

THE HOPKINS HIV REPORT

A bimonthly newsletter for health care providers

Antiretroviral News from the 41st ICAAC

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

The 41st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held in Chicago from December 16 to 19, had been postponed due to the events of September 11, 2001. As a result of the awkward timing, attendance was somewhat sparse. Antiretroviral news was somewhat sparse, as well, which probably has more to do with the growing number of conferences at which data pertaining to HIV infection and its treatment are presented.

Resistance

Not surprisingly, the most widely publicized presentation at ICAAC was Doug Richman's analysis of drug resistance from the HIV Cost and Service Utilization Study (HCSUS) [Abstract LB-17]. The media were quick to trumpet the bad news that drug resistance is common, but most of the time they got the story wrong. HCSUS is a longitudinal cohort of patients receiving care at a variety of U.S. sites that was established in 1996. Results from 1906 plasma samples were weighted and modeled to represent 208,724 patients with HIV infection under care in the U.S. Viral load was undetectable (<500 c/mL) in 698 of the 1906 samples, and was >500 c/mL in 1208 samples (63.4%). Of those with detectable viremia, phenotypic resistance testing could only be performed in 1080 samples, representing 117,976 U.S. patients. Drug-resistant virus was found in 78% of those samples, a figure that led to the erroneous headline that "three-quarters of U.S. patients have drug resistance." If one made the unreliable assumption that those with undetectable virus had no resistance, the proportion with resistance would be approximately 50%. Among those with



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viremia, nucleoside analog resistance was observed in 70% of the samples, the majority having 3TC resistance. PI and NNRTI resistance was observed in 42% and 31%, respectively. Over 50% of samples had resistance to two classes, and 14% had resistance to all three classes. Resistance was noted in 87% currently on therapy and 41% of those not currently under treatment, as well as in 20% of those who claimed to have never received antiretrovirals. Predictors of resistance in a multivariate model included lower CD4 nadir, higher baseline viral load, male sex, being treated in a smaller practice, and geographic region, with the lowest levels of resistance being observed in patients from the Midwest.

While these findings are disturbing, the gloom and doom message has been

exaggerated. First, it is important to remember that the presence of drug resistance does not mean that patients are untreatable. 3TC resistance, for example, was the most common type of nucleoside resistance observed in this study and is extremely common in patients who have been treated with that drug. While it decreases the antiviral activity of 3TC, it may have beneficial effects with respect to the activity of thymidine analogs and tenofovir. Second, the susceptibility cut-offs used in this study to define resistance to PIs and NNRTIs was a 2.6-fold change, which is lower than the cut-offs used clinically for some of these agents. This may have resulted in an over-estimate of resistance to

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some drugs. Finally, this cohort enrolled in 1996, a time when many patients had been treated with sub-optimal therapy and when our understanding of how to use HAART was primitive at best. The temporal effect may limit our ability to generalize these findings to patients beginning therapy today. It should also be noted that this study once again emphasizes the importance of care by experts. Patients seen in larger HIV practices had less resistance, a finding contrary to what might be expected, since patients are often referred to HIV experts only after they have failed initial regimens.

When to Start Therapy

Matthias Egger reported combined data from 13 European and U.S. cohorts looking at 12,574 patients initiating antiretroviral therapy [Abstract LB-18]. Mean duration of follow-up was 2 years, representing an impressive 24,310 person-years. The goal of the study was to estimate the probability of progression to a new AIDS event or death for naïve patients starting therapy and to determine factors associated with AIDS-free survival. There was a total of 1045 AIDS events and 344 deaths among patients in these cohorts during the follow-up period. As has been seen in other cohorts, the most important predictor of AIDS-free survival was CD4 count at initiation of therapy. Those who started therapy with CD4 counts >200 cells/mm³ had an estimated 3-year AIDS-free survival of 95%, compared with 75% in those with baseline CD4 counts <50 cells/mm³. There was no significant difference in AIDS-free survival for patients who started therapy in CD4 strata above 200 cells/mm³, but those with CD4 counts <200 cells/mm³ had a lower AIDS-free survival than those with higher CD4 counts at baseline. Using patients with baseline CD4 count <50 cells/mm³ as a comparator (RH=1.0), the relative hazard for AIDS events or death was 0.75 for those with CD4 counts of 50-99 cells/mm³, 0.53 for those with 100-199 cells/mm³, 0.25 for those with 200-349 cells/mm³, and 0.18 for those initiating therapy with ≥ 350 cells/mm³. In contrast, baseline viral load was not an important predictor of AIDS-free survival unless it was over 100,000 c/mL, in which case estimated 3-year AIDS-free survival was 85%, compared to 90-95% with a viral load $<100,000$ c/mL. Other factors significantly associated with AIDS events or death

included age >50 years, injection drug use, and CDC stage C disease.

These data from a very large cohort may have greater relevance to today's practice than data from cohorts in the pre-HAART era. They support current treatment guidelines which recommend deferral of therapy and emphasize the importance of the CD4 count as the most important indicator of need for therapy. However, it should be noted that the amount of follow-up time in this study is limited, as it is in a number of the other cohort studies that have led to a change in treatment practices and recommendations. Ongoing follow-up from these large and important cohorts will help to determine the safety of deferral of therapy, since we may never answer the question of when to start therapy based on randomized, controlled clinical trials.

Switching Therapy

Christine Katlama presented data from the TRIZAL study, in which patients on HAART with viral loads <400 c/mL for at least 6 months and viral loads <50 c/mL at screening were randomized to continue their current therapy (n=103) or to switch to AZT/3TC/ABC (Trizivir, n=106) [Abstract I-671]. At 48 weeks 22% of the patients in both arms had experienced treatment failure (virologic failure or premature discontinuation) by intent-to-treat analysis. However, at 24 weeks virologic failure had occurred in 5 patients in the AZT/3TC/ABC compared to 1 patient in the continued HAART arm. Three of the 5 patients failing triple nucleoside therapy at 24 weeks achieved undetectable viral loads at 48 weeks, one with the addition of efavirenz. Minimal data were presented regarding resistance patterns in patients experiencing virologic failure. Another question that needs to be answered by such switch studies is whether patients with baseline viral loads $>100,000$ c/mL, who appear to have poorer responses to initial therapy with AZT/3TC/ABC, can safely switch to a triple nucleoside regimen after achieving virologic suppression on other HAART regimens.

In the SWITCH study, regimens were proactively switched at pre-determined time intervals. Patients were randomized to receive d4T/ddI/EFV (n=52), AZT/3TC/NFV (n=54), or to alternate between these two regimens at 3 month intervals (n=55)

[Abstract I-672]. By intent-to-treat analysis at 48 weeks, 69% of those in the switch arm had a viral load <400 c/mL compared to only 57% of those on stable therapy (100% vs 85% by as-treated analysis). Adherence levels were high and did not appear to differ among the three arms. The reason for the improved response in the alternating therapy group is unclear.

