

THE HOPKINS HIV REPORT

A bimonthly newsletter for healthcare providers

Report From Boston: The 13th Conference on Retroviruses and Opportunistic Infections (CROI)

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Initial Therapy and Treatment Interruption

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

At the 13th Conference on Retroviruses and Opportunistic Infections, held in Denver from February 5-8, 2006, there were few presentations on treatment options for antiretroviral-naïve patients. However, there were several important treatment interruption trials as well as a number of studies that have implications for the timing of treatment initiation. Finally, I learned that “Denver” is not just a place where you go to change planes when traveling elsewhere, but is actually a real city, where people live and work, and where there is a superb conference center. Who knew?

Boosted vs. Unboosted Atazanavir

Since the approval of atazanavir (ATV) in 2003, there has been a tendency among many physicians to prescribe it using ritonavir (RTV) boosting, despite the lack of specific data on the use of boosted ATV in protease inhibitor (PI)-naïve patients and the absence of any recommendation about boosted ATV in the DHHS guidelines. There are a number of good reasons for this approach, including the demonstrated advantages of RTV boosting for other PIs with respect to pharmacokinetics, efficacy, activity against resistant virus, and emergence of resistance with failure. In the case of ATV, we know that trough levels are higher with RTV boosting, and also that the 2-year efficacy of RTV-boosted ATV (ATV/r) was comparable to that of lopinavir/ritonavir (LPV/r) in PI-experienced patients in the BMS 045 study [Johnson M, et al. *AIDS* 2005;19:685-94], whereas LPV/r was superior to unboosted ATV in PI-experienced patients in the BMS 043 study [Cohen C, et al. *Curr Med Res Opin* 2005;21:1683-92]. By extrapolation, it has been assumed that ATV/r must be at least as effective as unboosted ATV.

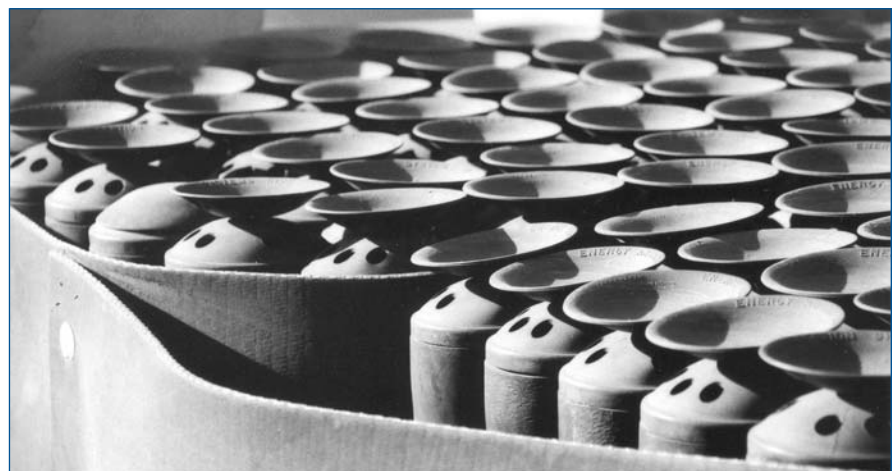
The A1424-089 study is the first study to directly compare boosted and unboosted ATV

in a treatment-naïve patients [Malan N, et al. Abstract 107LB]. The 200 patients randomized also received lamivudine (3TC) and stavudine (d4T) in the extended release (XR) formulation that was approved but never marketed and is no longer being developed. Median baseline viral load was approximately 5 log₁₀ c/mL, and median CD4 count was approximately 200 cells/mm³. By intention-to-treat (ITT) analysis, 75% of those in the ATV/r arm had a viral load of <50 c/mL at 48 weeks, compared to 70% in the ATV arm. For the <400 c/mL analysis, the results were 86% and 85%, respectively. While the efficacy appeared to be comparable, especially in the 400 c/mL analysis, it is worth noting that there

was more virologic failure in the unboosted ATV arm (10% vs. 3%), whereas there was more drop-out due to hyperbilirubinemia in the ATV/r arm. The study was able to conclude that ATV/r was non-inferior to the ATV arm, but it was not powered to answer the more relevant question of whether ATV was non-inferior to the ATV/r arm, and in fact the results would suggest otherwise.

There were some other important differences between arms in this study. Hyperbilirubinemia and jaundice were more common in the ATV/r arms, with 3%

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“East Colfax Avenue, Denver, Colorado, 2006” photograph by Joel Meneses

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developing grade 2-4 jaundice compared to <1% in the unboosted arm. Lipid levels were also higher with RTV boosting, although the majority of patients in both arms maintained lipid levels below NCEP targets, and few started lipid-lowering therapy.

Among the patients who failed therapy, resistance profiles were more favorable in the ATV/r arm. None of the 3 patients who failed ATV/r developed PI mutations compared to 3 of 10 failures on ATV, who developed I50L (1) or I50I/L + G73G/S (2). Emergence of M184V also appeared to be more common among those failing unboosted ATV.

In the end, these results support both the use of ATV and of ATV/r in treatment-naïve patients. On the one hand, the lower rate of virologic failure and the apparent resistance advantages suggest that ATV/r may be more potent than ATV, and may in fact be preferable if tolerated. On the other hand, the efficacy of unboosted ATV was reassuring, making this a reasonable alternative for patients who can't tolerate RTV. This study also demonstrates that there is a small price to be paid in lipid levels and the potential for jaundice with the use of even 100 mg of RTV per day.

Monotherapy with Boosted Atazanavir

Most studies looking at boosted PI monotherapy have involved LPV/r, in part because of its record of potency, its high genetic barrier to resistance, and the lack of resistance with failure. However, there is also interest in the use of ATV/r monotherapy, a strategy that is being studied in ACTG 5201 [Swindells S, et al. Abstract 108LB]. This is an open-label pilot trial in which patients with virologic suppression on antiretroviral therapy were first switched to ATV/r plus 2 nucleoside analog reverse transcriptase inhibitors (NRTIs). If they maintained suppression on that regimen, the NRTIs were discontinued after six weeks, leaving them on ATV/r alone. A total of 34 patients completed that second step of the protocol, of whom 1 withdrew consent and 3 experienced virologic failure. Two of the failing patients had undetectable ATV levels and were presumed to be non-adherent. However, the third patient had detectable ATV levels. His viral load resuppressed with continued use of ATV/r alone. None of the three patients developed PI mutations.

This study suggests that this is a viable concept and should be studied further.

However, the PI monotherapy studies reported to date have two things in common: (1) there is invariably at least one patient in each study who fails to maintain virologic suppression despite adherence and detectable or therapeutic drug levels, and (2) the sample sizes are never large enough to allow us to definitively conclude that this is a safe and effective strategy. Fortunately, larger, randomized trials are ongoing.

