia and were able to incorporate HPV type-specific testing into their study [Abstract TUAB0303]. The prevalence of cytologic abnormalities in this cohort was 76% (114/150), with high-grade squamous intraepithelial lesion (SIL) in 33% (49/150) and with suspicion for carcinoma in 20% (30/150). High-risk HPV types were found in 85% of women (128/150), and multivariable logistic regression modeling suggested that this was an independent predictor for severely abnormal cytology (adjusted OR 12.4,  $p < 0.02$ ). Interestingly, type-specific testing



## Delivering on Women's Health Issues

*continued from page 8*

showed that HPV type 52 was the most prevalent type in this cohort, with type 58 the second most prevalent. HPV types 16 and 18, which are the types targeted in the newly FDA-approved preventive HPV vaccine and in therapeutic HPV vaccine trials, were far less prevalent in this cohort, ranking 9th and 16th respectively. This correlates with the findings of Luque and associates, who also found that HPV types 52 and 58, not 16 or 18, were most prevalent among 229 HIV-positive women in Rochester, New York with high grade cervical SIL [*J Infect Dis*, 2006;194:428]. Studies such as these are important and may have implications for vaccine administration in HIV-infected women, who have not been included in vaccine trials to date; studies of vaccine effectiveness in immunocompromised populations are planned.

### Miscellaneous Issues in Women

Finally, three studies remind us that HIV-infected women may be especially prone to certain psychosocial and societal ills that may significantly affect clinical management and adherence, that much work remains to be done to support the prevention needs of women and the failure of the ABC approach. In a comparison of 629 women in the WIHS study and 1,829 men in the MACS, both large multi-center US cohort studies, women had a higher proportion of deaths due to accidents or injuries (7.3% vs 2.8%) [Cohen M, et al. Abstract WEAX0305]. Two-thirds of the deaths in women were attributed to drug overdose, poisoning or suffocation compared to less than 1/3 in the men. In the multivariate analysis, independent variables associated with mortality included being in the WIHS, unemployment, depression and injection drug use. In another study of 344 HIV-infected and 133 HIV-uninfected women from the WIHS, having HIV infection was associated with greater anxiety and feelings of hopelessness, with a positive association between feeling hopeless and suicidal ideation [Schwartz R, et al. Abstract THPE0612]. The final study comes from WHO and uses population data from 2000-2003 to assess the prevalence of physical and sexual violence against women in

15 sites in 10 countries, primarily in Africa, Asia, and South America [Watts C, et al. Abstract THPE0692]. Depending on site, a coerced first sexual experience was reported by 0.4-30% of women, and 9-59% reported sexual violence since the age of 15 (in 9 the sites prevalence was >30%). Of women who had ever been in a sexual partnership, 6-56% reported sexual partner violence, which was strongly associated with knowledge of the man's unfaithfulness.

### Summary

The XVI international AIDS Conference focused on several issues of importance for women with HIV infection. Presentations on prevention continue to highlight the challenges of risk reduction strategies in a world where women are often without power, while simultaneously offering the hope that new technologies such as microbicides will give women an opportunity for HIV prevention not dependent on the behaviors of their partners. Prevention of mother-to-child-transmission continues to be a major issue, as in previous conferences, and in the era of scale-up of PMTCT services, more studies will be needed regarding adverse events and resistance following HAART therapy in this setting. Fertility intentions of both women and men with HIV were shown to be a significant issue and one that should not be overlooked by health care providers, as there is often a disconnect between intentions and prevention behaviors. HPV type-specific testing provided new insights into cervical dysplasia, and in the era of vaccine development may have future implications for HIV-infected women. Finally, psychosocial and societal factors affecting women's HIV care remain a worldwide concern, both for treatment and prevention, and must continue to be addressed. ▲

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## Update on Metabolic Complications

*By Todd T. Brown, M.D.*

Several studies presented in Toronto provide further insight into the pathogenesis and treatment of metabolic problems in HIV-infected patients.

### Role of Specific Antiretrovirals

The KLEAN study was a 46-week, randomized, open label study in which 878 antiretroviral-naive patients received either fosamprenavir/ritonavir (FPV/r) or lopinavir/ritonavir (LPV/r), with a backbone of abacavir/lamivudine in both arms [Eron J, et al. Abstract THLB0205; also *Lancet* 2006;368:476]. As reviewed elsewhere in this issue, antiviral efficacy was similar in both arms. Somewhat surprisingly, both arms were also similar in the effect on lipids. Fasting triglycerides (TG) increased by 59% in the FPV/r arm and 66% in the LPV/r arm at 48 weeks, while the use of lipid lowering medications was similar in both groups (11%). HDL also increased similarly in both arms (40% vs. 41%). The important message is that FPV/r, which has been considered relatively "lipid friendly," is also associated with significant increases in hypertriglyceridemia.