Stopping Therapy

This author presented data from an observational study of 62 patients without a history of CDC-defined AIDS who discontinued therapy with the intention of restarting based on laboratory parameters [Parish M, et al. Abstract I-673]. At the time of the analysis, 74% remained off therapy after a mean interruption of 64 weeks. The remaining 26% resumed therapy after a mean interruption of 33 weeks. The estimated rate of CD4 decline was 409 cells/yr among those who resumed therapy vs 124 cells/yr among those who remain off therapy. The median estimated time to CD4 <200 cells/mm³ was 1.7 yrs vs 4.6 yrs, respectively. While 88% of resumers and 70% of non-resumers met earlier DHHS criteria for initiation of antiretroviral therapy (p=0.154), only 50% of resumers and 26% of non-resumers met criteria according to 2001 DHHS guidelines (p=0.077). Factors significantly associated with resumption of therapy and rate of CD4 decline included pre-HAART viral load and CD4 nadir as well as viral load rebound following treatment interruption. Although one patient in the cohort experienced symptomatic viral rebound, no opportunistic infections or other HIV-related complications occurred during treatment interruption. Most of the patients who resumed therapy achieved viral resuppression, and there was a suggestion of improvement in some of the metabolic complications of HAART during treatment interruption. These findings suggest that for a subset of patients, especially those with relatively high pre-treatment CD4 counts and/or low pre-treatment viral loads, prolonged treatment interruption may be possible, with resumption of therapy based on the same criteria that would be used in a naïve patient. This strategy is often referred to as "pulse therapy," and is being tested in large-scale randomized clinical trials. However, it is also likely that these results



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can be explained in part by a temporal effect: Many of the patients in this study may have done well off therapy because they had marginal indications for therapy to begin with. As we move toward later initiation of therapy, it is possible that fewer patients will be good candidates for prolonged treatment interruption.

Tenofovir

The 41st ICAAC was an important conference for tenofovir disoproxil fumarate (TDF, Viread™, Gilead Sciences), though the data would have been less anticlimactic had they been presented as planned in September before the drug was approved by the FDA. Tenofovir is a nucleotide reverse transcriptase inhibitor that is administered as a single 300 mg tablet once daily with food. Kathleen Squires presented data from the Gilead 907 study, a phase III randomized, double-blind, placebo-

controlled trial in which 552 patients experiencing virologic failure (HIV RNA 400-10,000 c/mL) on a stable antiretroviral regimen were randomized to add TDF (n=368) or placebo (n=184) to their existing regimen [Abstract I-666]. At 24 weeks, patients who added TDF had a drop in viral load of 0.61 log₁₀ c/mL compared to a drop of 0.03 in the placebo group (p<0.0001). Viral load was <400 c/mL in 42% of the TDF recipients and 13% of the placebo recipients (p<0.0001), and 22% vs 1% had viral loads <50 c/mL (p<0.0001).

Michael Miller presented data from a resistance sub-study involving 253 evaluable patients from the 907 trial [Abstract I-1928]. Patients with an isolated M184V mutation at baseline had a somewhat more pronounced drop in the viral load than the group overall, but when M184V was combined with thymidine analog mutations (TAMs), this difference

disappeared. Both the K65R mutation and the T69SSS insertion mutation are known to cause loss of susceptibility to TDF, but in the 907 sub-study, patients with 3 or more TAMs that included either M41L or L210W also had a poor response to addition of TDF. There is probably no single clinically relevant susceptibility cut-off for TDF. Patients with a <1-fold change in susceptibility have the best response, and those with >4-fold decrease in susceptibility can be considered resistant. However, those with a 1-4-fold loss of susceptibility may still respond to TDF, not unlike abacavir, where a 4.5-6.5-fold change in susceptibility indicates intermediate resistance and partial activity. Fortunately, the development of RT mutations appears to be uncommon in patients treated with TDF for 96 weeks [Schooley R, et al. Abstract I-1929].

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The demonstration of cross-resistance between TDF and nucleoside analogs suggests that this is not a salvage drug. It is currently being used as a nucleoside alternative in patients with prior nucleoside experience or for intensification in patients with low-level virologic failure, as in study 907. However, its simple once-daily dosing, excellent tolerability [Becker S, et al. Abstract I-1930; Schooley R, et al. Abstract I-1929], and apparent lack of mitochondrial toxicity make it a promising agent for use in initial therapy. The results of the ongoing Gilead study 903 will help us to determine the role of this drug for the treatment of naïve patients.

Although TDF appears to have few drug interactions, it also appears to increase the AUC of buffered ddI by 40% [Flaherty, et al. Abstract I-1729]. This is concerning, as co-administration of these two drugs could result in increased ddI toxicity, including neuropathy and pancreatitis. Studies have not been carried out yet using the enteric coated formulation of ddI (Videx EC). It may also be possible to offset this interaction by administering both drugs with food. If this approach is supported by ongoing studies, it would make it much easier to use TDF and ddI together in once-daily regimens.

Investigational Antiretroviral Agents

- **TMC 125** is a "second generation" NNRTI being developed by Tibotec-Virco. It demonstrates *in vitro* activity against highly NNRTI-resistant virus. Results of a phase 2 trial were presented by van't Klooster, in which 12 treatment naïve patients received 7 days of monotherapy with TMC 125 at a dose of 900 mg bid, compared with 6 patients who received placebo [Gruzdev B, et al. Abstract I-668]. All doses were directly observed. Patients receiving active drug experienced an impressive 2 log drop over the one-week treatment period (range 1.13-3.30 log₁₀ c/mL). Eight achieved viral loads <400 c/mL in 7 days, and two achieved viral loads <50 c/mL. Some formulation issues will have to be worked out before this promising agent is brought to large scale clinical trials, however. Patients on active drug swallowed 18 pills twice daily!

- **Tipranavir (TPV)** is a non-peptidic protease inhibitor being developed by Boehringer Ingelheim. It has promising

activity against a wide variety of PI-resistant strains. Charles Farthing reported 16-week data from an open-label, randomized trial comparing two doses of TPV/RTV (500/100 mg bid and 1250/100 mg bid) with SQV/RTV (400/400 mg bid) in patients who had failed a single PI (HIV RNA >1000 c/mL) and who had at least 2 NRTIs available [Slater L, et al., Abstract LB-15]. By a modified intent-to-treat analysis, viral load reduction was greater in the TPV/RTV arms than in the SQV/RTV arm (-1.41 vs -0.87 log₁₀ c/mL). Although the data were not presented orally, the abstract indicated that the proportion of patients who achieved viral loads <400 c/mL was somewhat higher in the high-dose TPV/RTV arm (55%) than in the low dose or SQV/RTV arms (39% and 40% respectively). GI toxicity was more common in the high dose TPV/RTV arm. Of note, 42% of the patients in this protocol had no demonstrable PI resistance despite experiencing virologic failure on a PI-based regimen. Clearly, the real test of this agent will be in patients with more extensive PI resistance than was seen in this trial. Dosing issues also need to be worked out: TPV/RTV doses currently being studied are 500/100, 500/200, and 750/200 mg bid.

- **Atazanavir (Zrivada™, Bristol-Myers Squibb)** will most likely be the next protease inhibitor approved by the FDA. It is administered once daily, and appears to have little if any adverse effect on lipid profiles. Sanne presented results from BMS 008, in which naïve patients (mean baseline viral load ~4.7 log₁₀ c/mL) were randomized to receive atazanavir (TAZ, 400 or 600 mg qd) or nelfinavir (NFV, 1250 mg bid) plus d4T/3TC. By intent-to-treat analysis (last observation carried forward), the proportion of patients in the 3 arms with viral load <400 c/mL at 48 weeks was 65%, 62%, and 59% respectively. The proportion with viral load <50 c/mL was 31%, 36%, and 38%. By as-treated analysis, the proportion with viral load <400 c/mL was 74%, 75%, and 60%, respectively (p<0.05 for TAZ vs NFV), and the proportion with viral load <50 c/mL was 40%, 41%, and 39% (NS). Increased cholesterol was seen in 5-7% of patients randomized to receive TAZ compared to 20-25% of those taking NFV, and diarrhea was less common among TAZ recipients. Indirect hyperbilirubinemia, including

clinically apparent jaundice, was more common in patients in the 600 mg arm, and further development will proceed with the 400 mg qd dose.

