

THE HOPKINS HIV REPORT

A bimonthly newsletter for healthcare providers

Report from San Francisco: The 11th Conference on Retroviruses and Opportunistic Infections (CROI)

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The Tenacity of NNRTI Drug Resistance

By Deborah Persaud, M.D. and
Joel E. Gallant, M.D., M.P.H.

The session on “Transmission, Selection, and Persistence of Drug-Resistant HIV” at the 11th CROI featured several abstracts highlighting the increasing problem of transmission of drug-resistant HIV, and, most importantly, the stable persistence of drug-resistant viral variants in the plasma of patients who either deferred antiretroviral therapy after primary infection, discontinued NNRTIs following treatment failure, or received single dose nevirapine (NVP) for prevention of mother-to-child-transmission (PMTCT).

Persistence of Resistance Following Primary Infection

Using standard genotypic assays in a longitudinal study of 12 patients found to have been infected with resistant virus during primary infection, Little and colleagues demonstrated that the NNRTI-resistant variants (K103N +/- 181C [N=7/12]; Y188L [N=1/12]) were the predominant variants that were transmitted [Abstract 36LB]. The mean time to the detection of a wild-type mixture was 375 days. The majority (11/12) of patients continued to have mixtures of wild-type and resistant virus detectable in plasma for years; complete replacement by wild-type virus

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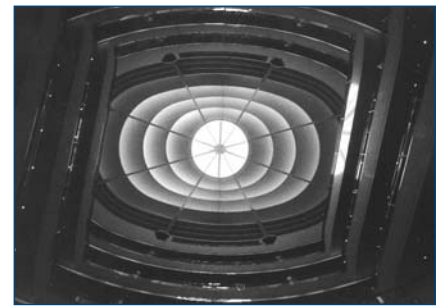
Antiretroviral Therapy: The Naïve Patient

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

The 11th CROI was marked by two “firsts”: It was the first time CROI was blessed with glorious weather, and it was the first time that many of the more clinically focused participants felt they were walking away somewhat empty-handed. There were certainly important basic science data presented, as well as some compelling data on drug resistance, prevention of mother-to-child transmission, and treatment of HIV/HCV coinfection. But for the most part, the large randomized trials of antiretroviral therapy either were not submitted, were not accepted, or were relegated to poster sessions.

All-Nucleoside Regimens

We did hear more data from clinical trials involving several unorthodox “all-nuke” regimens. Jemseck presented the results of his pilot trial using didanosine (ddI), lamivudine (3TC), and tenofovir DF (TDF), each administered once-daily with food, with ddI dose adjustment to compensate for the TDF-ddI interaction [Abstract 51]. These results had been made



“San Francisco Center”
photograph by Joel Meneses

public earlier in a letter to clinicians from Gilead Sciences. A total of 24 patients were enrolled in the trial, 38% of whom had baseline viral loads (VL) above 100,000 c/mL, and 58% of whom had CD4 counts <200 cells/mm³. The results were even more disastrous than those we’ve seen recently with the abacavir (ABC)/3TC/TDF combinations: 20 (91%) discontinued early due to a poor virologic response, and viral load response was only -0.75 log₁₀ c/mL at 4 weeks, -0.61 log₁₀ c/mL at 12 weeks, and -0.4 log₁₀ c/mL at 24 weeks or at the end of therapy. In fact, no patient achieved a viral load below 50 c/mL in this study. Genotypes were available in 20 patients, all of whom had the M184V or M184I mutations. Ten patients also had K65R, 7 of whom had K65R/K mixtures, suggesting emerging resistance.

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The third (and hopefully last) trial to study the ABC/3TC/TDF combination was the TONUS study from France [Landman R, et al. Abstract 52]. Results were similar to those from the Charles Farthing's study [Abstract 43, 2nd IAS, Paris 2003] and the ESS 300009 trial [Gallant JE, Abstract 1722a, 43rd ICAAC, Chicago 2003]. The study enrolled 38 patients, with a median CD4 count of 222 cells/mm³ and a median viral load of 4.87 log₁₀ c/mL. The study was stopped prematurely because of poor results: 12 (33%) of 36 enrolled patients experienced virologic failure by week 24. Response was correlated with baseline viral load: 64% of those with baseline viral loads above 5 logs failed therapy, compared to 29% of those with viral loads between 4 and 5 logs, and none of the 8 patients with baseline viral loads below 4 logs. Among the 11 patients with available resistance data after virologic failure, 9 had both the M184V and K65R mutations and 2 had M184V alone. The authors also looked at drug levels, since there has been speculation about whether drug interactions could explain the poor results seen with such regimens. The 4-week plasma C_{min} was adequate for all three drugs in 86% of patients, and there was no relationship between trough concentration and virologic response. They also presented preliminary data on intracellular concentrations, noting that metabolites of at least one drug were detected in all patients. Obviously, these early data don't rule out intracellular interactions, and we are looking forward to seeing more intracellular data from this and other studies in Bangkok later this year. The authors of the TONUS study noted that rescue therapy was always successful in this study, regardless of the resistance profile. This is consistent with both phenotypic and clinical data from other studies, including the GS 903 trial, in which patients failing therapy with various combinations of NNRTI resistance mutations, M184V, and K65R, were successfully treated with a variety of rescue regimens, some of which included TDF.

The uniformly negative findings from three ABC/3TC/TDF studies have raised questions about whether it is safe to use this combination with a fourth agent. There has been some interest in combining co-formulated AZT/3TC/ABC (*Trizivir*) with TDF, since this would be a simple and convenient NNRTI- and PI-sparing regimen, and since the addition of AZT would presumably alter resistance pathways and prevent the emergence of K65R. Richard Elion presented data from the multicenter COL40263 trial, in which 123 patients received AZT/3TC/ABC + TDF, all administered once daily [Abstract 53]. An interim analysis was performed on the 88 patients with at least 8 weeks of data because of the alarming findings from the ABC/3TC/TDF studies presented last year. They found that at week 24, 67% of subjects had VL <50 c/mL by observed analysis. Response was 79% for those with baseline VL <100,000 c/mL and 60% for those >100,000 c/mL. Of those who completed 24 weeks of therapy, virologic non-response was seen in 15%. It should be noted that an intention-to-treat analysis, while not presented, would have shown poorer results, since 22% of the 88 discontinued from the study prematurely, 8% because of virologic non-response. The resistance data from 8 patients who met criteria for virologic non-response were interesting and somewhat surprising: 3 had at least 1 thymidine analog mutation (TAM) with M184V, 2 had at least 1 TAM without M184V, 1 had K65R, and 2 had wild-type virus. No patient had an isolated M184V, which is the expected first mutation in patients failing AZT/3TC/ABC or a number of other AZT/3TC-containing regimens.

What can we conclude about the all-nuke regimens presented to-date? There are at least two that are completely unacceptable: ABC/3TC/TDF and ddiI/3TC/TDF. The reasons are unclear, but the evidence seems to point to the low genetic barrier to resistance, with strong selective pressure on pre-existing mutants: K65R reduces

susceptibility to all drugs in the regimen and M184V reduces susceptibility to all but TDF. Two triple-NRTI regimens, ddiI/d4T/3TC and ABC/ddiI/d4T, have essentially been made obsolete because of the ddiI/d4T component. In addition, they are less effective than standard HAART regimens. These unacceptable triple-nuke combinations should be distinguished from AZT/3TC/ABC, which, while less effective than efavirenz (EFV)-based HAART regimens in ACTG 5095 [Gulick R, et al. Abstract 41, 2nd IAS, 2003], may still have a limited role in antiretroviral therapy. Efficacy of this regimen is still in the "ballpark" of what we consider acceptable, and in fact is comparable to historical data with a number of standard HAART combinations. Moreover, one could argue that the consequences of failure on AZT/3TC/ABC are minimal, provided failure is detected and acted on early. One would expect to see wild-type virus or an isolated M184V mutation with initial failure of this regimen, rather than the NNRTI resistance that is so often seen with failure of EFV- or NVP-based combinations. The argument could be made that in some patients, primarily those in whom adherence is questionable, the use of a less potent but more forgiving regimen might be a reasonable compromise. **Where does that leave AZT/3TC/ABC + TDF?** All we can conclude from Elion's study is that it's not in the "completely unacceptable category." Whether this 4-nuke regimen is any better (or worse) than AZT/3TC/ABC alone can't be determined without a controlled trial, a trial that is unlikely to take place in light of ACTG 5095. One also wonders whether the once-daily dosing of this regimen, including once-daily dosing of AZT, might have contributed to the somewhat surprising resistance findings, with more TAMs and K65R than would have been expected. Perhaps once-daily dosing of AZT does not provide adequate protection against resistance, both to TDF and to AZT itself. Clearly, this regimen cannot be recommended based on the available data,



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but the results of Elion's study may be reassuring to patients who are already taking it with a good virologic response.