One explanation for these findings is that the increases in TGs are the result of the boosting doses of ritonavir. The impact of low-dose ritonavir on lipids was addressed in a switch study that compared lipid changes in those switched to atazanavir (ATV, n=559) or to ritonavir-boosted atazanavir (ATV/r, n=638) [Keiser P, et al. Abstract WEPE0163]. While this study was not randomized and therefore may be subject to confounding, a switch to ATV was associated with a 27% decrease in TGs, compared to a somewhat attenuated decrease of 20% in those who switched to ATV/r.

Another switch study quantified the lipid improvements in 88 patients who substituted ATV/r for LPV/r [Guillemi S, et al. Abstract WEPE0156]. After 6 months, there was an

*continued on page 10*



average 13% decrease in total cholesterol and a 30% decrease in triglycerides. When Framingham Scores [*Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults* - <http://hp2010.nhlbi.nih.net/atpiii/calculator.asp?usertype=prof>] were used to calculate cardiovascular risk, these changes corresponded to a decrease from 12% to 10% in the average 10-year risk of myocardial infarction or cardiovascular death, reminding us to place lipid changes into the larger perspective of cardiovascular risk reduction when contemplating interventions.

### Risk Factors for Cardiovascular Disease

Several studies examined emerging cardiovascular risk factors in HIV-infected populations. High levels of lipoprotein a [Lp(a)] have been independently associated with cardiovascular disease in the general population, although the role of Lp(a) in HIV-infected patients and its interaction with antiretroviral therapy are unclear. In a cohort of 109 HIV-infected patients beginning antiretroviral therapy, Lp(a) increased significantly after treatment initiation, but only among the 30% who had high concentrations at baseline [Mauss S, et al. Abstract WEPE0159]. The impact of this change on cardiovascular risk requires further investigation. In addition to LDL-cholesterol, LDL phenotype may also play an independent role in the pathogenesis of cardiovascular disease. Specifically, small dense LDL particles (so called, Pattern B) are thought to be more atherogenic than larger LDL particles in the general population. The prevalence of this phenotype has not been well described in HIV-infected patients. In one cohort of HIV-infected patients, hypertriglyceridemia (>300 mg/dL) was an important marker of small, dense LDL particles, with a prevalence of up to 50% in this group [Abstract WEPE0163]. These small, dense particles are thought to be more readily oxidizable, increasing their atherogenic potential. Another study showed that higher levels of oxidized LDL were found in HIV-infected patients on HAART, especially in those who had experienced body composition changes [Duong M, et al. Abstract WEPE0168]. While

these findings are interesting and deserve further investigation, their clinical utility has not been established, and it is premature to evaluate and treat based on these risk factors.

The metabolic syndrome (the constellation of high triglycerides, low HDL, central adiposity, hypertension, and hyperglycemia) is a cardiac risk factor that has attracted controversy in the general population in the past year, with some experts questioning its clinical utility. Several studies have examined the epidemiology in HIV-infected patients, but mostly in predominately male populations. In the first study reporting on metabolic syndrome in women, investigators from the WIHS observed a higher prevalence in HIV-infected women (33%) compared to HIV-negative women (22%) [Sobieszczyk ME, et al. Abstract WEPE0147]. In a multivariable analysis, traditional risk factors, such as age and BMI as well as disease and treatment factors (HIV viral load and stavudine use) were associated with the presence of metabolic syndrome.

### The Risk of Myocardial Infarction Compared to HIV-uninfected Patients

While data from cohorts of HIV-infected patients have demonstrated an increased risk of myocardial infarction that is in part related to antiretroviral therapy, there are few studies comparing the risk of myocardial infarction in HIV-infected and uninfected persons. In a large database study from two Boston hospitals, the rate of myocardial infarction in HIV-infected patients was 1.77-fold higher than that of HIV-negative patients, with a more pronounced effect in women, reinforcing the need for aggressive risk modification [Triant V, et al. Abstract WEPE0179].

### Specific Interventions

The case for the use of omega-3 fatty acids in HIV-infected patients with hypertriglyceridemia was strengthened with the report of a randomized controlled trial of salmon oil (1 g three times daily) in 58 patients [Baril J, et al. Abstract WEPE0138]. Over the 12 weeks of observation, there was a 20% decrease in TG levels in those randomized to salmon oil, compared to a 7% increase in those

who did not receive any additional treatment. This effect was present but somewhat attenuated in those receiving other lipid-lowering agents. Omega-3 fatty acids do indeed provide additional benefits for HIV-associated hypertriglyceridemia, but it is not clear whether patients can reach their target using omega-3 fatty acids, either as an adjunctive or single therapy.