Like ritonavir, TAZ increases levels of other protease inhibitors through its inhibitory effect on the CYP 3A4 enzyme system. The possibility of using TAZ to boost levels of other PIs is attractive, since it is less likely to cause hyperlipidemia than ritonavir. David Haas presented results of BMS 009, in which patients experiencing virologic failure on HAART (HIV RNA 2,000-100,000 c/mL) received TAZ/SQV at a dose of 400/1200 mg qd (n=34) or 600/1200 mg qd (n=28) or RTV/SQV at a dose of 400/400 mg bid (n=23) [Abstract LB-16]. Patients in each arm experienced a 1-1.5 log drop in viral load at 24 weeks, but those on the TAZ-based regimens had more favorable lipid profiles.

- **Emtricitabine (FTC, Coviracil™, Triangle Pharmaceuticals)** is a nucleoside analog with a resistance pattern that is essentially identical to that of 3TC. Its long-term safety profile also appears to be comparable to that of 3TC [Benson C, et al. Abstract I-1931], and patients who switched from 3TC to FTC had equivalent virologic results compared to those who remained on 3TC [Van der Horst C, et al. Abstract I-1932]. Although it doesn't appear to have any obvious advantages over 3TC (both have pharmacokinetics that support once-daily dosing), it might have a niche if it were to be co-formulated with other once-daily agents.

Boosted PI Regimens

- **SQV/RTV:** Julio Montaner presented data from the FOCUS trial, an open-label trial comparing once daily SQV/RTV (1600/100 mg) vs EFV, both in combination with 2 nucleoside analogs. The trial involved 161 naïve patients. EFV was clearly better tolerated: Eight patients discontinued therapy in the SQV/RTV arm vs one in the EFV arm. Nausea was seen in 22% vs 1%, and vomiting in 6% vs 0%. As a result, EFV was superior by intent-to-treat analyses, with 81% achieving viral loads <50 c/mL compared to 60% in the SQV/RTV arm (p=0.008). By as-treated analysis, the results were 90% and 81% (p=0.224). It was postulated that the hard-gel formulation of SQV (Invirase), which achieves similar drug concentrations when combined with RTV, might be better



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tolerated than the soft-gel formulation (Fortovase). Interestingly, there was no difference in potency in either arm between patients with baseline viral loads <100,000 c/mL or those with >100,000 c/mL, a finding that has previously been demonstrated with EFV and LPV/RTV (Kaletra), but not with SQV/RTV.

• **IDV/RTV:** Young presented data on 89 naïve patients treated with IDV/RTV (800/100 mg bid) plus d4T/3TC [Abstract I-1923]. By an intent-to-treat, non-completer=failure analysis, viral load was <50 c/mL in 42% of patients at 24 weeks, due in part to a high non-completion rate. Approximately half withdrew consent, and half had side effects, including a high incidence of nephrolithiasis. Katner presented data on 63 treatment experienced patients who received IDV/RTV at a dose of 800/200 mg bid in combination with 2 NRTIs [Abstract I-1922]. By as-treated analysis, 78% had viral loads <400 c/mL and 54% had VL <50 c/mL at 24 weeks.

• **APV/RTV:** A comparison of two APV/RTV regimens (600/100 and 900/100 mg bid) suggested that the lower dose is preferred because of similar efficacy and APV concentrations with decreased toxicity and discontinuation [Schooley R, et al. Abstract I-1924].

• **LPV/RTV:** Danner presented data assessing response rates to LPV/RTV among 57 treatment-experienced patients treated with standard dose LPV/RTV plus EFV and NRTIs [Abstract I-1925]. He found that patients with less than a 10-fold reduction in phenotypic susceptibility to LPV had a 93% response rate (<400 c/mL) at 72 weeks, and those with up to 5 PI resistance mutations had a 91% response. After 14 days, patients were randomized to increase the dose of LPV/RTV to 533/133 mg bid or to remain on the standard dose. It is now recommended that the higher dose be used in combination with EFV or NVP, especially in experienced patients where reduced susceptibility to LPV is expected.

Safety of Antiretroviral Therapy During Pregnancy

• Reassuring data from the CDC's Antiretroviral Pregnancy Registry were presented by Garcia [Abstract I-1325]. In an analysis of 1630 evaluable cases, the prevalence of birth defects after first trimester exposures was 12 per 638 live

Report from ICAAC: Update on Opportunistic Infections

By John G. Bartlett, M.D.

Henry Masur from the NIH [Abstract 586] reviewed selected topics in the category of opportunistic infections (OIs). He noted that the incidence of all OIs has decreased substantially. The incidence began to fall in the late 1980's with the advent of nucleoside analog therapy and prophylaxis of opportunistic infections, and dropped more dramatically with the introduction of HAART in the mid to late 90's. The most dramatic changes were in PCP, MAC, CMV, and toxoplasmosis. However, the frequency of these OIs has remained relatively stable since 1997, suggesting that "we've gone about as far as we can go." With regard to the frequency of OIs, more recent data indicate the following:

- 1) The current CD4 cell count rather than the CD4 nadir predicts the likelihood of developing OIs.
- 2) The viral load also correlates with OI risk.
- 3) Only about 50% of patients in clinical trials achieve the HIV viral load goal of <50 c/mL, which portends more therapeutic failures and an increase in the incidence of OIs.

With regard to cost effectiveness, the cost/quality-adjusted life year (QALY) for MAC prophylaxis with azithromycin is \$31,000-\$35,000 and \$2,300 for PCP prophylaxis with TMP-SMX. Both are cost effective compared with other commonly accepted medical interventions such as mammogram, dialysis, or coronary bypass.

Why does PCP, a preventable disease, still occur in the era of HAART and PCP prophylaxis? An analysis of 2,365 cases from 1996-1999 showed that 45% of patients with PCP had not been receiving HIV care; 14% were receiving care but not receiving prophylaxis; 34% were receiving prophylaxis; 6.5% were not receiving prophylaxis because criteria for prophylaxis had not been met. Dr. Masur also discussed the implications of *P. carinii* resistance due to mutations in dihydropteroate synthase (DHPS). DHPS is essential for folate metabolism and is the target for sulfonamides and dapsone. There are substantial geographic variations in the distribution of resistance mutations, and there is a correlation with prior exposure to sulfonamides. Nevertheless, the data demonstrating reduced response is considered inconclusive, so these drugs are still considered to be the preferred agents for both prophylaxis and treatment. However, Masur warns that this could be problematic in the future and needs to be carefully followed. He also pointed out that the trimethoprim component in TMP-SMX is superfluous, since trimethoprim has no activity against *P. carinii*. Leucovorin should not be given when treating PCP with TMP-SMX because it reverses the anti-folate effect.