Intensification of Therapy in Patients Taking *Trizivir*

In the last issue of *The Hopkins HIV Report*, I discussed Roy Guilck's presentation of ACTG 5095 comparing zidovudine/lamivudine/abacavir (AZT/3TC/ABC, *Trizivir*) + efavirenz (EFV) vs. AZT/3TC (*Combivir*) + EFV [46th ICAAC, 2005, Abstract H-416a]. That study demonstrated no difference in performance between the two arms. The original study also included a *Trizivir* arm, which was found to be inferior to the two EFV-containing arms [Gulick R, et al. *N Engl J Med* 2004;350:1850-61]. Patients who remained virologically suppressed on the *Trizivir* arm were randomized to intensify therapy with either EFV or tenofovir DF (TDF), and Gulick presented the results of this comparison at CROI [Abstract 519]. Overall, there was no difference between the arms in time to virologic failure or treatment discontinuation, in the proportion of patients with undetectable viral loads at weeks 24, 48, or 72, or in CD4 cell count responses at those three time points. However, it was noted that treatment failure occurred in 22% of those who added TDF vs. 15% who added EFV. While that difference was not statistically significant, Kaplan-Meier curves demonstrated more failure among EFV recipients in the first 28 weeks, but more failure among TDF recipients between 28 and 88 weeks. A reasonable assumption might be that early failure on EFV was likely to reflect discontinuation due to side effects, whereas later failure on TDF reflects virologic rebound on a less potent regimen. However, this assumption cannot be confirmed by the analysis presented at CROI. Suffice it say that while there is some support for the combination of *Trizivir* plus TDF, it should still be viewed as an investigational regimen.

A Setback for CD4-Guide Treatment Interruption

Several studies examining treatment

interruption strategies were presented at CROI, with the session culminating in the presentation of the large SMART trial, which demonstrated significantly greater morbidity and mortality among patients who interrupted therapy [El-Sadr W, et al. Abstract 106LB]. Prior to SMART, most studies looking at this strategy, in which therapy is stopped when the CD4 count reaches a predetermined threshold and resumed when it falls to another lower threshold, had suggested that this approach was safe, especially in patients with relatively high CD4 nadirs. However, these were much smaller studies than SMART, which involved nearly 5,500 patients. Before discussing SMART, it's worth mentioning the other treatment interruption studies presented at CROI. I will not discuss trials that exclusively studied fixed-interval interruption strategies [Palmisano L, et al. Abstract 103, Marchou B, et al. Abstract 104], as there has been less enthusiasm for this approach in recent years.

ACTG 5170 assessed treatment interruption in 167 patients who had been on HAART for at least 6 months and who wanted to stop therapy. Enrollment required that they have had a pre-treatment CD4 nadir >350 cells/mm³ and a pre-treatment viral load <55,000 c/mL, which meant that they did not meet criteria for HAART based on guidelines in place at the time. Eligible patients discontinued HAART for up to 96 weeks, with the potential to resume at the discretion of the health care provider. Those on non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens stopped their NNRTI two days before stopping their NRTI. After stopping, patients lost approximately 20 cells per week in the first 8 weeks, and 1.7 cells per week thereafter. Viral load rebounded quickly during the first 4-8 weeks and then stabilized. By week 48, 26 had resumed therapy, 12 had CD4 counts ≤250 cells/mm³, and there were 3 deaths. From weeks 49-96, 5 reached a CD4 count ≤250 cells/mm³, 2 each had developed CDC stage B or C conditions, and there were two deaths. None of the 5 deaths were from AIDS-related conditions, and most occurred in patients with relatively preserved CD4 counts. In a multivariate analysis, predictors of time to reaching a study endpoint by week 96 were low CD4 nadir and detectable viral load at entry.

The **Staccato Trial** has been discussed in several previous issues of *The Hopkins HIV Report*. This is a trial, conducted mostly in



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Thailand, in which 548 patients with CD4 counts above 350 cells/mm³ and viral loads <50 c/mL on HAART were randomized to continue therapy (CT, n=154), to interrupt therapy until their CD4 count fell below 350 (TI, n=299), or to take therapy on a week-on, week-off schedule [Ananworanich J, et al. Abstract 102]. As has already been reported, the week-on, week-off arm was terminated early because of high rates of virologic failure. Patients in the TI arm all took continuous HAART during the last 12-24 weeks of the study. At the end of that period, there was no difference in the proportion of patients who had CD4 counts above 350 cells/mm³ (86% vs. 97% in the TI and CT arms, respectively, p=NS). Not surprisingly, those in the TI arm, who spent 37.5% of the study period on

HAART, were more likely to experience oral or vaginal candidiasis, thrombocytopenia, or acute retroviral syndrome, while those in the CT arm had significantly more diarrhea and neuropathy, as well as higher total cholesterol levels and more self-reported lipodystrophy. There was no difference in mortality (1 non-HIV-related death in each arm) or in the frequency or patterns of resistance.

ANRS 1269, the **Trivicam** study, enrolled 940 treatment naïve, West African patients with baseline CD4 counts of 150-350 cells/mm³ [Danel C, et al. Abstract 105LB]. After achieving virologic suppression on continuous HAART, they were randomized to remain on continuous HAART (1:6), to interrupt therapy using a fixed-interval approach of 2 months off, 4 months on (3:6),

or to interrupt HAART when the CD4 count was above 350 cells/mm³ and to resume when it fell below 250 cells/mm³ (2:6). An interim analysis by the Data and Safety Monitoring Board resulted in discontinuation of the latter arm because of significantly greater morbidity and mortality compared to the other two arms. Mortality was 1.2 per 100 person-years (PY) in the TI arm vs. 0.6 in the CT arm, and the incidence of serious morbidity (any WHO stage 3 or 4 classifying event) was 11.6 vs 6.7 per 100 PY. The incidence of both tuberculosis and invasive bacterial infections was significantly higher in the TI arm, as were hospitalization and clinic visits.