Once-Daily Lopinavir/Ritonavir

Gathe presented 48-week data from an open-label comparison trial in which 190 patients were treated with lopinavir/ritonavir (LPV/r, *Kaletra*) dosed at either 800/200 mg (6 capsules) qd or 400/100 mg (3 capsules) bid, each given with the NRTI backbone of TDF plus emtricitabine (FTC) [Abstract 570]. Results in the two arms were similar, with 70% and 64% of patients on the qd and bid arms achieving suppression to <50 c/mL by intent-to-treat

analysis, respectively. Lipid levels were similar in the two arms, though moderate-to-severe diarrhea was significantly more common in patients on qd LPV/r (P=0.04). These data support once-daily dosing of LPV/r for naïve patients. However, patients with prior PI exposure and/or resistance should probably stick with bid dosing, since the higher and less variable trough concentrations are likely to lead to better suppression of PI-resistant virus. The higher rates of diarrhea may also be problematic, and suggest that once-daily dosing be reserved for those already tolerating twice-daily LPV/r. When the new formulation of LPV/r is developed, the lower pill

burden and the change in the excipients may make once-daily dosing more feasible and tolerable.

It should be noted that these are the best data to-date on the NRTI backbone of TDF/FTC, which is being developed as a once-daily coformulation. TDF levels are significantly increased when coadministered with LPV/r, raising concerns about an increased potential for nephrotoxicity. It was reassuring that no nephrotoxicity was seen in this trial. It is also interesting that lipid elevations were somewhat less pronounced than they had been in the

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earlier Abbott 863 trial, in which LPV/r was combined with a d4T/3TC backbone. This may reflect differences between d4T and TDF in their effects on cholesterol and triglycerides.

New Agents in the Pipeline

Shortly before CROI, we learned that development of two promising agents, T-1249 and amdoxovir (DAPD), was being halted by the manufacturers. Nevertheless, there is still a pipeline for new antiretroviral agents, some of which are now in clinical phases of testing.

D-D4FC (*Reverset*, RVT) is a novel NRTI that has activity against wild-type and NRTI-resistant virus *in vitro*, though it is not active against the Q151M or T69 insertion mutations associated with multi-nucleoside

resistance. Robert Murphy presented data from the RVT-202 trial, a dose-ranging, placebo-controlled trial involving 24 patients who received 10 days of monotherapy and 1 month of follow-up [Abstract 137]. Mean viral load reduction was approximately 1.7 logs, with no obvious dose response relationship at the three doses tests (50, 100, and 200 mg qd). The only reported adverse events were cold symptoms; there must have been something going around, because the placebo recipients reported the same symptoms at about the same frequency.

SCH-D, a CCR5 antagonist being developed by Schering, is a safer and more potent cousin of an earlier candidate drug, SCH-C. Laughlin presented a dose-escalation, placebo-controlled trial of 14 days of monotherapy, which demonstrated dose related virologic suppression, with 81% of patients on the highest dose (50 mg bid) achieving a reduction in viral load of $>1 \log_{10}$ c/mL (45% $>1.5 \log_{10}$ c/mL) [Schurmann D, et al. Abstract 140LB]. The drug was well tolerated; there were no serious adverse events that appeared to be drug related. One of the concerns about CCR5 antagonists is that they will either need to be restricted to those whose virus is exclusively R5 tropic or else coadministered with CXCR4 inhibitors, lest there be selection of potentially more virulent X4 virus. The one patient in this trial found to have a mixed R5/X4 population had only a 0.5 log drop in viral load. Another had transient detection of X4 virus after cessation of dosing, though he had more than a 1.5 log drop while on treatment.

GW873140 is another CCR5 antagonist that was studied in a double-blind, placebo-controlled trial involving 70 HIV negative volunteers [Demarest J, et al. Abstract 139]. The agent was well tolerated at doses ranging from 50 to 1200 mg and led to prolonged receptor binding.

BMS-488043 is an attachment inhibitor, a small molecule that binds to gp120, blocking the earliest step in the entry process: the attachment of gp120 to the CD4 receptor. Binding has been shown to be independent of coreceptor status. It is related to an earlier compound, BMS-378806, which had a shorter half-life and did not achieve target exposure levels. In a 7-day, placebo-

controlled monotherapy study involving 28 patients, 24 of whom received doses of 800 or 1800 mg bid, maximum viral load reduction was $1.23 \log_{10}$ c/mL in the high-dose arm and $1.01 \log_{10}$ c/mL in the low-dose arm, with 58% of the low-dose group and 67% of the high-dose group experiencing 1 log drops in viral load, respectively (25% and 42% ≥ 1.5 log drop) [Hanna G, et al. Abstract 141]. There were no serious adverse events and no discontinuations due to toxicity.

SPD754 is a deoxycytidine analog (like 3TC, FTC, and ddC), that is active against 3TC- and AZT-resistant virus in preclinical studies, and that shows no *in vitro* evidence of mitochondrial toxicity. However, coadministration of SPD754 with 3TC results in decreased intracellular concentrations of SPD754-triphosphate, which raises the IC_{50} of SPD754 against HIV with M184V [Bethell R, et al. Abstract 138].

Conclusions

The data presented at CROI won't be changing the way we treat naïve patients, but there were some useful studies. By now we should all be appropriately wary of untested regimens, especially triple-nucleoside combinations with low barriers to resistance. The role of the "4-nuke" combination of AZT/3TC/ABC + TDF remains uncertain. Once-daily dosing of LPV/r continues to show promise for PI-naïve patients, though gastrointestinal side effects and the high pill burden may prevent this approach from being widely accepted using the current formulation. Finally, there are some promising new drugs in the pipeline, especially among the entry inhibitor classes. Bangkok is not known for great July weather, so we'll hope for a lot of exciting presentations that will keep us in our seats. ▲

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ERRATUM

In the January, 2004 issue we published the following article: "From the IDSA Meeting – Important New Findings in HIV Treatment and Pathogenesis, 2003" (HHR 2004 Jan;16(1):2-3). The author was incorrectly listed as John G. Bartlett, M.D. The correct authors of this article were: Petros C. Karakousis, M.D., Kathleen R. Page, M.D., and William R. Bishai, M.D., Ph.D. We regret the error. ▲



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was only seen in 1 of the 12 patients 1,019 days following infection. This study demonstrates the fitness of the NNRTI-resistant variants and their ability to be transmitted and predominate at high frequencies in plasma for years. However, it should be noted that NRTI- and PI-resistant variants also persisted for long periods of time. The mean time to reversion of any NRTI mutation was 362 days, and for protease inhibitor mutations it was 517 days, with 4 patients showing no appearance of wild-type virus, even in a mixture, for follow-periods ranging from 64 to 689 days.

Persistence of Resistance in Chronic Infection

Even when wild-type virus in plasma replaces NNRTI-resistant virus, the resistant mutants persist and therefore can reemerge when NNRTIs are reintroduced. Studies by Palmer and colleagues showed that when more sensitive allele-specific RT-PCR genotypic assays are used, NNRTI-resistant variants can be detected in plasma, at levels of approximately 15%, for up to 5-years in the absence of selective pressure [Abstract 37]. In an analysis of data from the ACTG 398 trial, in which PI-experienced and NRTI-experienced participants were treated with a regimen of abacavir, efavirenz, adefovir, and a dual-PI combination, Mellors, and colleagues assessed whether NNRTI-resistant virus present at low-levels (detectable only by more sensitive genotyping methods such as single genome sequencing (SGS) and a Ty1/HIV-RT yeast system) contributed to treatment failure [Abstract 39]. In this trial, NNRTI-naïve patients did well on this salvage regimen, while NNRTI-experienced patients had similarly poor responses, regardless of whether NNRTI mutations were detectable on standard genotyping. Mellors then went on to show that at the time of failure the NNRTI-resistant virus in these patients clustered phylogenetically with the NNRTI-resistant virus detected at low-levels by SGS prior to the initiation of the study regimen. Based on these findings he concluded that NNRTI drug resistance,

present at levels not detectable by standard genotyping, could contribute to treatment failure when drug-selective pressure is reapplied in a salvage therapy setting.