Dr. Masur finished by summarizing data on IL-2 therapy and suggested that it is time to give this approach a hard look. IL-2 is now administered by subcutaneous injection rather than by IV, making outpatient treatment feasible. There have been successful trials in other countries (Thailand and Argentina), demonstrating feasibility even in resource limited settings. The flu-like side effects are self-limited. Masur also noted that prior studies have shown that once a CD4 cell count increase has been achieved, the effect may be prolonged so that repeated treatment is not required. Large trials in patients with baseline CD4 cell counts >350/mm³ have shown substantial increases in the CD4 count, averaging 232 cells/mm³, with no important changes in viral load compared with controls. Two major trials are ongoing: 1) ESPRIT, for patients with a baseline CD4 count >300/mm³, and 2) SILCAAT, for patients with a CD4 count of 50-299/mm³. These large, multicenter clinical endpoint trials will assess whether the CD4 count increases associated with IL-2 therapy result in a reduction in HIV-related complications and an improved prognosis. Masur concluded that future strategies may include HAART followed by IL-2. ▲

births (1.9%). Results were similar for AZT or 3TC, given either alone or in combination with other agents. This is similar to what is seen in the general

population, suggesting that there is no significant increase in birth defects with first trimester exposure to antiretroviral agents overall or for AZT or 3TC in particular. ▲



Update from the 3rd International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV

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

The 3rd International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, held in Athens, Greece on October 23-26, presented a number of well conducted studies that provide further hints into the pathogenesis of antiretroviral complications.

Thyroid

Two studies reported an increased prevalence of thyroid abnormalities in HIV infected patients. An evaluation of 221 consecutive patients (132 men, 59 women) found 12 with clinically apparent hypothyroidism, 7 with sub-clinical hypothyroidism, and 8 with transient abnormalities. Overall, 7.9% of men and

8.6% of women were hypothyroid. [Esnault JL, et al. Abstract 16]. Another 18 month study of 80 patients (65 male) on ART found 11 with autoimmune thyroiditis (transient in 9), 4 with hypothyroidism, 4 with "euthyroid-sick syndrome," and 4 with mild primary hyperthyroidism. A high prevalence of autoantibodies was seen, and the TSH was not found to be a sensitive screening test [Liognon M, et al. Abstract 80]. While these data are interesting, the message is unclear. Most patients were asymptomatic and abnormalities were often transient. However, hypo- or hyperthyroidism should be considered in a patient presenting with compatible symptoms.

Indinavir Nephrotoxicity

A nested sub-study within HIV-NET in Thailand found that the IDV dose schedule did not have an impact on renal stone formation. One hundred sixty-four patients receiving AZT+3TC plus IDV 800 tid or IDV/RTV 800/100 mg bid were followed for 64 weeks [Boyd M, et al. Abstract 10]. There was no difference in the incidence of kidney stones (17% tid vs. 22% bid) nor in IDV crystalluria (40%). Of concern, 27% of patients had at least a 25% decrease in creatinine clearance. Women were more likely to experience renal insufficiency than men (OR 2.3, 95% CI 1.3-4.2), and a multivariate analysis found that female sex was associated with pyuria (OR 2.0, 95% CI 1.3-3.2), hematuria (OR 3.2, 95% CI 1.6-6.3), and crystalluria (OR 2.3, 95% CI 1.3-4.2). Reduced baseline creatinine clearance was not associated with worsening renal function at week 64. However, the increased risk among women has important clinical implications, and the finding of a 25% loss of renal function is concerning. Furthermore, several unanswered questions remain. Were patients adequately hydrated? Does the early finding of crystalluria require that IDV be stopped? Can we prevent or slow deterioration of renal function with aggressive hydration? Finally, the creatinine clearance formula is affected by fat free mass, which can change with HAART.

Insulin Resistance and Hyperglycemia

A number of carefully-conducted studies suggested varying mechanisms for PI-induced insulin resistance. Most studies evaluated IDV, which may be the worst

offender in this class. Potential mechanisms include:

1. Direct inhibition of the Glut-4 transport, studied in *Xenopus laevis* oocytes [Murata H, et al. Abstract 1] and rodents [Hruz PW, et al. Abstract 2];
2. Acute decrease in total and non-oxidative insulin-stimulated glucose disposal, as measured by a sophisticated euglycemic, hyperinsulinemic clamp technique in 6 HIV-negative volunteers after a single oral dose of IDV 1200 mg, randomized in a double-blind, crossover fashion [Noor MA, et al. Abstract 3];
3. Skeletal muscle insulin resistance, measured by reduced glucose uptake and impaired intracellular glucose phosphorylation using PET scans and the insulin clamp in 5 subjects on HAART compared to 6 untreated HIV-infected subjects [Behrens G, et al. Abstract 4];
4. Hepatic insulin resistance and impaired peripheral glucose disposal suggested by similar hepatic glucose production in 18 male patients with lipodystrophy and 18 HIV-infected males without lipodystrophy, despite increased fasting insulin levels in the former group [Hugaard SB, et al. Abstract 5].

Taken together, there are multiple, complex and possibly interactive hypotheses to explain the mechanisms for PI induced insulin resistance.

Mitochondria

Mitochondrial damage can lead to lactic acidemia and may play a role in fat atrophy. Walker evaluated mitochondria (mt) DNA depletion in HepG2 hepatoma cells grown in a combination of NRTIs at concentrations equivalent to one third, full, and 10-fold steady state peak plasma levels in humans [Abstract 18]. MtDNA depletion was greatest with ddI, followed by d4T, and lowest for 3TC and AZT. The highest lactate levels were seen with ddI and ddI/3TC. AZT induced morphologic changes, but no changes in mtDNA. Cells grown in the presence of EFV demonstrated no changes, and ABC was not tested. With the exception of the ddI/d4T combination, which had the same effect as with ddI alone, combinations of NRTIs exhibited increased toxicity compared to individual drugs, and changes reversed when drugs were withdrawn. In a separate study, tenofovir,

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Update from the 3rd International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV

even at high doses, did not affect mtDNA [Biesecker G, et al. Abstract 37].

In vivo changes are often different than *in vitro*. However, this study demonstrates that nucleosides damage mitochondria. The damage is worse with combination therapy and varies according to the NRTIs used.

HAART: Metabolic and Body Shape Changes

• Protease Inhibitors:

Michael Dube [Abstract 14] reported 48-week data on sophisticated body and metabolic evaluations of 14 non-diabetic, PI naive patients (12 men, 2 women) with CD4 counts >100 cells/mm³ (mean 264) and mean HIV RNA 5.0 log₁₀ c/mL who were receiving open label ABC+3TC+APV 1200 mg bid. CD4 cells increased in all subjects, and 11 of 14 had viral loads <400 c/mL, and 9 had <50 c/mL. There was no short-term insulin resistance, but insulin resistance did occur by week 48, possibly due to weight gain. There was a trend toward increased fasting insulin levels without change in fasting glucose. On average, subjects' weight increased 5 kg. Bone content increased minimally (0.18 0.14 p=0.02), total/HDL cholesterol ratios did not change, and no subject reported loss of leg or face mass. This is an interesting study, but is limited by the open-label, non-comparative design and the small sample size.

Although PIs produce insulin resistance, the strength of the effect varies within the class. In an *in vitro* study [Caron M, et al. Abstract 24], IDV had a negative effect on a number of different adipocyte functions (adipogenesis, insulin action on MAP and kinases, expression of SREBP-1, PPAR γ , and apoptosis in 3T3-F442 adipocytes) in a dose-dependent fashion. Nelfinavir (NFV) had a less pronounced effect, and amprenavir (APV) lower still. Long-term treatment of cells with IDV or NFV, but not APV, promoted cell apoptosis (fat cell death). Treatment with rosiglitazone prevented these effects.