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That brings us to the Strategies for Management of Antiretroviral Therapy trial (SMART), a large NIH-funded trial in which 5472 patients from 33 countries and 318 study sites were randomized to what the investigators called the “virologic suppression” arm or the “drug conservation” arm, but which I will refer to as the CT and TI arms, respectively, to avoid confusion. All patients had CD4 counts >350 cells/mm³ at entry. This study was originally designed to look not only at CD4-guided treatment interruption, but also at the question of when to start therapy, so it enrolled both treatment naïve and treatment experienced patients. However, 95% of the participants were treatment-experienced at the time of enrollment. Those randomized to the TI arm discontinued therapy, resuming when the CD4 count fell

below 250 cells/mm³, and stopping again when it rose above 350 cells/mm³. Those in the TI arm spent approximately one-third of the study period on therapy, compared to 93% in the CT arm. The study was stopped prematurely because of a 2.5-fold greater risk of clinical progression or death in the TI arm (3.7 vs. 1.5 per 100 PY, p<0.0001). The difference favoring the CT arm was present in both men and women and in blacks and non-blacks. Moreover, outcomes were better in the CT arm regardless of nadir CD4 count, which has always been the best predictor of success with treatment interruption in other studies. Surprisingly, there were trends toward a *greater* incidence of severe “complications” in the TI arms, defined as cardiovascular, renal, or hepatic deaths or non-fatal events. These endpoints, which can be complications of antiretroviral therapy, were included as it was assumed that they would be *less* frequent in patients who interrupted therapy.

Interestingly, deaths among patients who interrupted therapy weren’t due to typical AIDS-related conditions; instead, they were the result of events such as myocardial infarction, which we normally don’t think of as being related to treatment interruption. However, the power of this large comparative trial to detect differences in outcome forces us to reconsider the implications of such deaths in other studies, such as ACTG 5170, discussed above. We’ve tended to dismiss those events as being unrelated to treatment interruption, but the possibility of a causal association is not biologically implausible. For example, patients on antiretroviral therapy, some of whom may have developed accelerated atherosclerosis as a result of treatment, will experience inflammation and immune activation when therapy is discontinued, which could lead to an increased risk of myocardial infarction.

Where do these studies leave us? The implications of these findings were controversial enough that the meeting organizers added a panel discussion at the end of the session to help sort out the conflicting data. Interpretations of the data varied widely among the panelists as well as the attendees talking the issue over in the halls. Some took the narrowest approach, concluding that if therapy is interrupted, it should be resumed well before the CD4 count has fallen to 250 cells/mm³, the threshold used in both SMART and Trivican. Others concluded that the entire concept of CD4-guided treatment

interruption is dead and should not be studied further. My own opinion falls somewhere between these extremes. Even before SMART, interest in physician-directed, CD4-guided treatment interruption was waning, primarily because options for initial therapy were becoming so much easier and less toxic than they were when the strategy was first proposed. Should a patient taking two pills once a day with no side effects and no toxicity interrupt therapy, even if it’s safe? In parts of the world where access to therapy is not an issue, the standard of care should be continuous therapy without interruption based on the data we have now. Patients who have to interrupt therapy because of toxicity or other reasons should resume before the CD4 falls below 350.

On the other hand, intermittent therapy approaches are attractive in resource-limited settings, where a strategy that allows use of one-third the amount of antiretroviral therapy per patient could allow the treatment of three times as many people. However, the Trivican study points out that in the developing world, tuberculosis and serious bacterial infections can occur at CD4 counts well above the 200 cells/mm³ threshold that we typically think of as marking the onset of risk for opportunistic infections. In such regions, an argument can be made for even earlier resumption (or possibly initiation) of therapy to decrease the risk of these complications.

When to Start Therapy

The SMART trial, while not addressing it directly, also speaks to the question of whether we should be starting therapy earlier. The higher rate of complications and death among patients who interrupted therapy despite having CD4 counts above 250 cells/mm³ is concerning, although we can’t assume that a treatment-naïve patient is the same as a patient who has interrupted therapy. There were several other studies presented at CROI that also addressed this issue, each of which suggested that there may be an advantage to earlier therapy.

Two cohort studies, one from the Hopkins database [Keruly J, et al. Abstract 529] and the other from the Dutch ATHENA cohort [Gras L, et al. Abstract 530] found that patients who start therapy with higher CD4 counts are more likely to experience normalization of their CD4 counts, despite a greater magnitude of CD4 increase in those with lower baseline CD4 counts. Assuming that it’s good to have a normal CD4 count (which has not been

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clearly demonstrated), this would argue for earlier initiation of therapy.

An analysis from the ART Cohort Collaborative, which includes data from over 10,000 patients from a variety of clinical cohorts, found that the cumulative probability of progression to AIDS or death was highest among patients who started therapy with CD4 counts below 200 cells/mm³. However, patients who started therapy with CD4 counts of 351-500 cells/mm³ were significantly less likely to progress or die than those with baseline counts of 201-350 cells/mm³, though the difference was much smaller than the difference between either group and those with the lowest CD4 counts at baseline. Weaknesses of this study included the fact that the data were modeled rather than directly observed and the fact that injection drug users were excluded from the analysis.

Kenneth Lichtenstein presented data from the HIV Outpatient Study (HOPS) demonstrating that patients who initiated therapy with higher baseline CD4 counts and who continued therapy without interruption were less likely to experience common drug-associated toxicities, including renal insufficiency, peripheral neuropathy, and lipatrophy [Abstract 769]. CD4 responses and rates of virologic suppression were higher and death and clinical progression were lower among those who started therapy earlier. These differences extended to those with pre-HAART CD4 counts of 350-499 cells/mm³ and even above 500 cells/mm³. While initial regimens used today would be less likely to cause complications such as lipatrophy or peripheral neuropathy, these data do suggest other potential benefits to earlier initiation of therapy.

Of course, observational studies like the ones discussed here are subject to considerable selection bias: for example, the better outcome associated with early initiation of therapy may have more to do with characteristics of patients who are treated aggressively than with baseline CD4 counts. Nevertheless, it should not be surprising that cohort studies originally suggesting no benefit to early therapy are now beginning to detect differences with longer follow-up. These data, together with the continued improvement in initial treatment options, may cause the pendulum to swing once again toward a more aggressive approach to antiretroviral therapy. ▲

Viral Hepatitis Review

Hepatitis B Co-infection

Therapy for hepatitis B virus (HBV) was addressed by Richard Colono with results from a trial of entecavir, a drug with potent anti-HBV activity and no activity against HIV [Abstract 832]. Consequently, entecavir is an option for co-infected patients where it is used: 1) to treat HBV without treating HIV, 2) as an alternative to tenofovir to combine with lamivudine/emtricitabine (3TC/FTC), provided at least two additional antiretroviral agents are used as well, or 3) to treat 3TC/FTC-HBV treatment failures. The trial included 50 HIV/HBV-co-infected patients with prior 3TC exposure for HIV therapy, including 48 with baseline HBV resistance to 3TC. At 48 weeks there was a mean reduction in HBV DNA of 4.2 log₁₀ c/mL, and no patient experienced virologic rebound. Two were found to have resistance mutations to entecavir at completion of treatment, but a retrospective analysis showed these mutations were present at baseline. The authors concluded that entecavir (1 mg/day) is effective in treating co-infected patients with 3TC-resistant HBV.