There are few effective treatments for fat accumulation in HIV-infected patients. In the late breaker session, results of a randomized trial were presented in which patients with evidence of body composition changes received either growth hormone (12-week induction of 4 mg qd) or placebo [Grunfeld C, et al. Abstract THLB0212]. Those who received active drug were randomized to 2 mg every other day or placebo for a 24-week maintenance period. Statistically significant reductions in visceral adipose tissue were observed after the induction period (20% vs. 4% in placebo), which generally persisted during the maintenance phase. However, the clinical significance of these changes requires clarification, and at this point growth hormone should not be recommended for this purpose.

### Body Composition Changes in the Developing World

Over the past decade, a substantial body of research has established the role of stavudine in the pathogenesis of glucose abnormalities, lipid alterations, and body composition changes, most notably lipoatrophy. There are few data reporting on the risk of these changes in patients in the developing world, where the use of stavudine is widespread. In a cohort of 226 HIV-infected patients in Rwanda, 25% had either lipoatrophy or lipohypertrophy after an average of 18 months on HAART, and these changes were seen more commonly in females [van Griensven J, et al. Abstract WEPE0140]. Given our understanding of the consequences of stavudine therapy on metabolic and morphologic parameters, a commitment to finding less toxic, low cost alternatives is critical. ▲



# Hepatitis: Limited Data, Lots of Unanswered Questions

By Kelly Gebo, M.D., M.P.H.

The lone oral session on hepatitis co-infection at IAS was called the “Hidden Epidemic.” Given the location of the session and the relative paucity of presentations on hepatitis, some thought that hepatitis was overlooked by the conference organizers. There were several studies of note, however.

## Prevalence of Hepatitis Co-infection

Dahoma and colleagues estimated the prevalence of HIV, HCV, and HBV in a study of patients using illicit drugs in Zanzibar, Tanzania in 2005 [Abstract WEAX0104]. Of the patients studied, 95% were male, and 93% were urban residents. In this study, they found that the risk behaviors of injection drug users (IDUs) in Zanzibar are concerning: 46% of IDUs share needles and 10% of performed “flashblood,” a technique used to obtain drug for those who can not afford it, in which a person who has money injects drug, then withdraws 2-3 cc of blood into the used syringe, which the next person then injects. Not surprisingly, the prevalence of HIV was high: 26% among IDUs vs. 5% among non IDUs. Of note, HIV prevalence was 17% in those who performed flashblood. In addition, 15% of patients had hepatitis C infection, with a greater prevalence in women than men (22% vs. 15%). Chamie and colleagues in San Francisco evaluated occult (seronegative) HCV co-infection among HIV-infected patients followed in several large HIV cohorts [Abstract WEPE0046]. They found that the prevalence of HCV, as determined by HCV RNA, was between 1.3 and 3.9% of HCV antibody-negative, HIV-infected patients. Factors associated with increased risk of seronegative HCV infection included history of injection drug use, increased ALT, and CD4 counts less than 200 cells/mm<sup>3</sup>.

## Treatment

Kruk and colleagues evaluated the success of treatment of acute HCV in a small study in Russia [Abstract WEAX0102]. They treated patients with acute HCV infection, seroconversion and positive qualitative HCV RNA of less than 6 months, with pegylated interferon (PEG IFN) alpha 2b (1.5 mcg/kg/week) and oral ribavirin

800 mg daily for 24 weeks. In an intention to treat analysis, the treatment response rates were 94%, 94% and 75% at 12, 24, and 48 weeks. As expected, response rates were lower in those with genotypes 1 and 4 compared to those with genotypes 2 or 3 (Table 1).

**Table 1. Treatment Response (HCV RNA Negative) By Genotype and Duration of Follow-up**

Duration of Therapy	Genotypic Group		
	Overall	Genotypes 2/3	Genotype 1/4
12 weeks	94%	95%	89%
24 weeks	94%	95%	89%
48 weeks	75%	78%	67%

Overall, this suggests that treatment of acute hepatitis C is of benefit, especially in those with genotypes 2 and 3. However, even in those with genotypes 1 or 4, the response rates were impressive, emphasizing the importance of diagnosing and treating hepatitis C in the acute phase.