• **AZT/3TC/ABC and Switch Studies:** A 48-week open-label study suggested that lipid profiles and self-reported body shape improve after switching to a triple nucleoside regimen while maintaining viral suppression on an earlier HAART regimen [Lafeuillade E, et al. Abstract 28]. Subjects were randomized to continue their current regimen or change to AZT/3TC/ABC if their CD4 count was >100 cells/mm³ and HIV RNA was <500

c/mL for 6 months and <50 c/mL at the time of switch. Between groups, there were no baseline differences in self-reported body changes, but by week 48, 42% of subjects on their original regimen reported ≥ 1 symptom of lipodystrophy, compared with 28% of those who switched (P=0.033). Reductions in cholesterol and triglycerides occurred more often in the switch group: Cholesterol -0.80 vs -0.44 mmol/L (p<0.0001), triglycerides -0.17 vs +0.01 mmol/L (p=0.006). However, important data are missing: Initial regimens were reported to "usually" be 2 NRTIs + 1 PI, with NFV being the most frequently used PI. The NRTI backbone usually consisted of AZT/3TC, but 15% were on d4T/ddI. We do not have the specifics of or sub-analysis based on initial regimen or initial CD4 count/viral load. It is not clear that the lipid changes are clinically significant. This study was open-label, making reports of body shape changes unreliable and potentially biased, and adherence, diet, and exercise would all need to be considered in interpreting results.

Treatments for Lipodystrophy

• **Anabolic Steroids:** Anabolic steroids used to treat wasting have been proposed as a treatment for lipodystrophy. Ninety-two subjects with 10% unintentional weight loss received oxymetholone 50 mg bid or tid in a double-blind, placebo-controlled phase II trial [Hengge UR, et al. Abstract 70]. After 16 weeks, there were significant increases in body cell mass and lean body mass, with no change in total body fat. Grade 3 or 4 toxicity was seen in 2 (7.4%) in the bid arm and 6 (21%) in the tid arm. In a related study, patients who received testosterone cypionate had less subcutaneous arm/leg fat, lower HDL cholesterol levels, and higher triglycerides, insulin, and C-peptide levels (p<0.05) [Ford P, et al. Abstract 62]. However, this was an observational study, and the patients in the two groups were likely very different. We do not have data on the indications for anabolic steroid use nor the dose(s) given.

Anabolic steroids are an excellent treatment for patients with muscle wasting. Most are inexpensive and, with proper monitoring, can be used safely. However, anabolic steroids do not appear to improve "lipodystrophy."

• **Human Growth Hormone (HGH):** HGH data have been presented elsewhere [Lo JC, et al. *J Clin Endocrinol Metab*. 2001

Aug;86(8):3478-9]. K Mulligan reported the 6 month impact of HGH (3 mg/day) in 5 patients with fat accumulation [Schwartz JM, et al. Abstract 26]. HDL cholesterol and triglycerides increased, as well as total and LDL cholesterol. Glucose homeostasis worsened due to increased hepatic gluconeogenesis and peripheral insulin resistance. There may be a role for this potent but expensive agent in patients with pure fat accumulation, but it must be used with caution, as such patients often have insulin resistance.

• **Thiazolidinediones (rosiglitazone and pioglitazone):** As noted above, the unfavorable *in vitro* effects of IDV, NFV and APV can be prevented if fat cells are co-treated with rosiglitazone [Caron M, et al. Abstract 24].

Pioglitazone (30 mg/d x 3 months then 45 mg/d x 3 months) given to 9 subjects on HAART with lipodystrophy was well tolerated and resulted in no change in the insulin resistance index, which was normal at baseline [Calmy A, et al. Abstract 43]. Six subjects reported subjective improvement in fat distribution, but there were no improvements in objective measures (anthropometrics or DEXA).

In a review from a Texas HIV clinic, 9 normoglycemic patients with baseline insulin resistance and lipodystrophy received rosiglitazone [Visnegarwala F, et al. Abstract 124]. After a median treatment of 24 weeks, 4 of 9 reported subjective improvement in lipoatrophy, and there was a trend towards a decrease in waist/hip ratios; there were no changes in cholesterol and no reported toxicity.

• **Metformin:** Martinez [Abstract 29] reported on a blinded study of 51 subjects with abdominal fat accumulation and plasma triglycerides >200 mg/dL on stable PI-containing regimens, randomized to receive metformin 850 mg, gemfibrozil 600 mg or placebo (all bid). Twelve-month results demonstrated negligible effects on triglycerides and insulin resistance. Sonography showed no effect found in regional fat. In contrast, Hadigan reported 9-month data on 19 subjects who previously completed a double blind, randomized 3-month trial of metformin leading into open-label treatment [Abstract 69]. All patients

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Bioterrorism clearly took center stage at this year's meeting of the Infectious Diseases Society of America (IDSA). Only one slide session was devoted to HIV-related issues, and, as in previous years, head-turning new data on antiretroviral therapy were sparse. However, there were some interesting abstracts presented on the pathogenesis of early HIV infection in women, opportunistic infections (OIs), and response to vaccinations.

Antiretroviral Therapy

• Viral Evolution During Effective HAART: Two groups added to the growing data on viral evolution during "suppressive" ART. Lisa Frenkel presented results of phylogenetic analyses on 10 children, with a median follow-up of 4 years, in whom HIV RNA levels were below the level of detection for some portion of the study [Abstract 20]. Three patterns were observed. First, some children had no forward evolution on therapy as measured by longitudinal phylogenetic analysis of sequences from HIV DNA in peripheral blood mono-nuclear cells (PBMCs). In fact, viral sequences regressed over time to resemble sequences observed during an earlier stage of infection. This pattern was associated with therapy that included 4 or more antiretroviral agents, infrequent blips in HIV RNA, and $\geq 1 \log_{10}$ c/mL decline in HIV DNA while on therapy. In the second pattern, no new resistance mutations were noted during therapy, but prior mutations that conferred a selective advantage to the current regimen increased in frequency, while mutations associated with agents used in prior regimens decreased in frequency. Third, some children had viral evolution and developed new resistance mutations over time, despite viral suppression at most time points. Persaud and colleagues conducted similar analyses on 20 HIV-infected individuals with HIV RNA consistently < 50 c/mL, and reported a static and archival pattern of drug resistance mutations [Abstract 778]. The conclusion from these studies is that a continuum of viral replication (and subsequently evolution) probably exists in patients with "good virologic response" to HAART. It is likely that achieving the optimal result, namely arrested viral evolution and regression to an archival wild-type pattern, is associated with minimal prior therapy and

antiretroviral resistance, a highly potent regimen, and rigorous adherence.