A humbling report from Southwestern concerned the failure of HIV care providers to apply the same care standards to HBV that they do to for HIV in co-infected patients [Jain M, et al. Abstract 837]. In review of 362 such patients, the median number of viral load measurements in the first year following initiation of HAART was 3 for HIV and 0 for HBV, and only 16% had measurements of HBV DNA levels or HBeAg at baseline. Only 31% of those positive for HBeAg had ultrasound of the liver; of the 115 who did have an ultrasound, 63 (55%) were abnormal. The authors concluded that adherence to standards of care by their clinicians was good for HIV, but not for HBV.

Hepatitis C Co-infection

A review of treatment success in hepatitis C (HCV)/HIV-co-infected patients at the Johns Hopkins Moore Clinic was particularly practical and important [Mehta S, et al. Abstract 884]. This HIV clinic has a dedicated unit for the management of viral hepatitis, and the purpose of the study was to determine the number of co-infected patients who achieved an HCV cure (sustained viral suppression). A total of 845 patients were followed for over 2 years and were considered eligible for HCV treatment referral. The sequential analysis was: 277/845 (33%) were referred, 185/277 (67%) kept the appointment, 125/185 (68%) completed medical evaluation, 81/125 (65%) were considered

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eligible for treatment, 29/81 (36%) started therapy, and 6/29 (21%) achieved a sustained viral response. Thus, in a clinic that offers specialty care for both HIV and HCV, only 3% were treated for HCV and less than 1% had a sustained viral response. These discouraging results may reflect the realities of both the efficacy of current treatment for HCV infection in patients with predominantly genotype 1 infection, and also of the challenges of completing therapy in this patient population.

Other HCV Treatment News

- HCV RNA at 4 weeks may be useful tool for adjusting duration of therapy genotype 2 or 3 [Crespo M, et al. Abstract 81]. The authors found that among 20 patients with a HCV RNA at 4 weeks <100 IU/mL, 18 (90%) had a sustained viral response compared to 6 (37.5%) of 16 patients with a 4-week HCV RNA >100 IU/mL.
- Longer treatment with peginterferon + ribavirin for HIV-co-infected patients with HCV genotype 1 did not increase the likelihood of a sustained virologic response [Uriel A, et al. Abstract 854]. The trial included 61 patients with undetectable virus at 24 weeks who were randomized to complete a standard 48-week course or a 72-week course. Among all patients with genotype 1a, sustained viral response was achieved in only 18/141 (13%), and 53% of those randomized at 24 weeks did not complete treatment. The longer course added no benefit, but most patients could not complete it, leading the investigators to conclude longer courses are unrealistic.
- High doses of peginterferon failed to improve outcome in an open-label trial from the Netherlands [Ruys T, et al. Abstract 852]. Twenty-three patients were randomized to standard treatment (peginterferon 2b 1.5 mcg/kg/wk) or high dose peginterferon (3.0 mcg/kg/wk x 4 wks, then 2.0 mcg/kg/wk x 4 weeks, then standard dose for 40 weeks). All patients received ribavirin 1000-1200 mg/day and were treated 48 weeks. Sustained viral responses were achieved in only 3/10 (30%) in the standard arm and 5/13 (38%) of the high induction dose arm. The high dose group also had more neuropsychiatric complications.
- New drugs for HCV include VX 950 (Vertex) and SCH5030304 (Schering), two protease inhibitors that show significant promise. Kwang from Vertex reviewed a trial in which 12 patients with HCV co-infection who failed peginterferon + ribavirin were treated with these two drugs plus VX 950 (750 mg bid) [Abstract 172]. Sustained viral responses were achieved in all 12. ▲



Antiretroviral Resistance Topics

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

Antiretroviral resistance issues garnered substantial attention at CROI. Attempts to define pathways to resistance are clearly incorporated into early drug development, and much of the resistance focus this year was on drugs that have yet to be FDA-approved.

Resistance Correlates of Drugs in Late-Stage Development

Etravirine (TMC-125) and darunavir (TMC-114), are new additions to the non-nucleoside reverse transcriptase (NNRTI) and protease inhibitor (PI) classes, respectively, that have demonstrated potent activity in heavily pretreated patients. At CROI, baseline resistance profiles were correlated with virologic responses in clinical trials for each drug.

Twenty-four-week results of the TMC125-C223 study, in which subjects with documented NNRTI-resistance were randomized to one of two doses of etravirine or to an optimized, non-NNRTI-containing regimen, were reported late last year [Grossman H, et al. 45th ICAAC, Abstract H-416c; Nadler J, et al. 10th EACS, Abstract LBPS3/7A]. The mean change in HIV RNA at week 24 was -1.18 log₁₀ c/mL in the arm receiving etravirine 800 mg twice daily, compared to -0.19 log₁₀ c/mL in the active control group (P<0.05). In Denver, Vingerhoets and colleagues assessed the association of baseline NNRTI mutations, fold-change in phenotypic resistance to etravirine, and 24-week viral load changes in a subset of participants in this trial [Abstract 154]. As expected, phenotypic fold-change increased and virologic response decreased with a higher number of NNRTI mutations at baseline (see Table below). However, the loss of virologic efficacy was much more attenuated than that observed with first-line NNRTIs, and no single mutation conferred >10-fold-change to etravirine. Twelve percent of baseline NNRTI mutation patterns were associated with >10-fold reduction in susceptibility to etravirine. Five specific codon mutations, K101P, V179E/F, Y181I/V, G190S, and M230L, were associated with resistance to etravirine, but resistance always required the presence of additional mutations.

Darunavir is a PI that has shown impressive results in heavily pretreated and PI-resistant participants in the POWER-1 and POWER-2 randomized controlled trials [Gallant J, *HHR* 2006;18(1):1]. De Meyer presented culled results from these studies and from POWER-3, a non-randomized, open-label, safety and efficacy study, to assess clinical resistance correlates for darunavir [Abstract 157]. Among subjects enrolled in POWER-1 and POWER-2, the authors reported that those with darunavir/ritonavir 600/100 mg twice daily were more likely to experience viral suppression than those randomized to a comparator PI, irrespective of the baseline susceptibility to the comparator PI. For example, 45% of darunavir/ritonavir recipients achieved HIV RNA <50 c/mL at 24 weeks, compared to 24% in the comparison arm with baseline susceptibility to the comparator PI, and just 7% in comparison subjects with baseline resistance to the comparator PI. A reduced virologic response rate to darunavir/ritonavir was found in patients with ≥10 baseline PI mutations. Mutations V32I, L33F, I47V, I54L, and L89V at baseline were associated with a lower rate of virologic response to darunavir/ritonavir, and emergence of these mutations was also observed in patients failing darunavir/ritonavir, though resistance appears to require the presence of multiple mutations, not just those listed. Unfortunately, this presentation, while helpful, does not leave us with a way to predict darunavir susceptibility based on genotype testing.