Persistence of Resistance and NNRTI Levels With PMTCT

The efficacy of single dose NVP for PMTCT was again demonstrated in this session. Data presented from a large clinical trial in Thailand (N=1844) showed that single dose NVP provided significant additional benefit when added to a regimen of AZT given to the mother starting at 28-weeks gestation and to the infant for 1 week after birth [Lallemant M, et al. Abstract 40LB]. In fact, the efficacy of this two-drug strategy was similar to that of HAART regimens in other PMTCT trials. However, other presentations during this session confirmed that the benefits of single dose NVP come with a price for mothers and for infants who ultimately become infected. Two abstracts explored the virologic consequences of single-dose NVP for PMTCT in two large trials conducted in South Africa [Martinson N, et al. Abstract 38], and Thailand [Jourdain G, et al. Abstract 41LB]. The first study confirmed previous findings by Eshleman and colleagues [*AIDS* 2001;5: 1951] demonstrating the emergence of NNRTI resistant variants following the use of single-dose NVP given to women in labor. Thirty-nine percent of the women and 42% of the infected infants had detectable NNRTI-resistant virus in plasma 6 weeks after NVP exposure. As previously reported by Eshleman, the distribution of the various NNRTI-resistant variants was different in the mothers and their infants. K103N was the predominant mutation (31%) in the mothers, while Y181C (32%) predominated in the infants. Furthermore, in the study reported by Jourdain, the authors found that in women receiving NVP for PMTCT, NVP levels remained detectable in plasma for weeks.

Other studies presented at CROI demonstrated the persistence of NNRTI drug levels in other settings [Taylor S, et al.

Abstract 131], and also found that efavirenz clearance rates are lower in blacks and Hispanics than whites [Ribaud H, et al. Abstract 132], which appears to be explained by racial differences in CYP2B6 G516T poly-morphisms (see Lucas G, "*The Treatment of Experienced Patients and Resistance Mechanisms*", p 6 and to be covered in detail in the next issue). These studies provide a basis for the high rates of resistance observed following limited exposure (single dose) to NVP in women and infants, and also raise concern about the timing of discontinuation of NVP when it is part of a failed regimen. Importantly, the authors also showed that in women treated with NVP-containing HAART regimens, there was a trend towards lower virologic responses (VL <50 c/mL) at 6-months in those who had detectable NNRTI resistance following single dose NVP (34%) compared with those who had no prior NVP exposure (75%). However, there was a suggestion that re-introducing NVP more than 6-months after exposure to single dose NVP may be associated with better response to therapy, which may be reflective of the diminishing proportion of viral quasispecies with detectable resistance over time following single dose NVP. Clearly, further data are needed regarding the kinetics of NVP resistance mutations following single dose NVP, including the prevalence of minority resistant quasispecies over time, and archiving of resistant virus within cellular reservoirs.

These results are not particularly surprising given what we know about NNRTI pharmacokinetics and the permanent nature of drug resistance. The conservative assumption has always been that resistance is clinically relevant, regardless of whether it occurs in the setting of primary infection, HAART, or PMTCT. The implications for resource poor countries are less clear, however, since single dose NVP is a practical and cost-effective way to reduce perinatal transmission. One response to these

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The Treatment of Experienced Patients and Resistance Mechanisms

By Gregory M. Lucas, M.D.

Groundbreaking new clinical trial results were few and far between at the 11th CROI. However, there were several trials worth highlighting related to the management of treatment-experienced patients and a great deal of new data and insights on antiretroviral resistance mechanisms.

Boosted Atazanavir vs Lopinavir in Treatment-Experienced Patients: 48-Week

Follow-up 48-week data from the BMS-045 trial were presented by Edwin DeJesus in a poster session [Abstract 547]. This trial randomized 358 subjects who had failed at least two HAART regimens and were PI-, NNRTI-, and NRTI-experienced to receive 1) atazanavir (ATV) / ritonavir (RTV) (300/100 mg qd); 2) lopinavir/ritonavir (LPV/r, 3 tablets bid); or 3) ATV (400 mg) / saquinavir (SQV) (400/1200 mg qd) each in combination with an NRTI backbone. Twenty-four-week data from this study garnered considerable attention at last year's IAS conference in Paris [Bardo et al., Abstract 118 2nd IAS, Paris, 2003], as ATV/RTV performed as well as LPV/r in this experienced study population, results that have been upheld by 48-week data presented at CROI. In an intent-to-treat analysis, 56% and 38% of patients randomized to the ATV/RTV arm achieved a VL <400 c/mL and <50 c/mL, respectively, compared to 58% and 46% of those in the LPV/r arm (differences not statistically significant). The efficacy of the ATV/SQV arm was inferior, as it was at 24 weeks. Increases in total cholesterol and triglycerides were significantly higher in the LPV/r group than the ATV/RTV arm, and more patients in the LPV/r arm were treated with lipid-lowering drugs (19% vs 12%, $P < 0.05$).

It should be noted that the participants in this trial were not highly treatment-experienced, and these results should not be extrapolated to true "salvage" situations. Extrapolation to PI-naïve patients may be appropriate, however. The results of BMS 045 will undoubtedly increase enthusiasm

for the use of ATV, and especially RTV-boosted ATV, as a first-line PI.

You Don't Need Suspenders if You're Already Wearing a Belt

Scott Hammer presented results from the ACTG 372A study, showing that intensification with abacavir (ABC) provided no benefit in patients whose viral loads were already suppressed on a 3-drug HAART regimen [Abstract 56]. A total of 229 AZT-experienced participants who had achieved VL <500 c/mL in the parent study with indinavir (IDV) and 3TC plus either AZT or d4T were randomized to add ABC 300 mg bid or placebo. Over a median follow-up of 4.4 years, the composite endpoint of virologic failure or treatment discontinuation was reached by 53% in the ABC group and 55% assigned to placebo. In secondary analyses, there were also no significant differences between the groups in rates of virologic failure alone, episodes of intermittent viremia >50 c/mL (blips), or low-level viremia measured using an ultrasensitive viral load assay with a limit of detection of 6 c/mL. It should be noted, however, that intensifying successful regimens is not often done, whereas there is some support for intensification strategies in patients with persistent low level viremia on HAART [Katlama C, et al. *AIDS* 2000, 14:781 and Schooley RT, et al. *AIDS* 2002, 16(9):1257].

3TC Forever?

Several rationales have been proposed over the years for continuing 3TC in the regimens of patients with known or suspected 3TC-resistance. The M184V reverse transcriptase mutation decreases viral fitness and antagonizes the development of thymidine analogue mutations (TAMs), K65R, and Q151M. Moreover 3TC is almost universally well tolerated, has a low pill burden, and does not appear to contribute to mitochondrial toxicity. The COLATE trial addressed the question of whether continuing 3TC after 3TC failure

is beneficial [Abstract 549]. One hundred thirty-one subjects who had a VL >1,000 c/mL on a 3TC-containing regimen (91% had M184V at study enrollment) were randomized to either continue or discontinue 3TC in an open-label format. Subjects' clinicians chose a regimen consisting of at least 3 drugs prior to randomization; the mean number of drugs, excluding 3TC, remained similar in the two arms over 48-weeks of follow-up. There were no differences in the average change in viral load ($-1.4 \log_{10}$ c/mL with 3TC vs $-1.5 \log_{10}$ c/mL with no 3TC) or in viral load <50 c/mL at week 48 (52% with 3TC and 44% with no 3TC). The authors concluded that the trial showed no evidence that continuing 3TC in the setting of known or suspected 3TC resistance provides benefit.

Notably, some drugs (like ABC and ddi) can maintain M184V, and the lack of difference between the study arms might be explained if M184V, and its purported beneficial effects, were maintained in the group not receiving 3TC. However, this did not appear to have occurred to a great extent: M184V was detected in over 80% of participants who experienced virologic failure in the 3TC arm during follow-up, while less than 20% of those failing therapy in the non-3TC-containing arm had a detectable M184V mutation during the last 6 months of the trial.