• When to Begin Therapy: In the past year there has been considerable interest in the issue of the optimal time to begin HAART in HIV-infected patients. Several presentations at the 8th CROI suggested that a CD4 count < 200 cells/mm³ at initiation of HAART was associated with a higher risk of mortality and disease progression [see Sterling, *HHR* 2001; 13(2):1]. However, starting HAART in CD4 strata above 200 cells/mm³ was not associated with discernable clinical benefit [Phillips AN, et al. *JAMA* 2001;286:2560]. Sterling and colleagues presented data at IDSA illustrating some of the downsides of starting HAART when the CD4 count is relatively high [Abstract 687]. With a median follow-up of 29 months, 253 patients in the Hopkins cohort who initiated HAART with CD4 count > 350 cells/mm³ were compared with 386 patients who started at lower CD4 cell counts. As has been previously shown by this group, HIV disease progression was not different in patients who did or did not start HAART when the CD4 cell count was > 350 cells/mm³. However, at most recent follow-up, only 49% of those starting HAART at higher CD4 cell counts had VL < 400 c/mL, while 49% had adverse drug reactions requiring regimen changes, 51% were on a second HAART regimen, and 5% were on a third HAART regimen. Lipodystrophy was reported in 11% and genotypic resistance in 22%. This study identifies the dark side of starting HAART in early HIV disease: Frequent virologic failure, drug toxicity, and progressive accumulation of resistance.

• First Line Therapy: Parenti and colleagues presented 48-week follow-up of the COL30336 trial in which antiretroviral naïve patients were treated with AZT/3TC (Combivir), abacavir (ABC) and efavirenz (EFV) [Abstract 697]. The median CD4 count and VL at enrollment were 285 cells/mm³ and 5.1 \log_{10} c/mL, respectively, and 68% had a baseline VL $> 100,000$ c/mL. By intent-to-treat analysis (switches included), 93% achieved VL < 50 c/mL at 48 weeks, and the median CD4 count had increased to 438 cells/mm³. Three patients were switched to didanosine for possible abacavir hypersensitivity reactions. This potent regimen is appealing because the addition of abacavir probably does not carry

the risk of broader resistance if virologic failure occurs, as might be the case in a triple-class regimen. Some clinicians prefer to start with Combivir and EFV, and add ABC only if viral suppression is not achieved. A definitive comparison of these strategies is underway in an AIDS Clinical Trials Group study.

Lucas and colleagues found that EFV-based therapy outperformed PI-based therapy in a clinical cohort setting [Abstract 686]. Treatment outcomes were compared in minimally experienced patients who started therapy with NRTIs plus EFV (n=61), a single PI (excluding saquinavir, n=416), or ritonavir and saquinavir (RTV/SQV, n=68). Viral suppression (< 400 c/mL) was achieved by 72% in the EFV group, 51% in the RTV/SQV group, and 49% in the single PI group (P < 0.05 for both comparisons with EFV). Discontinuation of the regimen within 4 weeks was strongly associated with the use of RTV. In patients who achieved viral suppression, the time to viral rebound (> 1000 c/mL) was similar in the three groups, suggesting no differences in durability once viral suppression was achieved.

• Switch Studies: Recently, numerous trials have been presented demonstrating the safety of switching from effective PI-containing therapy to a PI-sparing regimen. Pulvirenti and colleagues presented similar findings in the COL30305 study [Abstract 689]. This trial included patients on a first PI regimen who had maintained VL < 400 c/mL for at least 3 months with at least 2 documented VL < 50 c/mL. Patients were randomized 2:1 to switch their PI for ABC or continue the PI. Methodologically this trial was somewhat cumbersome, in that patients randomized to ABC continued to take their PI for 4 weeks after starting ABC. Fifty-eight patients were randomized to ABC and 29 to PI continuation. By intent-to-treat analysis, 78% of ABC patients and 76% of PI continuation patients maintained viral suppression < 50 c/mL at 24 weeks. Perfect 7-day adherence was reported by 92% of ABC recipients and 68% of PI-continuation patients at 24-week follow-up. Total and low-density-lipoprotein cholesterol were significantly lower in the ABC arm than in the PI arm. However, 8 of 58 in the ABC arm discontinued due to adverse reactions compared to none of the 29 in the PI arm.



Lieu and colleagues presented their experience with RTV-boosted IDV therapy in 66 patients with at least 1-year follow-up (49 patients switched from tid IDV, and 17 were previously IDV naïve). RTV and IDV were dosed at 100 mg and 800 mg bid, respectively [Abstract 682]. The main finding of this study was the poor tolerability of the RTV/IDV regimen. Only 55% (36 of 66) of individuals remained on the regimen at 1-year. RTV/IDV was stopped because of nephrolithiasis (n=12), nausea (n=6), virologic failure with resistance (n=5), and rapid progression of hyperlipidemia or lipodystrophy (n=4). Although RTV/IDV used in this combination has potential advantages (simplified dosing, no food restrictions, and improved serum IDV concentrations), the results from this and other studies cast doubt on the long-term tolerability of this regimen.

Primary HIV Infection in Women: Implications of Viral Uniformity or Diversity

Over the past few years interest in sex-based differences in HIV transmission and early pathogenesis has been growing. Women appear to have significantly lower viral loads than men, particularly during the first 3-5 years after seroconversion, although overall rates of disease progression are similar [Sterling, et al. *N Engl J Med* 2001; 344:720]. It has previously been observed that when studied early after primary HIV infection, a majority of women in Africa have multiple viral variants compared to men, who tend initially to have a homogeneous viral population. Sagar and colleagues studied a cohort of female commercial sex workers in Kenya who were followed monthly with HIV-1 antibody testing and other evaluations [Abstract 21]. A qualitative heteroduplex assay was used for determining the presence of viral diversity in blood samples available at HIV seroconversion. Of 102 women who seroconverted during the study, 61 showed a heterogeneous viral population and 41 had viral homogeneity.

The heterogeneous and homogeneous groups had similar demographic characteristics and sexual behaviors, including condom use. Additionally, the presence of genital ulcer disease and other sexually transmitted diseases was similar in the two groups. Interestingly, use of a hormonal

contraceptive was the only risk factor identified for a heterogeneous viral population at the time of HIV infection (OR 4.2, 95% CI 1.8-10.1). Compared to women with a homogeneous initial infection, women who were infected with multiple viral variants had higher viral setpoints (median VL 100,000 vs 46,000 c/mL) and lower CD4 cell counts (390 vs 460 cells/mm³) measured 4-12 months after seroconversion. Sagar hypothesized that hormonal contraception may lead to changes in the epithelial barrier in vaginal tissues that increase the risk of infection with multiple viral variants, and that early heterogeneous infection may be better able to allude the immune system and produce rapid disease progression than an initially homogeneous viral population.

Opportunistic Infections

As the rate of clinical disease progression has plummeted in developed countries since the introduction of HAART in 1996, the incidence of opportunistic infections (OIs) may have reached their nadir. McNaghten and colleagues from the CDC's Adult and Adolescent Spectrum of HIV Disease project reported a leveling of OI rates in 1999 [Abstract 751]. This cohort includes approximately 20,500 HIV-infected individuals in 11 U.S. cities. The annual trends in incidence decreased for 20 of 26 OIs between 1995 and 1998. However, trends leveled off for 24 of 26 OIs between 1998 and 1999. McNaghten hypothesized that this trend may represent the peak effect of HAART in their cohort. As data become available from 2000, it will be interesting to see whether significant increases in OI rates are observed. Rebounding hospitalization rates in HIV-infected individuals have been reported in other cohorts [Gebo KA, et al. *AIDS* 2001;27:143].