Different Enfuvirtide Resistance Pathways Associated with Variable Immunologic Response

Aquaro and colleagues evaluated the evolution of resistance mutations in the gp41 segment of the envelope protein in a cohort of 54 heavily experienced patients who added enfuvirtide (ENF) as a single drug to a failing regimen [Abstract 596]. The addition of ENF was accompanied by a fleeting decline in the median HIV RNA from 5.1 to 4.2 log₁₀ c/mL at week 8, with rebound to near baseline occurring shortly thereafter. However, a 136 cells/mm³ increase in the median CD4 count was observed in the cohort over 48 weeks. Resistance

mutations in gp41 emerged rapidly during treatment and were detected in 45 of 54 patients (83.3%). Patients with emergent V38A/E or N126K mutations experienced a median 24-week CD4 cell increase of approximately 95 cells/mm³, compared to a median decrease of 25 cells/mm³ in subjects with gp41 that remained wild type. In contrast, the Q40H and L45M mutations, which generally emerged together, were associated with a decline in CD4 cell count relative to patients with virus that remained wild type. None of the mutations was associated with differences in virologic response relative to those with wild type gp41. These results imply that different mutational pathways to ENF resistance in gp41 are associated with differences in pathogenic fitness that are independent and viral load, and challenge earlier suggestions that there was no benefit to continued use of ENF in patients who were not virologically suppressed.

AZT is Key with K65R

The K65R mutation in reverse transcriptase is selected by non-thymidine-containing NRTI combinations and decreases the activity of tenofovir, abacavir, didanosine, lamivudine and emtricitabine. However the K65R mutation confers hypersusceptibility to zidovudine (AZT) and rarely, if ever, occurs in concert with thymidine analog mutations (TAMs). For this reason an AZT-containing regimen is preferred when K65R is known to exist. Staszewski and colleagues highlighted this point in a case series of three patients in whom AZT was added as a single drug to a failing regimen in the presence of K65R [Abstract 635]. No patient had TAMs or a history of TAMs, two patients had M184V, and two patients had NNRTI resistance. No patient had clinically significant PI resistance. The patients experienced 1.4 to 3 log₁₀ c/mL viral load declines with the addition of AZT, and all achieved durable HIV RNA <50 c/mL for more than 1 year. While adding a single drug to a failing regimen is not recommended as a clinical strategy, this study emphasizes the clinical relevance of K65R-mediated hypersusceptibility to AZT.

Boosted ATV Clinical Cut-Off Validated

A clinical cut-off for an antiretroviral drug is the fold-change in HIV susceptibility to the drug that provides the greatest statistical discrimination between virologic response rates above and below the cut-off. The previously defined cut-off for ritonavir (RTV)-boosted atazanavir (ATV) of 5.2 was confirmed by Coakley and associates in

Table. Relationship of Baseline NNRTI-associated Mutations, Phenotypic Fold-Change and Virologic Response to Etravirine

Number of Baseline NNRTI Mutations	Fold-Change for Efavirenz	Fold-Change for Etravirine	24-week log ₁₀ HIV RNA Change (Etravirine 800 mg bid)
0	0.6	0.6	-1.82
1	8.4	1.1	-1.65
2	74.5	1.8	-1.00
≥3	353.1	3.1	-0.66

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This year's meeting offered a broad smattering of topics directly relevant to health care practitioners serving HIV-infected women, whether they are based in resource poor settings or wealthier nations. This is a limited summary of some of the highlights.

Survival of Women

Monica Gandhi gave a well organized and comprehensive presentation that systematically reviewed data on HIV outcomes in men and women along several parameters, including response to therapy, adverse effects and disease progression in the HAART era [Abstract 116]. Although women initially have lower viral loads than men, survival rates in both sexes are similar in studies that control for access to HAART and socioeconomic factors.

Genital Lesions and HIV Transmission

Perhaps the roster of known risk factors for acquisition of HIV infection among women in endemic areas should be expanded to include genital schistosomiasis. As noted by Eyrun Kjetland, the worldwide infection rate for schistosomiasis is approximately 1 in 30 adults, 85% of whom live in Africa [Abstract 34 LBa]. In a cross-sectional study of 479 sexually active non-pregnant, non-menopausal women between the ages of 20-49 who were followed for one year, there was a significantly increased risk of HIV infection among women with genital schistosomiasis. Genital schistosomiasis is found in 65% of women with urinary schistosomiasis. It is associated with friable cervical lesions known as "sandy patches" that may bleed during intercourse, thereby facilitating viral access and HIV infection. The prevalence of HIV among women with genital schistosomiasis was 41% versus 26% among those without genital schistosomiasis. Although this is an observational study and thus inconclusive, the previously documented 3-6 fold increased rates of HIV transmission among patients with genital ulcers make these results biologically plausible. The frequency of genital schistosomiasis in some populations and its potential role in HIV acquisition calls to question the role that adequate treatment for schistosomiasis would play in thwarting the HIV epidemic. Additional studies are needed.

Male Circumcision

The role of male circumcision in promoting HIV acquisition in men and HIV transmission to women was an important highlight of this year's meeting. In a plenary session Tom Quinn

summarized observational studies and a recently completed randomized trial that provide convincing data that circumcised men are at lower risk for acquiring HIV infection than uncircumcised men [Abstract 120]. In an observational study based in Rakai, Uganda, the impact of circumcision on the rates of HIV and other sexually transmitted diseases (syphilis, HSV-2, HPV, gonorrhea, *Chlamydia*, *Trichomonas* vaginitis, and bacterial vaginosis) was assessed [Gray R, et al. Abstract 128]. In the prevalence analysis using 3,949 married couples, the rate of HIV in wives of circumcised men was 16.1% compared to 21.7% in the wives of uncircumcised men for a significant rate ratio of .74. The rates of *Trichomonas* vaginitis and bacterial vaginitis were also significantly higher among the wives of the uncircumcised HIV-infected men. Rates of HSV-2 and HPV were also higher but these differences were not significant. The rates of gonorrhea, *Chlamydia*, and syphilis were not associated with the circumcision status of the male partner. The authors then followed 44 HIV-uninfected women with circumcised HIV-infected husbands and 299 HIV-uninfected women with uncircumcised HIV-infected husbands. The incidence of HIV infection in the wives of circumcised HIV-infected men was higher than in the wives of the uncircumcised men, although this difference was not significant (6.6/100 person-years versus 10.3/100 person-years, IRR .64, p=0.22).