In a sub-analysis of the APRICOT data, Sasadeusz and coworkers presented a study on the effect of baseline fibrosis on the safety and efficacy of PEG IFN alpha 2a (180 mcg/week) plus ribavirin 800 mg daily in HIV/HCV co-infected patients [Abstract WEPE0040]. They stratified their analysis on treatment response by baseline fibrosis score F0/1, F2, F3/4 and F5/6. Overall treatment response rates were lower in

patients with advanced fibrosis (Table 2). Adverse event rates were high in all categories; however, dose modification was required in more patients with advanced fibrosis than in those with no or minimal fibrosis.

## Solid Organ Transplantation

Roland and colleagues studied HIV-infected transplant recipients in San Francisco, following 18 with kidney transplants and 11 with liver transplants for 3 years [Abstract WEPE0052]. The rejection rates for kidneys were 52, 64 and 73% at 1, 2, and 3 years of follow-up, respectively. Ten percent of liver transplant recipients experienced rejection at years 1 and 3. There was no progression of HBV in HBV/HIV co-infected patients; however 67% of HCV co-infected patients had evidence of progression of liver disease on biopsy despite treatment with IFN and ribavirin. This suggests that liver transplantation may not be a panacea for patients with HIV-HCV co-infection with end-stage liver disease.

In summary, there were a few important hepatitis studies presented at IAS, emphasizing the importance addressing the high risk behaviors of many drug users, the need for education on risks of HIV and HCV transmission in those most at risk, the effectiveness of therapy for acute HCV infection, the importance of looking for seronegative HCV infection in immunosuppressed patients or those at high risk, and the potential limits of liver transplantation in HCV/HIV co-infected patients. ▲

**Table 2. Outcomes By Fibrosis Score**

Variable	Genotypic Group			
	F0/1	F2	F3/4	F5/6
Overall SVR	40%	50%	40%	28%
SVR genotype 1/4	28%	42%	25%	18%
SVR genotype 2/3	61%	78%	61%	50%
Any AE	96%	95%	98%	94%
Serious AE	15%	15%	21%	14%
Dose modification	56%	33%	56%	59%



## New Data on the Treatment of Antiretroviral-Experienced Patients

continued from page 1

conducted at several sites in Africa that is primarily designed to compare a less intensive with a more intensive monitoring strategy in patients initiating highly active antiretroviral therapy (HAART) with advanced disease. Nested within this study is a substudy assessing the feasibility and safety of structured treatment interruptions (STI). Participants who had attained a CD4 count of >300 cells/mm<sup>3</sup> after 48 to 72 weeks of HAART were randomized to continuous treatment versus cycled STI (12-week on/12-week off). At the late-breaker session, J. Hakim presented results from this sub-study, which has been halted due to a higher risk of disease progression in the STI arm than in the continuous therapy arm [Abstract THLB0207].

Unlike typical Western HIV clinical trials, three-quarters of the 813 participants in the DART STI sub-study were women. Clinical variables were well matched in the two arms, and participants had a median pre-HAART nadir CD4 cell count and a median current CD4 cell count of 130 and 360 cells/mm<sup>3</sup>, respectively. The most commonly used HAART regimen was zidovudine, lamivudine, and tenofovir. The median follow-up in the study was 51 weeks, with participants in the STI arm spending just 50% of follow-time taking HAART, as intended by the cycling strategy. The trial was halted by the data and safety monitoring committee in June 2006 when the STI arm was found to have a 2.7-fold higher risk of death or new WHO category 4 events (p=0.007) than the continuous therapy arm. The difference was driven by morbidity, not mortality: The mortality rate was low overall and was similar in the two study arms (1.3% vs. 1.0% annually in STI and continuous HAART, p=0.7). *Candida* esophagitis was the condition that accounted for a large proportion of the difference in the event rates between the two arms.

Preliminary results from the post-mortem on the Strategies for Management of Antiretroviral Therapy (SMART) trial were reported in two oral abstracts at a session devoted to STI strategies. SMART was a multinational study in which 5,472 participants who were doing well on HAART were randomized to continuous

**Table 1. Clinical Event Rates in SMART Study Arms According to Most Recent CD4 Cell Count During Follow-up**

Most Recent CD4 Cell Count (cells/mm <sup>3</sup> )	Opportunistic Disease or Death per 100 Person-Years		
	Structured Treatment Interruption	Continuous HAART	P value
<250	10.2	10.9	NS
250-349	3.7	3.0	NS
350-499	2.4	0.9	<0.05
>500	2.4	1.0	<0.05

HAART versus CD4-guided STI. According to the STI protocol, treatment was interrupted when the CD4 count was >350 cells/mm<sup>3</sup>, and was restarted when the CD4 count was <250 cells/mm<sup>3</sup>. The SMART trial was halted in January 2006 when the STI arm was found to have a 2.6-fold higher risk of death or opportunistic condition than the continuous HAART arm [El Sadr W, et al. 13th CROI, 2006, Abstract 106LB], a relative risk that was remarkably similar to that found in the DART study.