• **A Simple, Accurate Blood Test for PCP?** M. Skelly from NYU presented intriguing data regarding a potential diagnostic assay for *Pneumocystis carinii* pneumonia (PCP) [Abstract 19]. At present, confirming this diagnosis is often tricky. Examination of induced sputum for organisms has a poor sensitivity, frequently necessitating bronchoscopy with bronchoalveolar lavage (BAL) to definitively confirm or rule-out PCP. Skelly's group observed that *Pneumocystis carinii* is the only known organism that is unable to synthesize S-adenosylmethionine

(AdoMet), a critical biochemical intermediate, meaning that this pathogen is dependent upon a continuous external supply of this substrate. His group previously reported that serum levels of AdoMet decline in correlation with organism burden in a mouse PCP model.

In the study presented, serum AdoMet levels were determined by high performance liquid chromatography in 15 PCP patients (7 confirmed, 8 presumed) and a variety of control groups. The median AdoMet concentration was 106 nM (range, 86-128) in 12 healthy controls but was below the limit of detection (0.5 nM) in 14 of 15 PCP patients at presentation. The other PCP patient, who did have confirmed infection, had a concentration of 8 nM. Importantly, other more relevant control groups were also studied, including individuals with asymptomatic HIV infection, bacterial pneumonia, tuberculosis, and cryptococcosis. AdoMet concentrations in these other groups were not significantly different from those in healthy controls, and there was no overlap with levels in PCP patients. Additionally, AdoMet concentrations rose to normal within 1 week of successful therapy for PCP. Skelly reported that a cutoff of 25 nM would have had 100% sensitivity and specificity for PCP in their cohort. This promising assay deserves further prospective study, specifically where all enrolled participants are evaluated by the current gold-standard, BAL.

• **Treatment of HIV/Hepatitis C Virus Co-infection.** Sulkowski presented preliminary results for the Hepatitis Resource Network Clinical Trials Group of a randomized study of ribavirin plus daily vs thrice weekly interferon (IFN) α -2b in HIV/HCV co-infected patients [Abstract 433]. IFN was dosed at 3 MU in both the daily and thrice weekly groups. Inclusion criteria included CD4 >100 cells/mm³ and compensated liver disease. Exclusion criteria included active drug or alcohol use or serious psychiatric illness. The two groups were similar with respect to baseline characteristics. In the on-treatment analysis, 33% in the daily IFN group achieved undetectable plasma HCV RNA levels at 12 weeks, compared to 13% in the thrice weekly group (P=0.01). The authors concluded that the superiority of

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daily IFN suggests that pegylated IFN (which has a long half-life and is dosed weekly) will be beneficial in the treatment of co-infected patients. As a side note, approximately one third of patients in each group dropped out of the study prior to 12 weeks. The authors suggested that this drop-out rate was largely due to problems with side effects and adherence.

While these results are promising, they also point to the difficulties of using IFN and ribavirin in the co-infected population. Fleming and colleagues presented data from their clinic at Boston University echoing these difficulties in clinical practice [Abstract 755]. Of 93 co-infected patients in their clinic who completed evaluation for HCV treatment, only 31 (33%) were offered HCV therapy. Of the 62 who were not suitable for therapy, 26% were non-adherent with clinic visits, 24% had active psychiatric disease, 22% were actively using drugs or alcohol, and 23% had decompensated liver disease or medical contraindications to therapy. Of the 31 offered therapy, only 9 have commenced therapy at this point (6 have refused and 16 are deferring therapy). Thus, only 10% of those evaluated for HCV co-infection were eligible and agreed to start treatment.

• **Management of High Intracranial Pressures (ICP) with Cryptococcal Meningitis.** Garcia-Gonzalez and colleagues presented results from 21 patients with cryptococcal meningitis and elevated ICP (>200 mm H₂O) accompanied by headache and impaired consciousness who were randomized to repeated lumbar punctures (LP) or dexamethasone (0.15 mg/Kg/d tapered over 15 days) [Abstract 760]. All were treated with amphotericin B (1 mg/Kg/d), and all had LP performed on days 3, 7, 14, 21, and 30 to assess improvement. Patients assigned to repeated LP had LP performed daily with cerebrospinal fluid (CSF) drained until the ICP was less than 200 mm H₂O or was reduced by half in those with ICP >400 mm H₂O. The two groups had similar demographic and clinical features at presentation (mean ICP 260 and 350 mm H₂O in the dexamethasone and LP groups, respectively). Clinical improvement was observed in 89% in the dexamethasone group and 83% of the LP group at day 30 (one patient in the former and two in the latter group died). ICP fell rapidly in both

Hepatitis A Seroconversion Following Vaccination in HIV-positive and -negative Individuals

Patient Group	Proportion Seroconverting	
	After 1st Dose	After Booster Dose
HIV-negative	98%	100%
HIV-positive		
CD4 >300 cells/mm ³	90%	100%
CD4 <300 cells/mm ³	70%	87%

groups. CSF fungal cultures were negative in 50% of the LP group, but only 22% of the dexamethasone group at day 14. However, by day 30 the microbiologic cure rate was similar in the two groups. This study suggests that repeated LP and dexamethasone have a similar clinical efficacy in patients with increased ICP from cryptococcal meningitis, but that the latter may be associated with slower sterilization of CSF.

Response to Vaccination in HIV-infected Individuals

Studies in the pre-HAART era focused on the association between CD4 count and serological response to vaccines in HIV-infected patients. However, there is considerable ambiguity about what factors predict serological response to vaccines in patients on HAART, and which patients would be most likely to benefit. Hupriker and collaborators presented data suggesting that suppression of the viral load is an important predictor of response to vaccination, regardless of the CD4 cell count [Abstract 380]. The study was a retrospective review of 41 HIV-infected patients who received the 3-dose hepatitis B vaccine series and had follow-up hepatitis B serology performed (table below).

Hupriker noted that the low seroconversion rate overall may have been a byproduct of the retrospective design and the broad time interval (2-14 months)

Seroconversion Rates After Hepatitis B Vaccine Stratified by CD4 Count and Viral Load

Viral Load	CD4 Cell Count	
	>200/mm ³	<200/mm ³
<400 c/mL	8/14 (57%)	2/4 (50%)
>400 c/mL	4/17 (24%)	0/6 (0%)

between vaccination and determination of serologic response. The group is planning a larger, prospective study to better explore these issues.

Wallace and colleagues presented data indicating that hepatitis A vaccine with VAQTA (Merck) effectively produced seroconversion in HIV-infected patients, but that this group may be more dependent on the recommended 6-month booster than HIV-negative individuals [Abstract 379]. Sixty HIV-infected and 90 HIV-negative individuals were given the 2-dose hepatitis A series and were evaluated for seroconversion (table above).

Not surprisingly, Wallace reported that hepatitis A seroconversion rates in HIV-infected patients with CD4 counts below 300 cells/mm³ declined linearly at lower CD4 counts, but these data were not presented.

In summary new data presented at IDSA suggest that potent antiretroviral therapy, which suppresses viremia to below detectable limits using standard assays, is generally not associated with viral evolution in long-lasting reservoirs. Women who use hormone contraceptives and acquire HIV sexually may be at increased risk for early infection with multiple viral variants, which may have implications for clinical disease progression. Additional data was presented showing the downside of starting HAART in early stage HIV disease, namely frequent virologic failure, adverse effects, and antiretroviral resistance. An assay for a serum biochemical intermediate, on which *Pneumocystis carinii* is uniquely dependent, may hold promise as a non-invasive diagnostic test for PCP. Last, data presented at the conference indicate that viral suppression on HAART may be as important a predictor of serologic response to vaccination as the CD4 cell count. ▲



IDSA Update: Sexually Transmitted Diseases and HIV

By Emily J. Erbelding M.D., M.P.H.