Two caveats about this trial should be noted. First, a potential benefit of maintaining M184V with 3TC is thwarting the development of some of the more troubling nucleoside resistance mutations. While this issue will be further explored in the COLATE trial, analysis of mutations other than M184V that emerged during the study had not been completed as of the presentation at CROI. Second, the relative benefit of M184V on viral fitness may be most evident in true salvage situations. The participants in COLATE were not heavily pretreated; nearly 70% achieved a VL <400 c/mL at week 48, and approximately 50% achieved a VL <50. These rates of viral



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suppression are similar to those seen in ART-naïve trials and may have obscured a modest benefit of M184V on viral fitness.

K65R: Balancing the Effects of Mixed Mechanisms

The K65R mutation is a recent upstart in the world of NRTI resistance because of the use of thymidine analog-sparing regimens, and, most notably, the spectacular failures of triple nucleoside HAART regimens that do not contain AZT or d4T (see Gallant JE, “*Antiretroviral Therapy: The Naïve Patient*”, p 1). Considerable attention was focused on the K65R mutation and its mechanisms of action at this year’s CROI. In a symposium, Lisa Demeter [Abstract 162] provided an overview of mechanisms of resistance to NRTIs, and U. Parikh [Abstract 54] and K.L. White [Abstract 55] presented oral abstracts focusing on the interactions between K65R and other NRTI-associated resistance mutations.

Thymidine analog mutations (TAMs) cause resistance to NRTIs by increasing the ability of HIV’s reverse transcriptase enzyme to excise these agents from transcripts after they have been incorporated, with T215Y being the most efficient (Table, above right). As these mutations accumulate, the result is broad resistance to all NRTIs. In contrast, the M184V mutation potently blocks incorporation of 3TC into growing RNA transcripts, producing complete resistance to this drug (Table, above right). However, M184V also has a detrimental effect (from the point of view of the virus, that is) on the ability of HIV to excise previously incorporated NRTI. M184V also blocks incorporation of other NRTIs, but much less efficiently than it blocks incorporation of 3TC (ABC, ddI >> AZT, d4T, TDF). Thus, in the cases of ABC and ddI, the aggregate effect of M184V’s counteracting influence on incorporation and excision is to produce detectable but clinically insignificant loss of susceptibility to these agents. Conversely, in the case of AZT, d4T, and TDF, the aggregate effect of M184V is to antagonize HIV’s primary mechanism of

Table. HIV Mechanisms of Resistance to NRTI

NRTI-Associated Resistance Mutations	Resistance Mechanisms	
	Blocked Incorporation of NRTI into RNA Transcripts	Excision of NRTI After Incorporation
TAMS (41, 67, 70, 210, 215, 219)	—	↑↑
M184V	↑↑ (3TC); ↑ (Others)	↓
K65R	↑↑	↓

resistance to these agents: NRTI excision.

There is a similar trade-off for K65R. In combination, K65R and M184V cause complete resistance to 3TC and substantial loss of susceptibility to ddI and ABC. Interestingly, although TDF plays an important role in selecting the K65R, the net effect of the K65R/M184V combination on TDF is much less pronounced, because the decreased incorporation of TDF and the antagonized excision balance out.

The interplay between these two primary NRTI resistance mechanisms was used to explain the nearly universal failure of triple NRTI regimens containing TDF, 3TC plus either ABC or ddI [Demeter LM, et al. Abstract 162]. Emergence of the K65R/M184V combination produces high-level resistance to 3TC, ABC, and ddI, effectively leaving TDF monotherapy. In cell cultures HIV susceptibility to AZT is increased by K65R, and this has been borne out in clinical experience, where K65R is a rare mutation in AZT-containing regimens [White KL, et al. Abstract 55]. Additionally, from a clinical perspective, triple NRTI regimens that contain AZT (or d4T), while not as effective as PI or NNRI-based regimens, are not afflicted by the Achilles heel of non-thymidine-containing triple NRTI regimens (see Gallant JE, “*Antiretroviral Therapy: The Naïve Patient*”, p 1).

It’s the Drug Levels, Stupid!

In deep salvage situations, the ability to achieve virologic suppression probably

hinges on the ability to overcome existing PI resistance with serum drug concentration. R. Bertz presented preliminary results from the ABT 049 study, in which 33 heavily experienced patients were randomized to receive LPV/r (*Kaletra*) 667/167 mg (5 capsules) bid or LPV/r 400/300 mg (3 capsules) bid plus RTV 200 mg bid both in combination with 2-3 NRTIs selected by participants’ clinicians [Abstract 134]. LPV trough levels were similar in the two arms and 60% to 70% higher than those historically seen with regular LPV/r dosing. Viral suppression was similar in the two arms, but there was a trend toward better tolerability in the arm containing 5 LPV/r capsules than in the arm with extra RTV. In a multivariate analysis both the LPV inhibitory quotient (IQ, defined as the LPV trough divided by the protein-binding adjusted IC₅₀ for the subject’s particular HIV isolate) and the number of active NRTIs in the regimen were strongly associated with the log₁₀ decline in viral load on therapy as well as the likelihood of achieving a VL <400 c/mL.

Of course toxicity is the other side of the double-edged sword when attempting to increase drug concentrations. For example, IDV concentrations have been correlated with nephrolithiasis and cutaneous toxicity. Similarly, Barrios reported that higher ATV plasma concentrations were significantly associated with the degree of hyperbili-

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Hepatitis: Glimpses of Optimism Tempered by Sobering Mortality Statistics

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

Hepatitis C was a prominent topic at the 11th CROI. The meeting started off with a plenary session by Charles Rice of Rockefeller University [Abstract 8]. Overall, advancement in the study of HCV drugs and vaccines has been hampered by issues such as difficulty with viral cultivation in the laboratory and limited animal models. New antivirals under investigation include the NS3-4A protease inhibitors and NS5B polymerase inhibitors. However, significant cardiotoxicity has led researchers to search for other cellular targets for treatment. Progress in the development of an HCV vaccine is slow due to the high incidence of chronic infection, the possibility of reinfection, as well as the multiple genotypes and rapid molecular evolution of the hepatitis C virus. On the other hand, given the demonstrated viral clearance on treatment and the progress made in developing subunit vaccines to prevent chronic infection, there is reason to hope that vaccine development will be more advanced by the 12th CROI.

Dr. Rice's talk served as an excellent prelude to the rest of the meeting, where the hepatitis data presented were both positive (treatment trends in HIV/HCV coinfecting patients) and sobering (continued increases in mortality secondary to advanced liver disease).

Treatment

Three treatment trials were presented which had treatment arms that included pegylated interferon (PEG-IFN) in various doses with or without ribavirin; all were compared to standard interferon plus ribavirin [Chung, et al. Abstract 110; Dietrich, et al. Abstract 112; and Perronne, et al. Abstract 117]. The treatment arms and results of these trials are presented in the table, p 9. In these studies, nearly 80% of patients were male and white, and 60% had genotype 1 virus. Liver disease and HIV disease were relatively mild, and no patients with advanced HIV or decompensated liver disease were included in any of the studies. Overall, treatment responses were better than expected, but sustained virologic

response, particularly for genotype 1, was far worse than in HCV-monoinfected patients. Response rates for all genotypes combined varied from 41% to 49% at end of treatment, but decreased to 26% to 40% by 6 months following the completion of therapy, the time when sustained virologic response is defined. Treatment discontinuation rates varied from 12% to 39%, although most treatment discontinuation was due to lack of response, not adverse effects. Future studies will need to be performed that include more women, African-Americans, and those with more advanced HIV disease.

In addition, data were presented from ACTG A5071 demonstrating that failure to achieve a 2 log₁₀ decrease in HCV RNA by 12 weeks had a negative predictive value of 100% for achieving sustained virologic response [Chung, et al. Abstract 110]. This has important implications in identifying patients who are unlikely to benefit from long term HCV treatment.

Transplantation

Several groups presented data on organ transplantation. Roland and colleagues presented combined data from UC San Francisco on 10 liver and 15 kidney transplants [Abstract 826]. At a median of 480 days, 90% of liver and 93% of kidney transplant patients were alive. Recurrent HCV was noted in two liver recipients, and one liver recipient required re-transplantation due to a small-for-size graft. With anti-rejection treatment, all patients experienced a decrease in CD4 count, and three new opportunistic infections (OIs) occurred post-operatively, but there were no recurrences of OIs that had occurred prior to transplant. Rufi presented data on 21 orthotopic liver transplants from Spain that had been performed since January 2002 [Abstract 827]. Seventy-five percent of liver recipients suffered from HCV recurrence and were treated with PEG-IFN and ribavirin. In addition, 38% suffered from acute rejection. Teicher presented data on 11 French liver transplant patients, with a 27% mortality rate [Abstract 828]. Of note, there were no

opportunistic illnesses in the post-operative period; however, HCV replication resumed quickly in all patients, and seven patients reinitiated PEG-IFN and ribavirin.