J.D. Lundgren presented a follow-up analysis from SMART using time-updated (i.e., the latest available) CD4 cell counts and HIV RNA values. The results indicated that differences in the time spent at various CD4 and HIV RNA strata explained much of the difference in clinical event rates between the two arms [Abstract WEAB0203]. Not surprisingly, the risk of disease progression was strongly linked to the time-updated CD4 counts and viral loads, irrespective of study arm. Equally unsurprising was that the subjects in the STI arm spent much more time with lower CD4 counts and higher viral loads than participants in the continuous treatment arm. For example, 69% of STI participant time was spent with a CD4 count <400 cells/mm<sup>3</sup>, compared to just 22% in the continuous therapy arm. When the analysis was adjusted for these differences, much of the difference in clinical outcomes between the arms was explained.

What remains remarkable, however, is the relatively high CD4 cell counts at which clinical events occurred. For example, in subjects who experienced a clinical event, the median CD4 counts closest to the event were 417 cells/mm<sup>3</sup> and

617 cells/mm<sup>3</sup> in STI and continuous therapy arms, respectively. It is also worth noting that the higher risk of disease progression in the STI arm can not be readily attributed to frequent failure to restart participants' HAART at the protocol-defined threshold of 250 cells/mm<sup>3</sup>. Only 3.1% of participant follow-up time in the STI was spent with a CD4 count <200 cells/mm<sup>3</sup>, compared to 0.8% in the continuous therapy arm.

While differences in current CD4 cell counts between the arms explained a substantial proportion of the risk difference, there was also evidence of excess risk in the STI arm at the highest CD4 cell count strata. As shown in Table 1, the clinical event rates were much higher at lower CD4 cell counts, but were similar in the STI arm and the continuous HAART arms in these lower strata. In contrast, the relative risk of clinical events was over 2-fold higher in the STI arm versus the continuous HAART arm at the highest CD4 cell counts.

At higher CD4 cell counts the differences in current HIV RNA levels tended to be larger between STI and continuous therapy subjects than in the lower CD4 count strata. This makes sense because continuous therapy patients with the highest CD4 counts were most likely to be doing well on HAART and to have suppressed viral loads. In contrast, participants in the STI arm with high CD4 cell counts would be the most likely to be off therapy, according to the CD4-guided protocol, and hence have high viral loads. The finding that the STI strategy was associated with excess risk in the highest CD4 strata may reflect viral load-mediated immune impairment that not is captured by the current CD4 cell count.

Waafa El-Sadr presented subgroup analyses from SMART [Abstract WEAB0203]. The



## New Data on the Treatment of Antiretroviral-Experienced Patients

increased risk of clinical progression associated with STI compared to continuous therapy was generally consistent across sub-groups analyzed, and no subgroup was identified in which STI was beneficial. Consistent with the Lundgren presentation, El-Sadr reported that the beneficial effects on disease progression with continuous therapy compared to STI was most evident in patients with the highest CD4 counts and undetectable HIV RNA levels at baseline (i.e., subjects who were doing the best on HAART at enrollment). The lesson here is that those who have gained the most from HAART have the most to lose by stopping.

One intriguing finding from sub-group analysis was that the relative risk of non-opportunistic condition-associated deaths in the STI arm compared to the continuous therapy arm was significantly higher in black than non-black participants. Some have speculated that immune activation or other adverse consequences of interrupting HAART may mediate progression of non-HIV associated disease, and that blacks may be more susceptible to these effects than other racial/ethnic groups. Additional investigations underway on the SMART data set may shed light on this issue.

At the STI session, Maggiolo presented 4-year clinical follow-up from the BASTA study (Italian for “enough!”) [Abstract WEAB0202]. This small study (n=114), which was not

powered to detect differences in clinical outcomes, found low and similar rates in disease progression in patients randomized to CD4-guided STI or continuous HAART. The STI guidance protocol in BASTA was also substantially more conservative than that use in DART or SMART. To be included in the study, subjects had to have a CD4 count >800 cells/mm<sup>3</sup> and HIV RNA <50 c/mL on HAART, and therapy was restarted in the STI arm when the CD4 count fell below 400 cells/mm<sup>3</sup>. Over prolonged follow-up, disease progression occurred in 3 participants assigned to continuous therapy (2 deaths and one case of cervical cancer) and no subjects assigned to STI. A longer duration of the first treatment interruption in the STI arm was strongly correlated with higher nadir CD4 cell count, as has been noted by others. The small sample size of BASTA is not sufficient to tell us that this safety-conscious STI protocol does not pose higher risk to participants than continuous HAART. Additionally, the proportion of the in-treatment HIV-infected population that would be eligible for STI under this protocol is quite small.