Though bioterrorism was clearly the issue of the day at the 39th Annual Meeting of the IDSA, new observations regarding the important epidemiologic interactions between sexually transmitted diseases (STDs) and HIV were brought to the fore at this conference as well.

Genital Herpes and HIV

In the Enders lecture, Dr. L. Corey of the University of Washington presented more data indicating a large, and perhaps even growing role, for HSV-2 in driving sexual transmission of HIV [Abstract P88]. In a meta-analysis that included 9 prospective or nested case-control studies, the relative odds of prior HSV-2 infection and subsequent HIV acquisition was 2.1 (95% CI 1.3-3.2). He also cited new, recently published data from the Rakai study [HHR 10(5) 8/98; HHR 11(1) 1/2000] examining risks for HIV transmission among 174 couples discordant for HIV [Gray RH. *Lancet*, 357:1149, 2001]. Reactive HSV-2 serology conferred a 2-4 fold greater risk of HIV transmission within every stratum of HIV viral load. There was no increased risk of transmission if a symptomatic genital ulcer was reported, indicating that subclinical HSV-2 microulcerations and shedding confer significant added risk, even equal to the risk conferred by clinically apparent ulcers. An increasing proportion of genital ulcerations from clinical cohorts in sub-Saharan Africa over the past 2 decades appears to be due to HSV-2. Suppression of subclinical genital HSV-2 shedding with antivirals may help to prevent HIV transmission in Africa.

Resurgent Sexually Transmitted Diseases in the AIDS Era

In a symposium covering biologic, epidemiologic, and behavioral interaction of STDs and HIV, Dr. Myron Cohen of UNC summarized what is known to date regarding biologic determinants of HIV infectiousness and HIV susceptibility, as well as biomedical interventions that might prove effective in preventing HIV transmission while we await the arrival of an HIV vaccine [Abstract S79]. In what he called the "biologic view of sub-Saharan Africa," Cohen listed the following factors that facilitate the spread of HIV as tipping the balance against control of the epidemic: Higher blood:semen viral HIV

concentrations; clade C predominance, with a fixed non-syncytium-inducing (NSI) phenotype, which may be more efficiently sexually transmitted; and the high population prevalence of STDs. Cohen pointed to the following factors that increase biologic susceptibility to HIV acquisition: High prevalence of STDs and bacterial vaginosis; low prevalence of CCR5 gene deletions; and the low rate of male circumcision (keratinized epithelial surfaces created by male circumcision in infancy are probably protective). There may also be higher rates than previously recognized of iatrogenic or occupational exposures in Africa through percutaneous instrumentation (needlesticks, etc).

In a presentation entitled, "Sex, Drugs, and Perestroika," Dr. Adrian Renton of the London Imperial College of Medicine summarized alarming epidemiologic trends in syphilis and HIV that have occurred in the Russian Federation [Abstract S80]. Disease control strategies in the former Soviet Union were entirely publicly-funded and focused on government-supported compulsory hospitalization to prevent syphilis spread, along with strictly enforced contact tracing. In the current Russian Federation most STD services are provided on a fee-for-service basis with a more relaxed approach to contact notification and preventative treatment. A surge in injection drug use (IDU) and commercial sex has occurred simultaneously with this shift in infrastructure and delivery of STD services. The result has been an explosion in syphilis and HIV transmission. Estimated primary/secondary syphilis rates have exceeded 250 cases per 100,000, with the peak age of occurrence in the late teenage years. Current strategies to prevent HIV transmission are to focus on STD control among IDUs and aggressively promote condom use among young people.

Dr. Connie Celum of the University of Washington summarized recent data on STDs among men who have sex with men (MSM) [Abstract S81]. Surveillance data from several urban centers in the U.S. and Europe has described multiple syphilis outbreaks among MSM in the last half of the 1990's. To study determinants of sexual risk-taking and STDs among MSM in Seattle, approximately 1000 MSM (30% were HIV-seropositive) were recruited from STD clinics and HIV primary care clinics.

Overall, HIV-infected MSM were not sexually safer, with 31% reporting meeting partners anonymously at bath houses or sex clubs, compared to 22% of HIV-seronegative men reporting this behavior. The prevalence of gonorrhea or chlamydia (isolated from oral, anal, or rectal sites) was 10% among HIV-infected MSM and 13% among HIV-uninfected MSM, with most infections being asymptomatic. These findings have significant implications for HIV clinical providers: Discussion of sexual risk behaviors, especially specific types of sexual practices and the use of anonymous venues to meet partners, along with periodic screening for bacterial STDs should be a consistent standard in clinical practice.

Dr. Steven Morin presented recent epidemiologic trends in San Francisco that demonstrate a new rise in HIV incidence over each successive quarter of 2000 [Abstract S82]. To design effective prevention interventions to address this trend, focus groups comprised of MSM in San Francisco were assembled. The questions presented to the focus groups were as follows:

- Why have HIV infections increased?
- What has changed in the past 10 years that may have contributed to this increase?
- What can be done about it?

The groups identified the following as factors contributing to HIV transmission, but that had not changed significantly over the past several years:

- Denial of risk, especially among adolescents.
- Sense of inevitability of getting HIV infection.
- Commodification of HIV (i.e., more chance to get social services, housing assistance), especially among the poor.
- Loneliness and low self esteem.
- Drug use, including metamphetamines.

The following were phenomena that the groups identified as having changed in the past several years that may be contributing to the recent increase in HIV incidence:

- Decreased perception of HIV as a health threat among the HIV-uninfected.
- Decreased communication, either with friends or in the media, about HIV
- A gradual shift in community norms

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Sexually Transmitted Diseases & HIV

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about sex, including peer pressure to be unsafe, and a celebration of "barebacking."

The focus groups endorsed health promotion advertisements that focused on friends talking to friends about safer sex, that provided facts on the rising rates of HIV in San Francisco, that explained that HIV still has very negative health consequences, and that promoted safer sex as "still the norm."

As we move into the third decade of the HIV/AIDS epidemic without a prophylactic vaccine, improved STD control is as important as ever in preventing the spread of HIV. New data indicate that clinical trials of genital herpes suppression, along with a more aggressive focus on STD screening and prevention services in HIV clinical practice, should now be high priority items on the HIV prevention agenda. ▲

Adverse Drug Reactions and Lipodystrophy in HIV

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had lipodystrophy and insulin resistance at entry. Metformin was well tolerated and lactic acid levels did not increase. Insulin AUC improved, and there was a reduction in waist circumference in patients who received 9 vs 6 months of metformin.

Metformin and the thiazolidinediones treat insulin resistance and may have a role in the treatment of lipodystrophy. Patients with documented insulin resistance are likely to benefit most. Taken together, these studies offer some hope for patients with or at risk for the metabolic and physical changes associated with "lipodystrophy," while demonstrating that well controlled, blinded randomized trials with objective endpoint measures are critically necessary.

"Lipodystrophy" describes a set of overlapping phenomena involving fat accumulation in some body parts, fat loss in others, with varying associated metabolic changes, and a solid understanding of these

phenomena remains elusive. Metabolic changes influence physical changes and vice versa. Trials that are designed to address these complex issues are under way. Many of us left Athens hopeful that the scientific advances presented will be translated into clinically useful advances for our patients, but frustrated by the ever growing complexity of the field. ▲

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