Hepatic Fibrosis

Previous data have suggested faster progression of HCV in those coinfecting with HIV. Liver biopsy is often indicated for disease staging and determination of the need for treatment, but biopsy can have significant associated morbidity. Mehta and colleagues proposed an alternative measure of assessing fibrosis severity using a panel of potential fibrosis markers, including hyaluronic acid, AST, and albumin [Abstract 809]. Patients with albumin >3.5 g/dL, AST <60 IU/L, and hyaluronic acid >40 ng/mL exhibited low rates of medium-to-advanced fibrosis. Longitudinal studies using serial measurements are needed to determine whether these serum markers may be used to follow patients at low risk of progression to fibrosis in place of or in conjunction with liver biopsies.

Wilson and colleagues performed paired liver biopsies on a cohort of injection drug users and demonstrated that fibrosis progression did not appear to occur any faster in HIV positive patients than in HIV negative patients, with an increase in fibrosis scores of approximately 0.11 units/year (Modified Histologic Activity Index fibrosis scores with range 1-6) [Abstract 815]. A non-significant trend was seen toward increased risk of fibrosis progression in those on HAART.

Vaccination

While current recommendations include hepatitis A vaccination for HCV-infected patients, Weissman and colleagues demonstrated that the efficiency of this vaccination is dramatically reduced in a study of 278 HIV-infected patients [Abstract 830]. They demonstrated a response rate of 49% compared to 100% in HIV negative controls. Risk factors for non-response included male gender and CD4 <200 cells/mm³ at the time of vaccination. However, CD4 nadir did not predict response.



Hepatitis: Glimpses of Optimism Tempered by Sobering Mortality Statistics

Mortality

Consistent with last year's abstracts, several groups presented data on increased liver-related mortality in HIV-infected cohorts from the United States and Europe. Data from New York City demonstrated that liver-related mortality among HIV-infected individuals increased significantly from 0.3% to 4% between 1993-2003 [Schlanger K, et al. Abstract 797]. Hispanics and injection drug users had increased risk of HCV-related mortality compared to blacks, whites, and non-drug users. Salmon presented data from France that demonstrated increased mortality in HIV/HCV- and HIV/HBV-coinfected patients compared to HIV-monoinfected

patients [Abstract 798]. End-stage liver disease (ESLD) was a more common cause of death than OIs in HCV-infected patients (31% vs 29%; statistical significance not reported). Patients infected with all three viruses (HIV, HBV, and HCV) had the highest rates of ESLD mortality (44%). Of note, nearly 50% of the patients who died of ESLD had a CD4 count >200 cells/mm³, suggesting that they were in fact not overtly immunocompromised. The EuroSIDA cohort found nearly identical results, with increased ESLD mortality in HIV/HBV- and HIV/HCV-coinfected patients [Abstract 799]. Unlike HCV, HBV was associated with an increased risk of all cause mortality as well. Of note, there were no virologic or immunologic differences

between coinfecting patients and HIV-monoinfected patients.

Conclusion:

In conclusion, while encouraging treatment data were presented at CROI, including data suggesting improved sustained virologic responses with the new PEG-INFs, the reality of more liver-related deaths, and the lack of progress in HCV vaccine development was sobering. In addition, the limited data on liver transplants in HIV/HCV-coinfected patients demonstrated that early mortality from transplantation is relatively low; however there were high rates of HCV recurrence requiring treatment. ▲

Table: Summary of HCV Treatment in Trials of HIV/HCV Coinfected Patients Using Pegylated Interferon

Abstract	110, 112, 117 N=67-286	110 N=67	112 N=286	112 N=286	117 N=205
Treatment	IFN 3-6 MU TIW + RBV 600-1,000 mg/d	PEG α-2a 180 µcg qwk + RBV 600-100 mg/d	PEG α-2a 180 µcg qwk	PEG α-2a 180 µcg qwk + RBV 800 mg/d	PEG α-2b 1.5 µcg/kg qwk + RBV 800 mg/d
Duration (weeks)	48	48	48	48	48
Male	81%	—	82%	80%	74%
White	78%	—	79%	80%	—
Mean Age (years)	40	—	40	40	40
Genotype 1	60%	—	61%	61%	58%*
Tx Discontinuations	39%	12%	31%	25%	40%
HCV Outcomes					
End of Treatment Response Overall	12% to 14%	41%	33%	49%	—
Genotype 1	—	29%	21%	38%	—
Non-Genotype 1	—	80%	57%	64%	—
Sustained Virologic Response Overall	8% to 31%	27%	20%	40%	26%
Genotype 1	7%	14%	14%	29%	11%
Non-Genotype 1	20%	73%	36%	62%	43%

** Genotypes 1 + 4

References:

- ACTG A5071 [Chung, et al. Abstract 110]
- APRICOT [Dietrich, et al. Abstract 112]
- ANRS HC02-RIBAVIC [Perronne, et al. Abstract 117]



Complications of Antiretroviral Therapies and HIV

By Jeanne Keruly, M.S., C.R.N.P.

There was ample coverage of metabolic complications at CROI this year. This report focuses on additional complications related to treatment and HIV.

Diabetes

In a retrospective cohort study, Crane and colleagues examined predictors of developing type-2 diabetes [Abstract 878]. Eligible subjects were those followed in the clinic for at least 6 months. Among 699 patients, 40 developed diabetes. They were significantly more likely to be black (45% vs 17%), over 40 years old (55% vs 29%), have hepatitis C (HCV) coinfection (43% vs 23%), and have a history of acute pancreatitis (13% vs 4%) compared to those who did not develop diabetes. In an adjusted multivariate analysis, compared to patients without HCV or history of pancreatitis, the odds of developing diabetes increased by 2.1 with HCV infection and 3.1 with pancreatitis. Blacks had 3 times the risk of developing diabetes compared to whites. CD4 cell count, viral load, gender, and history of PI therapy were not significantly associated with diabetes.

Brown and colleagues used data from the Multicenter AIDS Cohort Study to report the prevalence and incidence of diabetes among 563 HIV positive and 544 HIV negative men [Abstract 73]. Diabetes was defined as a fasting glucose ≥ 126 mg/dL, use of anti-diabetic medication, or self-reported history of diabetes. After adjusting for age and body mass index (BMI) the presence of diabetes at baseline was 14% in HIV positive men compared with 6% of HIV negative men (odds ratio [OR]=5.4). Incident hyperglycemia developed in 53 (20%) of 272 HIV infected men on ART for an overall rate of 9.1 cases per 100 person-years, compared to 11% among HIV negative subjects (4.9 cases per 100 person-years). After adjusting for age and BMI (but not HCV status), the hazard of hyperglycemia among the HIV positive/ART group was 2.2 times that of the HIV negative group, and the hazard of incident

diabetes among the HIV positive/ART group was 4.4 times higher. Exposure to ART was significantly associated with higher rates of diabetes, but no particular drug was implicated.

These studies support earlier work demonstrating that metabolic complications, including diabetes mellitus, are more common among HIV-infected persons compared to those who are HIV negative. In addition to demographic and co-morbid conditions such as HCV, use of antiretroviral agents increase the risk of this complication. Clinicians should consider these data in the context of screening, risk reduction and aggressive management for diabetes.