### Em-POWER-ed

Forty-eight week results from the pooled POWER-1 and -2 studies of ritonavir-boosted darunavir (DRV) in highly treatment-experienced subjects were reported by Lazzarin

[Abstract TUAB0104]. Twenty-four week results of these trials have been presented previously and were sufficiently impressive to earn FDA approval of DRV in June of this year. The similarly designed POWER-1 and POWER-2 were phase IIb studies in which triple-class experienced subjects were treated with an optimized background regimen (OBR) and were randomized to 1 of 4 doses of DRV or to a comparator protease inhibitor (CPI), which was selected by the investigator prior to randomization. Participants had a median of 8 protease resistance mutations at baseline, had received nucleoside reverse transcriptase inhibitors (NRTIs) for a median of 8.5 years, and most had been treated with enfuvirtide previously. Results were presented only for 124 participants in the CPI arm and 131 participants in the arm that received DRV 600 mg bid plus RTV 100 mg bid, which was the dose selected for further development and approved by the FDA. The results strongly favored DRV, with 61% achieving an HIV RNA reduction of  $\geq 1 \log_{10}$  c/mL from baseline at week-48, versus just 15 % in the CPI arm (P<0.001). A phenotypic susceptibility fold-change to DRV of >10 at baseline was associated with decreased response to DRV, and a fold-change of >40 appeared to obviate the possibility of achieving viral suppression in either arm.

### CCR5 Inhibitors Offer Next Ray of Hope for Patients with Highly Resistant Virus

In AIDS Clinical Trials Group (ACTG) 5211, 118 patients who were failing their current regimen and had R5-tropic virus at screening added either placebo or 1 of 3 doses of vicriviroc (VCV, a CCR5 coreceptor inhibitor under development) to their failing regimen for 14 days [Gulick R, et al. Abstract THLB0217]. Following the 14-day addition phase, all subjects substituted an OBR for their previously failing regimen. At 14 days the median HIV RNA decrease was approximately 1  $\log_{10}$  c/mL in the VCV arms versus no change in the placebo arm

**Table 2. Outcomes in Treatment-Experienced Subjects Assigned to Receive Darunavir or a Comparator PI in the POWER Trials**

Outcome	DVR/RTV (600/100 mg bid) n=131	Comparator PI n=124
Change in HIV RNA, baseline to week-48, $\log_{10}$ c/mL	-1.63	-0.35
HIV RNA <50 c/mL at 48 weeks		
Overall	46%	10%
Subjects with $\leq 1$ primary PI mutation	67%	19%
Subjects with $\geq 3$ primary PI mutation	44%	5%
Subjects with baseline FC $\leq 10$ to DRV	56%	14%
Subjects with baseline FC 10-40 to DRV	34%	0
Subjects with baseline FC $\geq 40$ to DRV	0	0
Mean CD4 count change from baseline to week-48, cells/mm <sup>3</sup>	+102	+19

PI, protease inhibitor; FC, fold-change in phenotypic resistance assay

*continued on page 14*



## New Data on the Treatment of Antiretroviral-Experienced Patients

continued from page 13

( $p < 0.001$ ). At week 24, 11% of subjects in the control arm had HIV RNA  $< 400$  c/mL compared to a range of 43% to 53% in the VCV arms. The lowest dose of VCV (5mg daily) was discontinued due to trends for a higher virologic failure rate and more frequent co-receptor switching in this arm. Although participants were required to have R5-tropic virus at screening, 10 participants had R5/X4 dual/mixed tropic virus at enrollment. The average HIV RNA change at 24 weeks was  $-0.77 \log_{10}$  c/mL in R5/X4 subjects compared to  $-1.83 \log_{10}$  c/mL in subjects with exclusively R5-tropic virus at enrollment. Five malignancies were diagnosed in VCV patients (2 non-Hodgkin's lymphomas, 2 Hodgkin's lymphomas, and 1 gastric adenocarcinoma) and 2 malignancies occurred in placebo recipients (1 case each of cutaneous and perianal squamous cell carcinoma). The potential association of malignancy with VCV is unclear, but is being followed closely.