ANRS 1285 Trial

To determine the role of active genital HSV-2 lesions on genital HIV-1 viral shedding, a randomized clinical trial was conducted enrolling 140 HIV-1/HSV-2 co-infected women in Burkina Faso [Nagot N, et al. Abstract 33LB]. The women, who were not eligible for HAART, were randomized into two groups: group 1 was treated with valacyclovir suppression (1 g/day) for 3 months, and group 2 received a placebo. HIV-1 genital shedding, HSV-2 genital shedding, and HIV-1 plasma viral loads were monitored biweekly. HIV-1 and HSV-2 genital viral shedding were reduced among the women treated with valacyclovir. In addition, HIV-1 plasma viral loads were also significantly reduced among the patients on HSV suppressive therapy (-0.39 vs +0.12 log₁₀ c/mL, p <0.001). This may have important implications for the risk of transmission of both HSV-2 and HIV-1 to partners of co-infected women, as well as reaffirming the practicality of HSV suppression therapy in co-infected women during pregnancy.

Pregnancy and HIV

Mechanisms for Mother-to-Child Transmission (MTCT). Maternal screening for HIV and advances in therapeutic options have culminated in a dramatic reduction in the risk of perinatal HIV transmission. Earlier studies have demonstrated that the majority (70%) of congenitally infected neonates are infected intrapartum, with the remaining 30% being infected prior to the onset of labor (intrauterine). In an elegantly designed study, Elizabeth Russell and coworkers were able to elucidate distinct mechanisms for intrauterine versus intrapartum transmission [Abstract 124]. By amplifying a specific region of the HIV env gene (highly variable V1/V2 region) and tracking the diversity of the viral population in maternal and newborn plasma samples, this group was able to demonstrate that intrauterine HIV infection results in transmission of fewer maternal viral variants, and notably, the transmitted virus most often represents the predominant circulating virus. In contrast, infants infected during the intrapartum period are more often infected with rare viral variants that represent compartmentalized or highly selected virus. Although we have made tremendous progress in reducing the risk of transmission, this study demonstrates that we have a lot to learn.

Repeat single dose Nevirapine in Subsequent Pregnancies. Single dose Nevirapine (sdNVP) effectively reduces the risk of MTCT of HIV. Efficacy, ease of administration, and low cost make this an attractive regimen. However, high rates of maternal resistance following a single exposure, over 40% in some studies, left many questioning its efficacy in subsequent pregnancies and the legitimacy of its role as a first-line agent in many resource poor settings. Eure and colleagues sought to answer this question [Abstract 125]. There were retrospective and prospective components to this trial.

The retrospective study compared Ugandan women who had received sdNVP in the HIVNET 012 trial and who had received the same treatment during a subsequent pregnancy with a control group of women who were treated with AZT in the HIVNET 012 trial and sdNVP in the subsequent pregnancy. The prospective component compared a group of pregnant women with prior sdNVP exposure to a group of NVP-naïve pregnant women. There were 198 mother infant pairs. The infants were followed for 6 weeks. The interim analysis showed no

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A number of important studies of metabolic and fat complications were presented at the 13th CROI in Denver.

Fat Loss and Fat Gain Are Not Linked

Phyllis Tien reported an analysis of 338 HIV-infected women in the FRAM study, all of whom underwent rigorous metabolic and body shape measurement [Abstract 749]. The authors found that the duration of stavudine (d4T) use was associated with less subcutaneous fat in all compartments but not with increases in visceral fat, and that indinavir (IDV) use was associated with more upper trunk fat, confirming that lipoatrophy and fat accumulation are not linked phenomena and have different risk factors. This study also found that in women, the effects of age and physical activity were stronger than drug effects.

Cardiovascular Disease (CVD) Risk

Everyone agrees there is an increase in CVD risk in HIV-infected patients, but there is controversy about whether the risk is due to antiretroviral therapy or HIV infection itself. Fueling the controversy were several studies presented at CROI. The SMART study (reported in this issue by Joel Gallant) randomized over 5,000 subjects with CD4 cell counts above 350 cells/mm³ to continue HAART or to discontinue, resuming when the CD4 count fell below 250 cells/mm³. In the interruption arm, in addition to more HIV progression, the relative risk (RR) for a serious complication or death was 2.2, and for a nonfatal cardiovascular event was 1.5 [El Sadr W, et al. Abstract 106LB]. It has been hypothesized that the increased risk following discontinuation of therapy may be due to inflammation resulting from rebound of HIV viremia. These results should give us pause before we consider stopping HAART to correct metabolic abnormalities.

The D:A:D group continued to report on its 23,400 patients in 11 cohorts from Europe, Australia and Europe [Friis-Moller, et al. Abstract 144]. After adjusting for other risk factors and other drug class use, the authors found that for myocardial infarction (MI), the RR increase was 1.16 per year of PI use (p=0.0001) and 1.05 per year of NNRTI (p=0.17). PI-specific data were not presented. Even after adjusting for lipids, the mechanism by which PIs presumably increase risk, the risk associated with PI use was maintained, suggesting additional medication-related factors independent of lipid effects. Importantly, the authors found fewer MIs in more recent calendar years, in large part explained by increased use of cholesterol-lowering agents.

However, Judith Currier reported on ACTG 5078, a smaller study of 134 subjects in 45 “triads” (the triads were: HIV-infected patients taking PIs, HIV-infected patients not taking PIs, and HIV-uninfected patients, all matched on age, race, sex, BP, smoking status, and menopausal status) [Abstract 145]. The authors found that neither HIV infection nor PI use predicted the 3-year change in carotid intima thickness, a predictor of heart disease. Models in the HIV-infected subjects did suggest that ritonavir (RTV) use, longer PI use, elevated fasting glucose, and high C-reactive protein were suggestive of more progression.

As with several other studies, the HOPS cohort of over 78,000 patients found that traditional risk factors were most predictive of CVD [Lichtenstein K, et al. Abstract 735]. Risk factors from multivariate analyses included age over 40 (AOR 3.3), hypertension (AOR 2.2), diabetes (AOR 2.4), and low HDL cholesterol (AOR 2.6). In their model, CD4 cell count at the initiation of HAART, time on HAART, switching HAART, and specific agents were not significant predictors. In those with hypertension or hypercholesterolemia, the use of antihypertensive and cholesterol lowering agents decreased risk.