Nephrotoxicity

There was sparse information on renal related complications. Using the Johns Hopkins database, Parish and coworkers compared changes in renal function in patients using tenofovir DF (TDF) versus regimens containing nucleoside analogs without TDF [Abstract 751]. In this observational cohort, pre-HAART estimated creatinine clearance (Cockcroft-Gault equation) was compared to post-HAART creatinine clearance in patients receiving TDF or NRTI for up to one year. There were 211 patients on TDF and 265 using non-TDF NRTIs, with a median duration of follow-up of 204 days for TDF users and 289 days for NRTI users. There was no difference in the median serum creatinine at start of treatment between the groups. However, there were significant reductions in median creatinine clearance in both groups (-15.2 and -12.8 mL/min for TDF and other NRTIs respectively) and median percent decline in creatinine clearance (-12.5% for TDF vs -11.1% for NRTI). Factors significantly associated with a decline in creatinine clearance were higher viral load and lower CD4 at the start of treatment, diabetes, and hypertension. In a multivariate analysis adjusting for these factors, TDF use, concurrent use of ddI with

TDF, prior use of adefovir, age, sex, and injection drug use were not significant predictors of creatinine clearance decline. The authors suggested that further studies are needed to evaluate disease state and the concurrent use of nephrotoxic agents as predictors of creatinine clearance decline in this population.

Harris reported data showing an increased risk of developing nephrotoxicity if the estimated glomerular filtration rate (GFR) was < 80 mL/min on TDF [Abstract 750]. Cases included 12 male patients who started TDF through expanded access beginning in 2001 with a pre-TDF serum creatinine in the normal range (40 to 120 mMol/L), and who developed TDF-related renal toxicity. Renal toxicity was defined as clinically significant creatinine increases on TDF with no other etiology, which then resolved when TDF was discontinued; 8/12 also had evidence of drug toxicity on renal biopsy. For each case, two gender-matched controls were randomly selected who started TDF in the same month and who remained on TDF with normal serum creatinine. GFR was estimated using the modified Modification of Diet in Renal Disease formula of Levey, and colleagues. Baseline creatinine was higher in cases compared to controls (101 mMol/L vs 76 mMol/L, $P=0.0035$), though still within the normal range. Mean baseline estimated GFR in the cases was 74 mL/min (range 58 to 98, despite normal serum creatinine at baseline, with 10/12 (83%) having a GFR < 80). The 24 sex-matched controls had mean GFR 104 mL/min (range 80 to 152). Baseline GFR was < 100 mL/min in 10/24 controls but none had GFR < 80 . Using logistic regression, the OR for renal toxicity was 1.16 per mMol/L increase in creatinine and 1.19 per mL/min decrease in GFR.

Bone Density

Reports on bone density changes and its relationship to HIV and treatment were presented in women and children. Anastos presented data on 88 HIV negative and 184



Complications of Antiretroviral Therapies and HIV

HIV positive women from the Women's Interagency HIV Study investigators [Abstract 744]. Of the HIV positive women, 51% were on HAART. Bone mineral density was measured by sequential Dual-Energy X-ray Absorptiometry (DEXA) at 3 sites: spine, femoral trochanter, and femoral neck; and found to be 6% to 8% lower in the HIV positive women ($P < 0.03$ at all sites). HAART use was not associated with bone mineral density. Only 5 women (1.8%) had a z-score indicative of osteoporosis. The prevalence of osteopenia/osteoporosis at any site was 6.4% in the HIV negative women, 18.9% in the HIV positive women not on HAART, and 20.4% in women receiving HAART (adjusted OR=3.15, $P=0.03$ in all HIV positive vs HIV negative women). White race (adjusted OR=2.57), lower body mass index (adjusted OR=0.89), and self-reported postmenopausal status (OR=4.74) were also significantly independently associated with lower bone density. In a subset analysis, longer nevirapine use was associated with higher mineral density whereas abacavir use was associated with lower bone density. Osteopenia or osteoporosis in women was associated with HIV infection and with specific antiretroviral agents, suggesting that this group of predominately premenopausal women may be at increased risk of bone fracture.

Ramos and colleagues assessed bone density over time in 35 children who were HIV-infected by vertical transmission and who had at least 2 DEXA scans for comparison [Abstract 745]. Osteopenia was defined as a z-score of < -1 for the lumbar spine (L1-L4). Bone turnover markers were also assessed. They also assessed serum vitamin D 25, PTH, osteocalcin, and urine deoxypyridinoline, N-terminal telopeptide of type I collagen (NTx) and calcium/creatinine ratio. Thirty-five children were followed with 2 DEXA scans for a median interval of 13 months (range 10 to 19). The median age was 129 months (58 to 219); 20 children were prepubertal (Tanner I); 30

patients were on HAART (28 PI-based, 2 PI-sparing regimen with NNRTI), 2 with 2 NRTI, and 3 without therapy. The median time on HAART at first DEXA was 62 months (16 to 69). Forty percent were found to be osteopenic at the first DEXA although there was no increase in the rate of osteopenia at the second DEXA (45%). Those children on PI-based regimens had greater decreases in bone mineral density than those on other regimens ($P=0.06$). All markers of bone resorption were significantly greater in osteopenic children.

Hypertension

In one large observational study, high blood pressure was found to be associated with traditional risk factors, but not related to antiretroviral therapy [Thiebaut R, et al. Abstract 75]. The investigators evaluated predictors of changes in systolic and diastolic blood pressure and the occurrence of hypertension using the 16,002 patients enrolled in the D:A:D cohort. Patients who enrolled with normal blood pressure ($N=8,341$) were evaluated for the development of hypertension defined as systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90 mmHg or initiation of antihypertensive treatment. A total of 43,501 blood pressure measurements with a median of 3 per patient were recorded over a median follow-up of 1.5 years. Risk factors significantly associated with increases in systolic blood pressure: Older age, male gender, higher BMI, and use of antihypertensive medications. In 8,341 patients with normal blood pressure at baseline, 487 developed hypertension, providing an incidence of 35.8/1000 person-years. Factors associated with the development of hypertension were male gender, higher BMI, older age, and higher blood pressure at baseline. The cumulative duration of exposure to each class of anti-retroviral as well as type of treatment at baseline were not significantly associated with occurrence of differences in blood pressure and/or the risk of hypertension.

In another study of hypertension, Khalsa presented data from the Women's Interagency HIV Study of 2046 HIV positive and 564 HIV negative women who were followed every 6 months [Abstract 741]. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg, or the use of antihypertensive medications reported at the time of a visit. The baseline prevalence of hypertension was 19% for both the HIV positive and HIV negative women. The overall incidence of developing hypertension was not significantly different between the HIV positive and HIV negative women (47% vs 46%, respectively) through visit 16. Both the univariate and multivariate models found increasing age, black race, lower education level, smoking, increasing BMI (30+), and HAART use to be significantly associated with hypertension. They also found a time-dependent relationship between hypertension and duration of time on HAART measured in six-month intervals; relative risks were 1.32, 1.36, and 1.51 for 1, 2 or ≥ 3 six-month intervals on HAART, respectively. Interestingly, current pregnancy, and AZT monotherapy showed significant protective effects. The mechanism for the protective effect of these factors is not known.

In summary, many metabolic complications have been found to be more common in HIV-infected persons, although the data do not consistently support that these manifestations are directly related to antiretroviral therapy. However, antiretroviral toxicity may contribute to cumulative or additive risk of developing a complication. In addition to considering an agent's potency and durability, careful consideration must be given to factors that may place a patient at increased risk of a complication. Harris' study is an excellent reminder that we should always consider estimated creatinine clearance before for any agent that is cleared through the kidney. ▲



A number of abstracts at the 11th CROI meeting focused on long-term complications of HIV treatment. Although there were excellent basic science reports, I will focus here on the clinical studies.

Complications of Stavudine

In a randomized study of 237 participants receiving stavudine (d4T) or ABC combined with lamivudine (3TC) and efavirenz (EFV), patients in the d4T arm had significantly more moderate-to-severe lipodystrophy (20% vs 3%, $P=0.001$), with more loss of fat in the face, upper extremities and buttocks after 48 weeks [Podzamczar D, et al. Abstract 716]. DEXA scans performed at baseline and 48 weeks in 78 patients confirmed these results. Fasting cholesterol and triglyceride levels increased in both arms of the study, while lactate levels increased only in the d4T arm ($P<0.001$ compared to baseline). Baseline characteristics were similar between arms. Drug discontinuation rates were similar in both arms (14% vs 15%), and there were no differences in virologic response (VL <50 c/mL by intent-to-treat analysis). These results are quite consistent with those of the GS 903 trial, which compared tenofovir DF (TDF) with d4T, both in combination with 3TC and EFV.