R5-tropic virus is the infecting phenotype in the vast majority of HIV-infected individuals. However, tropism switches to X4 or dual/mixed tropism in approximately 50% of individuals during the natural history of infection. In the absence of effective therapy, this co-receptor tropism switch is correlated with increased viral load, more rapid CD4 decline, and a higher risk of clinical disease progression and death, although the causal pathway of this association has not been established. The possibility of accelerating disease progression with CCR5 inhibitors by selecting X4-tropic virus, either *de novo* or from pre-existing X4 variants that are below the limit of detection of current assays, has always been a concern for this drug class.

Mayer and coworkers addressed this concern to some degree in a study in which multi-class experienced patients with X4-tropic or dual/mixed-tropic virus were treated with 1 of 2 doses of maraviroc (MVC, another CCR5 co-receptor inhibitor under development) or placebo plus OBR [Abstract THLB0215]. The placebo and MVC groups experienced similar HIV RNA declines of approximately  $1 \log_{10}$  c/mL by week-24. However, CD4 cell increases were somewhat greater in the MVC arms than

in the placebo arm, even in subjects who had only X4-tropic virus at the time of virologic failure. This study provides some reassurance that using a CCR5 inhibitor in patients with dual/mixed-tropic virus, which will undoubtedly occur, will not subject those patients to more rapid immunologic deterioration by selecting X4- over R5-tropic virus.

### Transmitted Drug Resistance Holding Steady at 9%

The SPREAD study is a European surveillance cohort designed to track the prevalence of transmitted drug resistant in newly-diagnosed treatment-naïve HIV-infected individuals. In the 2002-2003 SPREAD cohort of 1,083 subjects, drug-resistant virus was detected in 9%, with 5.4% having NRTI resistance, 3.0% having PI resistance, and 2.6% having NNRTI resistance, and just 0.7% having multi-class resistance [Wensing AM, et al. Abstract TUAB0101]. In comparison with data from previous European surveillance studies conducted since 1996, the overall prevalence of drug resistance appears stable, with a decreasing prevalence of NRTI resistance, and trends toward increasing or stable prevalence of PI and NNRTI resistance. It's worth mentioning that the absence of an upward trend in transmitted drug resistance in Western Europe may be affected by the influx of HIV-infected immigrants from Africa, where transmitted drug resistance would be less likely than in developed countries with longstanding access to HAART.

Interestingly, in the SPREAD cohort, the prevalence of resistance was similar in subjects with documented HIV infection in the previous 12 months and in those with longer or unknown duration of HIV infection (10.6% vs. 8.7%, respectively). This supports other studies that have suggested that transmitted drug resistance mutations in treatment-naïve individuals may remain detectable in plasma longer than in patients with treatment-related drug resistance who have stopped therapy; presumably when resistant mutants are transmitted, wild-type virus is not present. Reversion to wild-type virus requires back-mutation rather than outgrowth of

pre-existing wild-type variants, a more time-consuming process. If true, this supports the recommendation for the routine clinical use of genotypic resistance tests in newly diagnosed treatment-naïve patients, regardless of their likely duration of infection.

### Conclusion

While treatment interruptions will continue to occur and may be needed in many HIV-infected patients over decades of treatment, data continue to amass from large well-conducted clinical trials suggesting that using STI as a strategy to lower cost or reduce drug toxicity places patients at higher risk of disease progression. These data also imply that delaying the initiation of HAART in patients with early-stage disease may not be as safe as we once believed. The impressive early results of DRV in highly drug-resistant participants in the POWER studies have been borne out to 48 weeks. Finally, CCR5 inhibitors offer hope for heavily treatment-experienced patients in need of a new drug class for salvage therapy. ▲

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The most relevant clinical pharmacology presentations during the XVI International AIDS Conference pertained to etravirine (ETV, TMC125), the second-generation investigational NNRTI from Tibotec that will soon be available through an expanded access program. ETV is a cytochrome P450 (CYP450) enzyme CYP3A4 substrate and also an inhibitor and inducer of several other CYP isoforms, making it susceptible to pharmacokinetic interactions with drugs metabolized through this pathway. Discussed below are data presented on drug interactions of etravirine with opioid replacement therapy and with acid-reducing agents.

### Etravirine and Methadone

Substance abuse is prevalent in the HIV-infected population. Methadone, a  $\mu$ -opioid receptor agonist used for the treatment of opioid addiction, is a substrate of CYP3A4, 2B6, and 2C19. Pharmacokinetic interactions with methadone have been established for a number of antiretroviral drugs, including the induction of its metabolism by the NNRTIs efavirenz and nevirapine. Thus, questions about the safety of coadministering methadone and HAART surface frequently in clinical practice. ETV inhibits CYP3A4 and 2D6 and induces 2C8, 2C9, 2C18, and 2C19 *in vitro* and thus could potentially alter methadone plasma concentrations and lead to narcotic overdose or withdrawal.