These studies remind us to be aware of CVD risk, which likely comes from a combination of antiretroviral therapy, HIV itself, and traditional risk factors. This is becoming increasingly important as our patients age. A large proportion of the risk can be reduced by focusing on traditional risk factors: stop smoking, control hypertension, lower lipids, and add aspirin where appropriate.

To that end, John Gerber presented data suggesting that fish oil (3 g twice daily, each gram containing 500 mg eicosapentaenoic acid and 310 mg docosahexaenoic acid) could help those with high TG levels [Abstract 146]. Approximately 100 subjects entered step 1, randomly receiving open-label fish oil or fenofibrate for 8 weeks; those in both groups with TG>200 at week 8 went onto step 2, in which both fish oil and fenofibrate were administered. At baseline, participants in both groups were similar, with a mean age of 43 years and TG of 660-690; 90% were male and 56% were white. Enrollment criteria included having an LDL <160 mg/dL; diabetics and those on other lipid-lowering medications were excluded. A small percentage of subjects achieved TG <200 mg/dL after step 1 (8.5% for fish oil and 16.7% for fenofibrate); the remainder were offered step 2. By ITT analysis, 17/75 (22.7%) achieved TG <200 mg/dL, and even for those who did not,

there was an average decrease in TG from 377 mg/dL to 279 mg/dL. LDL cholesterol increased in each group, as is known to occur with fish oil, (22, 37, and 14 mg/dL for the fish oil, fenofibrate, and combined groups, respectively), although it is not clear if this was clinically significant. There were no negative effects on a variety of immune stimulation parameters measured, and there were few dropouts, suggesting good tolerability of the medications. Fish oil had no effect on lopinavir trough concentrations, suggesting no significant drug interactions. This study suggests a role for high dose fish oil in patients with high TG levels; in many cases it may need to be used in combination with fibrates and/or statins.

Malan reported 48-week data of a 96-week trial of the efficacy and safety of atazanavir (ATV) in 199 ART-naïve subjects, beginning to answer the question of whether low-dose RTV increases lipids. [Abstract 107LB, also discussed in this issue by Gallant]. Subjects were randomized to receive open-label ATV 400 mg daily or ATV 300 mg plus RTV 100mg daily in combination with d4T and lamivudine (3TC). There was more jaundice (grade 2-4) (3% vs. <1%), a slightly larger increase in total cholesterol (15% vs. 6%, P<0.01), and a larger increase in TG (26% vs. -3%, p<0.01) in the boosted arm. LDL cholesterol increased (23% vs. 16%) and HDL cholesterol decreased (-30% vs. -9%) in both arms. The study demonstrates that 100 mg of RTV does cause statistically significant changes in cholesterol, though they were relative small and may not be clinically significant. Patients with untreated HIV infection tend to have low cholesterol levels, and any treatment can raise them to what would have been the patient’s “healthy” baseline. Also, all subjects in this study received d4T, which can negatively affect cholesterol levels. This study supports the characterization of boosted and unboosted ATV as a “lipid friendly” PI.

Fat Gain/Loss

The large HOPS cohort studied 2,304 subjects who had at least 2 visits to a one of multiple HIV clinics from 1996-2005 and found that patients starting and remaining on HAART at higher CD4 cell counts were significantly less likely to experience toxicity [Lichtenstein K, et al. Abstract 769]. In a multivariate analysis the adjusted odds ratio for lipoatrophy suggested a benefit from starting HAART with a CD4 count of 200-349 cells/mm³ (AOR 0.5) or CD4 >350 cells/mm³ (AOR 0.4). Tenofovir use was associated with less lipoatrophy (OR 0.6), whereas white race (2.7) and use of d4T (1.8),



Metabolic and Fat Complications

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didanosine (ddI) (1.6), and any PI (2.1) were associated with more lipoatrophy. Lipoatrophy is not generally associated with PI use; however, subjects were not randomized in this observational study, and there may be residual confounding even after adjustment. Providers may have used PIs in patients with more advanced disease, or PI use may be a marker for longer and/or more ART use.

In ACTG 5082, 105 subjects were randomized to receive metformin 1000 mg bid, rosiglitazone 4 mg qd, both drugs, or no drugs in a placebo controlled randomized trial [Mulligan K, et al. Abstract 147]. Subjects had an increased waist-to-hip ratio (>0.95 in males or >0.85 in females) or waist circumference >100 cm, indicative of fat accumulation, and evidence of impaired glucose tolerance but not diabetes; 66% percent were male, 65% were white, 65% were taking PIs, 43% were taking NNRTIs, and 96% were taking NRTIs. Many metformin subjects dropped out (12/26), primarily due to diarrhea, which limited the analysis. However, the study failed to show significant decreases in abdominal visceral fat or subcutaneous adipose tissue over 16 weeks in any of the treatment arms. Not surprisingly there was a decrease in the insulin area under the curve concentration (AUC), indicating improved insulin sensitivity, but there were no changes in 2-hour glucose by oral glucose tolerance test. Limb fat also tended to decrease with metformin, a potentially undesirable effect for patients with lipoatrophy, but increased significantly with rosiglitazone (+4.8% vs. -8.3% in the placebo group, $p=0.034$). Combining drugs ameliorated this effect on fat. There was also a decrease in HDL cholesterol with rosiglitazone. There was no significant increase in lactate.

Similarly, Kohli and colleagues found no benefit with respect to fat accumulation or lipid levels in 25 subjects receiving 1,500 mg metformin daily for 24 weeks compared to 23 receiving placebo [Abstract 148]. There was a trend in the metformin arm toward reduction in appendicular fat mass. Metformin may be a less viable option than previously thought for the treatment of fat accumulation, especially in patients who also have lipoatrophy. This study says nothing about patients with diabetes, however, and the literature in HIV-uninfected patients suggests that metformin is a good choice for diabetic patients who are obese.

There are conflicting studies on the efficacy of rosiglitazone to improve lipoatrophy. Some show a small benefit (see above), while others have demonstrated no benefit. No study has demonstrated a “normalization” of fat. At CROI,

we heard results of another “glitazone” study, in which 130 subjects were randomized to receive pioglitazone 30 mg qd or placebo for 48 weeks [Slama L, et al. Abstract 151LB]. Approximately 80% of the subjects were male, 27% had AIDS, and 25-30% remained on d4T. Overall, there was improvement in limb fat (+0.38 kg, $p=0.051$) without a change in visceral fat. However, it is important to look at the sub-analysis. Improvement only occurred in patients not currently receiving d4T (+0.45 kg compared to +0.04 kg with placebo, $p=0.013$). Pioglitazone patients also experienced improved limb circumference and triceps skin fold measurement as well as small but statistically significant increases in HDL cholesterol. However, patients perceived no improvement in their lipoatrophy. Here we see a small but real increase in subcutaneous fat, but we are reminded that we must also remove offending agents (e.g., d4T) and that the changes may not be noticed by patients, at least in the short-term. It is possible that the differences will become more noticeable if fat continues to increase over time.