Another prospective, double blind randomized trial of 751 ART naïve subjects compared emtricitabine (FTC) with d4T, both combined with enteric coated didanosine (ddI) and EFV [Powderly W, et al. Abstract 717]. Patients in the FTC arm had more favorable lipid profiles and body habitus over 72 weeks of follow-up. Finally, Murphy reported on a sub-study of 82 patients from the large Atlantic study, which compared indinavir (IDV), nevirapine (NVP) and 3TC with a nucleoside backbone of d4T/ddI in naïve subjects [Abstract 718]. Based on questionnaires, DEXA scans and abdominal CT scans, peripheral lipodystrophy was common (25% at baseline) and progressed over 4 years in

all arms. IDV use was associated with significantly higher visceral adipose tissue by abdominal CT scan after a median of 144 weeks ($N=53$). NVP was associated with significant increases in HDL cholesterol compared to the other arms.

Taken together these studies continue to confirm that the choice of the NRTI backbone has an important impact on the likelihood of developing metabolic and morphologic changes. These data from large blinded trials in naïve patients offer strong support to prior cross-sectional studies that implicated d4T as the NRTI most likely to cause lipodystrophy, and also as a contributor to drug-related hyperlipidemia.

In an attempt to evaluate the safety of extended-release formulation of d4T, investigators at Bristol-Myers Squibb performed a *post-hoc* analysis from two different randomized, multinational, double-blind, placebo-controlled studies of comparing immediate versus extended release d4T used in combination with 3TC and EFV in antiretroviral naïve patients [Noor M, et al. Abstract 722]. A subgroup of 877 (94%) had available fasting triglyceride levels. Baseline characteristics were similar between groups. Lipodystrophy was noted in both arms, although less overall lipodystrophy was seen in the extended release group (8% vs 14%). Multivariate logistic regression found that triglyceride levels <200 mg/dL at baseline, age <40 years, and use of the extended release formulation predicted a lower risk of lipodystrophy, while gender, race, baseline BMI, fasting glucose, waist circumference, baseline CD4, and viral load did not. These data are encouraging, as they suggest that the extended release formulation of d4T, which is not yet commercially available, may be less toxic than standard d4T. However, the data are limited by the fact that this study did not compare d4T to other NRTIs, and by the fact that this was a *post-hoc* analysis of data from two different studies.

Enfuvirtide (ENF, T-20)

Whole body DEXA and single slice CT scans at the L4 level were performed at baseline, week 24, and week 48, along with multiple fasting chemistry measurements, in a subset of TORO 1 and 2 patients [Cooper DA, et al. Abstract 715]. Only a small number of patients had DEXA or CT evaluable at week 48 ($N=12$), so caution is needed in evaluating results. Nonetheless, glucose levels, lipid profiles and C peptide levels were similar in the ENF-containing regimens compared to those on optimized background therapy without ENF, and there was no appreciable impact of ENF on body composition.

Coronary Artery Disease

The increased prevalence of metabolic abnormalities raises concern for cardiovascular damage. Following up on their recent publication [*N Engl J Med* 2003; 349(21):1993], the D:A:D study group found that 199 patients experienced at least 1 cardiovascular event (myocardial infarction [MI], cardiovascular death, invasive cardiovascular procedure, or stroke), for an incidence of 5.5/1,000 person-years, which increased with longer exposure to ART [Law MG, et al. Abstract 737]. Rates were comparable and generally higher than predicted using Framingham equations. Similarly, the Kaiser Permanente Northern Californian HMO group presented additional follow-up on HIV-infected patients who were hospitalized for coronary heart disease (CHD) [Klein D, et al. Abstract 739]. During the 7.5-year observation period 4,726 HIV-infected patients experienced 111 CHD events, including 66 MIs. Rates of CHD and MI were significantly higher among HIV-infected participants aged 35-64 compared to HIV negative participants (CHD: 6.6 vs 3.0 events/1000 person-years, $P<0.0001$; MI: 3.9 vs 2.2, $P<0.005$). The age-adjusted relative risk for CHD hospitalization per 2 years of PI exposure was 1.17 ($P=0.01$), but



Lipodystrophy And Metabolic Complications

the difference was not statistically significant for MI.

Taken together, these studies offer further support that coronary artery disease in HIV-infected individuals will increase over time, and the D:A:D study demonstrated a strong association with duration of ART use. As much of the risk is attributable either to reversible hazards (e.g. smoking, hypertension, hyper-lipidemia, physical inactivity, and obesity) or to alterations in CAD risks induced by ART (e.g. hyperlipidemia, diabetes), it is important that clinicians attempt to modify those conditions, especially in patients at high risk due to multiple risk factors.

Lipoatrophy Treatments

One of the most noteworthy presentations related to complications of HAART was Andrew Carr's report on the disappointing results of the rosiglitazone study, recently published in *Lancet* 2004;363:429 [Abstract 79]. A total of 108 patients with lipoatrophy on stable antiretroviral therapy were randomized to receive maximum dose rosiglitazone (4 mg bid) or placebo in a double-blind, 48-week trial. The intention-to-treat analysis demonstrated a modest increase in limb fat in each group (0.14-0.18 kg) with no significant difference between groups. There were no benefits associated with rosiglitazone with respect to subcutaneous thigh fat, subcutaneous abdominal fat, or visceral fat by computed tomography, nor in total fat mass, lean body mass, or objective and subjective severity of lipoatrophy. There were significant increases in plasma adiponectin (101% increase to 4.1 mMol/L) but not leptin (6% increase to 0.2 mMol/L), and significant decreases in 3 markers of insulin resistance in the active arm. No benefits were seen in subgroup analyses, whether by PI use, thymidine analog use, limb fat mass, or insulin resistance at baseline. In each arm, 6 patients discontinued the study drug, 2 in each arm for adverse events attributed to

study drug. Key adverse events included asymptomatic hypertriglyceridemia and hypercholesterolemia. In a substudy rosiglitazone did not alter endothelial function at 48 weeks, as measured by brachial artery ultrasound reactivity at rest and after two vasodilatory stimuli [Martin A, et al. Abstract 729].

Prior studies have suggested a possible improvement in lipoatrophy with the use of rosiglitazone, but this carefully conducted trial failed to demonstrate any beneficial effect. Limitations include ART switches: 3 participants in each arm changed from d4T to another NRTI, and 5 and 3 participants in the rosiglitazone and placebo groups changed PIs, potentially affecting the results. However, it is unlikely that these factors would have hidden a true benefit. It is unclear what the effect of this drug will be in HIV infected diabetics as they were excluded from this study. However, given the lack of benefit in glucose intolerant patients, significant benefit in diabetics seems unlikely. Ultimately, it is becoming increasingly clear that clinicians should not count on medications to "reverse" lipoatrophy; prevention is by far the best approach.

Poly(lactic acid) (*New-Fill*) injections, given every 15 days, were evaluated in 94 lipoatrophic subjects (88 male, 6 female) followed for a median of 12 months [Lafaurie M, et al. Abstract 726]. Satisfactory results were reported in 73% on follow-up questionnaire, 59% (at best) by blinded re-ordered digital photos, and 48% by 3D photo (N=50). There was a very low correlation factor between observers (Kappa <0.3), and there were no changes in measured quality of life. The probability of requiring additional injections at 15 months was 45%. Significant side effects included grade 1 or 2 pain in 80%, malaise after the first injection in 7 patients, non-inflammatory small nodules in 12 patients, and minor bleeding in 4 patients. Treatment was stopped in one subject after the first

injection because of an anaphylactic reaction. This study, relatively large in comparison with other studies of cosmetic interventions for lipoatrophy, showed a high level of patient satisfaction, which may in part reflect the unblinded nature of the study. Clinicians, however, should be sobered by the <50% success according to 3D photos, the frequent complications, and the need for additional injections within 1-2 years. Also, this was predominantly a study of white males, and it is not clear if results can be extrapolated to other populations. The long term results of *New-Fill* have yet to be demonstrated.

Treatment of Fat Accumulation

Don Kottler reported 60-week data for low-dose "maintenance" therapy with recombinant human growth hormone (rhGH) for patients with central fat accumulation [Abstract 80]. A subset (127/142) subjects from an earlier placebo-controlled rhGH study were re-randomized to receive 24 weeks of maintenance therapy at a dose of 1 or 2 mg daily. Subjects with glucose intolerance or diabetes were excluded from the initial study. Significant reductions were found in both the 1 mg and 2 mg maintenance groups at week 60 for trunk fat (-1.1, -1.4 kg), non-HDL cholesterol (-21.2, -23.8 mg/dL), and total cholesterol (-16.9, -18.5 mg/dL). Oral glucose tolerance testing revealed no change from baseline to week 60 in insulin area-under-the-curve, and there were no between-group differences between the 1 and 2 mg doses in any parameters baseline to weeks 36. Arthralgia, however, was more common with the 2 mg dose (12.5% vs 5.7%).