Scholler-Gyure and her colleagues from Tibotec evaluated the two-way interaction between methadone and ETV in an open-label, steady-state pharmacokinetic study [Abstract TUPE0084]. Methadone is a chiral mixture of the inactive S-(+) and active R-(-) enantiomers; all opioid activity resides in the active R-(-) form. Sixteen HIV-negative males on individualized methadone maintenance therapy (dose range, 60-130 mg/day) were treated with ETV 100 mg bid for 14 days. The mean methadone  $AUC_{12h}$ ,  $C_{max}$  and  $C_{min}$  decreased by 7%, 6%, and 9%, respectively, on day 7 for S-(+) methadone, and increased by 8%, 12% and 3%, respectively, for R-(-) methadone. The mean methadone  $AUC_{12h}$ ,  $C_{max}$  and  $C_{min}$  all decreased by 11% on

day 14 for methadone S-(+), and they increased by +6%, +10% and +2%, respectively, for methadone R-(-), when coadministered with ETV compared to when given alone. These changes were not considered to be clinically significant and were not associated with opiate withdrawal symptoms requiring modification of the methadone dose. ETV plasma concentrations were not affected by methadone coadministration.

These results suggest that the combination of methadone and ETV does not result in harmful pharmacokinetic drug interactions. It remains to be determined whether the lack of pharmacokinetic interaction with ETV will hold true for other opioid replacement agents such as buprenorphine, which is also a substrate of the CYP3A4 enzyme.

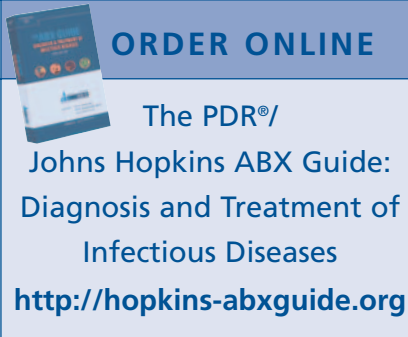
### Etravirine and Acid-Reducing Agents

Gastroesophageal reflux disease is a prevalent condition in patients with HIV infection and requires treatment with acid-lowering agents. For some antiretroviral agents, absorption is highly dependent on optimal acidic gastric pH. Thus, coadministration of antiretrovirals and acid-lowering agents could potentially interfere with antiretroviral absorption and lead to subtherapeutic levels and treatment failure.

The same group of investigators from Tibotec investigated the effects of the proton pump inhibitor omeprazole and the H2 blocker ranitidine on plasma concentrations of ETV [Scholler-Gyure M, et al. Abstract TUPE0082]. In this open-label, three-period, cross-over pharmacokinetic study, 19 HIV-negative healthy volunteers (7 females/12 males) were evaluated: In period 1 subjects received a single dose of ETV 100 mg; in period 2 they were given ranitidine 150 mg po bid for 11 days + a single dose of ETV 100 mg on day 8; in period 3 they were given omeprazole 40 mg po qd for 11 days + a single dose of ETV 100 mg on day 8. Treatment periods were separated by 14 days. The ETV steady-state mean  $C_{max}$  and the  $AUC_{last}$  decreased by 3% and 16%, respectively, in the presence of ranitidine and increased by 13% and 41%, respectively, when

coadministered with omeprazole. The reduction in ETV plasma concentrations when coadministered with ranitidine was not considered clinically significant. The increase in ETV plasma concentrations probably reflects inhibition of CYP2C19 by omeprazole and is not thought to have clinical relevance given the safety profile of ETV. There were no serious adverse events or discontinuations, and the study drugs were well tolerated.

In summary, ETV can be safely coadministered with methadone, ranitidine or omeprazole. This is fortunate, since these drugs are commonly used in the treatment of patients with HIV disease. ▲



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### Antiretroviral News: Initial Therapy

*continued from page 5*

guidelines recommend a nucleoside backbone of either TDF/FTC, AZT/3TC, or ABC/3TC plus either EFV or one of four boosted PIs: LPV/r, ATV/r, FPV/r, or saquinavir/ritonavir (SQV/r). Nevirapine is listed as an alternative NNRTI for selected patients. In contrast to the DHHS guidelines and previous versions of the IAS-USA guidelines, no alternative regimens are listed, which now seems appropriate, since it's unlikely that there would ever be a reason to stray from the recommended options in patients infected with wild-type virus.

For the immediate future, the 2 NRTI plus NNRTI or boosted PI approach is unlikely to change, though there are a number of new agents in development, especially the integrase inhibitors, which could eventually challenge our approach to treatment-naïve patients. ▲

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