It appears as though low dose maintenance therapy of 1 mg daily rhGH dosage in patients who initially received high dose therapy may serve some benefit for those with fat accumulation and no insulin

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Lipodystrophy And Metabolic Complications

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resistance. However, rhGH at 1 mg/day is still a supra-physiologic dose, and most clinicians are not yet ready to keep patients on life-long, daily growth hormone. Prior reports suggested that high dose rhGH worsened lipoatrophy, which many patients can't afford. Finally, glucose intolerant or insulin resistant patients were excluded, and probably should be excluded from use of rhGH, which further limits the number of patients for whom this therapy might be appropriate.

Treatment of Hyperlipidemia

Jim Sosman presented a placebo-controlled, double-blind cross-over study evaluating the impact of 40 mg/day of pravastatin on lipoprotein subfractions and endothelial function, assessed by flow-mediated vasodilatation (FMD) of the brachial artery using high-resolution ultrasound, in 20 patients receiving PIs [Abstract 77]. At entry, many participants had unfavorable lipid parameters. FMD was also impaired, indicating endothelial dysfunction. Pravastatin significantly reduced total cholesterol by 18%, LDL cholesterol by 20%, and non-HDL cholesterol by 22%. Pravastatin therapy was associated with a reduction in LDL by 21% ($P=0.03$), small LDL by 27% ($P=0.1$), and small VLDL by 45% ($P=0.023$). There was also a trend toward improvement in FMD ($P=0.08$). This is the first placebo-controlled, blinded study to use sophisticated Nuclear Magnetic Resonance technology to confirm the benefits of statin therapy, which is already being widely used in clinical practice. Pravastatin demonstrated a modest benefit in improving parameters of the lipid profile which would predict a modest decrease in overall cardiovascular risk. Taken with the data on CHD discussed above, it is clear that clinicians can modify a number of important cardiac risk factors, including drug-induced hyperlipidemia. ▲

Early Treatment of HIV

By Joel N. Blankson M.D., Ph.D. and Joel E. Gallant, M.D., M.P.H.

Much of the support for the potential benefit of treating patients during primary or early HIV infection comes from Bruce Walker's group in Boston, where preliminary data suggested that very early treatment, especially during high-level viremia prior to Western Blot seroconversion, might lead to an improved virologic set-point, ultimately improving the long-term prognosis. Data were particularly encouraging for structured treatment interruptions (STIs) in this setting. It was hypothesized that early treatment would preserve the HIV-specific CD4+ T-cell proliferative response. This key component of the immune response is absent in the majority of chronically infected patients but maintained in long-term non-progressors (LTNP) who remain immunologically stable without the need for chronic antiretroviral therapy [Rosenberg, et al. *Nature* 2000;407:523]. It was also felt that STIs would have an "auto-immunizing" effect, further improving HIV-specific cellular immunity. It was thus hoped that the combination of these two strategies would turn acute seroconverters into LTNPs. Patients in Walker's cohort underwent STI in a protocol that mandated the re-initiation of HAART for a single viral load (VL) of $>50,000$ c/mL or 3 consecutive VL of >5000 c/mL. This strategy initially looked very promising, with 5 out of 8 patients maintaining VL of <5000 c/mL in the first year of the protocol [Rosenberg, et al. *Nature* 2000; 407:523].

Unfortunately, longer-term data presented at CROI by the same group of investigators suggests that the resulting immune control of viral replication is of limited durability [Kaufmann K, et al. Abstract 24]. Fourteen patients have now undergone from 1 to 4 STIs over a median of 3 years since the beginning of the first STI. Only 3 of these patients have maintained VL of <3000 c/mL off therapy, and 1 of these 3 patients has had a significant drop in his CD4 count. The other patients all experienced a decline in CD4 count and a gradual rise in viral load, eventually leading to the re-initiation of HAART. Interestingly, the time between diagnosis and initiation of HAART, the baseline viral load, the number of STIs performed, and the breadth and magnitude of HIV-specific cytotoxic T-lymphocyte response all failed to show a correlation with protection. There were no distinguishing features or predictors that separated the three successes from the remainder of the subjects.

It's not clear why the initially observed immune control of viremia is not sustained, but preliminary data presented by the same group at least year's conference suggest that gradual genetic evolution of the virus may play a role [Walker BD, et al. Abstract 164, 10th CROI, Boston, 2003]. While the results of the study are disappointing, a randomized control study is needed to determine whether there is any clinical advantage to starting HAART during acute infection. There is a hypothetical advantage to early treatment, as it does preserve the HIV-specific proliferative CD4 T-cell immune response [Rosenberg, et al. *Nature* 2000;407:523]. Many studies have shown that this response plays a key role in helping cytotoxic T-lymphocytes control viral infections [Reviewed by Kaech and Ahmed, *Science* 2003;300:263]. Thus treatment during primary infection, followed by therapeutic vaccination when available, may be a viable strategy for improving long-term immune control of viral replication. ▲



The Tenacity of NNRTI Drug Resistance

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studies has been to urge that pregnant women be treated with standard HAART regimens, as they are in the developed world. This would almost certainly reduce transmission of resistant virus to the infant and would probably be more beneficial to the mothers as well. However, giving a NVP-containing regimen throughout pregnancy could increase the risk of serious hepatotoxicity, which is more common among women, especially those with high CD4 counts. Moreover, the problem of prolonged drug levels and low genetic barrier to resistance following discontinuation of NNRTIs is not solved by using combination

therapy; there may still be a risk of resistance with discontinuation of temporary NNRTI-based HAART regimens. Protease inhibitors may be a better choice, either for PMTCT or to provide a pharmacologic “tail” while NNRTI levels fall, but they are prohibitively expensive in many parts of the world. This is clearly an evolving controversy, and in many cases, scientific data will have to take a back seat to political, economic, and practical considerations. Given present-day realities, NVP may remain the most feasible option for PMTCT for most women in resource-poor settings. ▲

The Treatment of Experienced Patients and Resistance Mechanisms From the 11th CROI

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rubinemia [Abstract 606]. Additionally, considerable attention was focused on efavirenz (EFV) pharmacogenomics, race, and central nervous system side effects. In substudies of ACTG 5095, the trial comparing EFV/AZT/3TC/ABC, EFV/AZT/3TC, and AZT/3TC/ABC (the latter arm discontinued due to high failure rate), EFV clearance and central nervous system side effects were found to be strongly associated with a CYP2B6 polymorphism (the cytochrome P450 enzyme most directly involved with EFV metabolism) an allelic variant that is more common in blacks than whites [Haas D, et al. Abstract 133]. These differences may explain the significantly lower EFV clearance (and significantly higher drug concentrations) in blacks and Hispanics than in non-Hispanic whites in the ACTG 5095 sub-study [Ribudo H, et al. Abstract 132].

Conclusion

Forty-eight-week data from BMS 045 continued to show similar virologic efficacy of ATV/RTV and LPV/r in treatment experienced patients, with better lipid parameters in the former group. This suggests that boosting drug concentrations well above the viral IC₅₀, reasonable dosing and pill burdens, and tolerability are the main factors currently driving the overall effectiveness of PI-based regimens. Adding ABC to IDV-based regimens was not associated with any durability benefit in patients with suppressed viral loads, and continuing 3TC in the presence of M184V was not associated with benefit in minimally to moderately antiretroviral-experienced patients initiating a salvage regimen. Finally, additional basic science and clinical research has shed light on the K65R resistance mutation and how its effects on NRTI incorporation and excision lead to different net effects for different drugs, particularly in combination with M184V. ▲

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June 17 and 18, 2004; Baltimore, Maryland

The Johns Hopkins University School of Medicine is pleased to announce its first conference on information technologies. The theme of the conference is “Exploring the new technologies that are changing clinical decisions and patient care—what does the future hold.” The conference planners welcome clinicians and others interested in medical informatics; CME credit will be offered. For more information go to <http://hopkinscme.org/cme/events/inftech04.html> or call (410)955-2959.

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May 10 and 11, 2004; Baltimore, Maryland

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