The jury is still out on the use of these compounds. Metformin didn't decrease visceral fat and tended to worsen lipoatrophy; rosiglitazone and pioglitazone caused small increases in limb fat, but the changes were not dramatic. We still need to find better ways to deal with fat accumulation and lipoatrophy. The best approach is still to select medicines that don't cause the problems in the first place.

Testosterone and anabolic steroids can be useful in rebuilding muscle mass in patients with HIV wasting. However, they have also been used by some clinicians to treat fat accumulation. Shikuma reported a study of 75 male subjects with mild hypogonadism (total testosterone 125-400 ng/dL) and a waist-to-hip ratio >0.95 or waist circumference >100 cm, who were randomized to receive testosterone gel 10 mg/day or placebo for 24 weeks in a double blinded fashion [Abstract 149]. The study had mixed results: In the treatment group, total body fat by DEXA decreased (-7.9% vs. +4.5%, $p<0.001$), extremity fat decreased (-10.1% vs. 3.8%, $p=0.001$), and lean body mass (muscle) increased (+1.3% vs. -0.3% $p=0.02$). The loss of limb fat was also seen on CT scan, with no effect on visceral fat. The results of lipids, glucose and hormone levels were not presented. The men in this study were only mildly hypogonadal and received twice the standard replacement dose. Muscle mass improved, but limb fat decreased and there was no decrease in visceral fat. It may be that the usual 5 mg daily dose would have had

different effects. Once we see the hormone level data we may be able to extrapolate further. Clinicians must remember there are often benefits with respect to mood, sexual function, energy, anemia, bone density, and overall quality of life when a frankly hypogonadal man receives testosterone at replacement doses, so the decision to treat cannot be made based solely upon this study. But as other studies in this report, clinicians should not assume that testosterone, and by extension other anabolic steroids, will decrease visceral fat. In addition, use of these agents may exacerbate pre-existing lipoatrophy.

Metabolic Effects in Children

Although not the focus of this report, there were a number of presentations confirming that the metabolic effects of antiretroviral therapy we see in adults also occur in children and adolescents. These include studies demonstrating better lipid outcomes with nevirapine (NVP) compared to efavirenz (EFV) [Huhtamaki T, et al. Abstract 688], that use of PIs, especially RTV-boosted PIs, but not NNRTIs, increases total cholesterol and triglycerides, [Ramos JT, et al. Abstract 690], and that there are no significant lipid changes with ATV other than mild increases when boosted [Samson P, et al. Abstract 689]. HIV-infected children have worse cardiovascular markers and carotid intima media thickness [McComsey G, et al. Abstract 691] and changes in fat depots [Vigano A, et al. Abstract 692] compared to HIV-uninfected children. In children, switching from d4T to tenofovir DF (TDF) can lead to significant increases in total and limb fat, but without restoration to baseline levels [Vigano A, et al. Abstract 693].

Conclusions

CROI was a helpful meeting for those interested in fat changes, metabolic toxicity, and cardiovascular risk. Well beyond the scope of this report but quite promising is the movement toward using various genetic markers to predict who may or may not be at risk for specific complications [Ranade K, et al. Abstract 763; Arnedo M, et al. Abstract 764; Owen A, et al. Abstract 765; De Luca A, et al. Abstract 766; Cossarizza A, et al. Abstract 767; Gometz ED, et al. Abstract 768]. We also saw confirmation that changes occur not only in adults but also in children. There appears to be agreement on the increased risk of cardiovascular disease in our patients, but the relative contributions of

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4 + 5 = 9: New Drug Targets Add Up

By Charles Flexner, M.D.

Today there are only four classes of approved antiretroviral drugs: the nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and one fusion inhibitor, enfuvirtide. These agents attack four different targets on three different HIV proteins. Identification of drugs that block other steps in the HIV life cycle is a major goal of new drug development. In part, this is based on the assumption that drugs attacking new targets will not be cross-resistant with those in existing classes.

The 13th CROI in Denver provided promising clinical results for several new classes of antiretroviral drugs. Drugs aimed at five new targets were reported to have anti-HIV activity in patients (including the CXCR4 antagonists not discussed here). If all of these agents continue to show promise and advance to approval by the FDA, there will be a minimum of nine different classes of antiretroviral agents. In a few years, choices for providers and patients are likely to be more numerous, and options for treatment-experienced patients will grow.

The Integrase Race Takes Off

Integrase is an HIV enzyme that catalyzes a strand transfer reaction essential for the integration of proviral DNA into the host chromosome. At the 12th CROI we learned that the first integrase inhibitor tested in HIV-infected patients showed substantial antiviral activity, reducing plasma viral load by more than two \log_{10} [Flexner C, *HHR* 2005;17(2):8]. The bad news is that one inhibitor, Merck's L000870810, had to be pulled from further development because of animal toxicity, even though it was well tolerated in patients.

Fortunately Merck had a back-up compound, MK-0518, that has moved very quickly into human trials. A study in treatment-naïve patients was presented at the European AIDS Clinical Society meeting in Dublin last November, and reported a 1.7-2.2 \log_{10} drop in viral load after 10 days of monotherapy, similar to results seen with L-000870810 [Morales-Ramirez et al. 10th EACS, Abstract LBPS1/6; see also Gallant J, *HHR* 2006;18(1):5]. A new study presented in Denver evaluated MK-0518 added to an optimized background regimen (OBR) in 167 heavily treatment-experienced patients [Grinsztejn B, et al. Abstract 159LB]. Subjects received 200, 400, or 600 mg bid of MK-0518 or placebo. After 8 weeks of treatment, 63-67% of MK-0518 treated patients had a viral load <50 c/mL, compared to only 8% of patients treated with OBR plus placebo. Similar results were reported at Week 16, but only about half of subjects had reached

this timepoint at the time of the presentation.

This is an impressive result given the highly drug resistant patient population studied. MK-0518 has shown no significant drug-related toxicities in clinical trials to date. This drug is mainly metabolized by glucuronidation (like zidovudine and abacavir), and thus should be less susceptible to drug interactions. Its metabolism is partially blocked by atazanavir, which is a selective inhibitor of the UGT-glucuronosyl transferase enzyme UGT1A1; 16 subjects received atazanavir with MK-0518, although the PK results from that arm are not yet available.

Early success with L-000870810 encouraged several of Merck's competitors to pursue integrase inhibitors of their own. One of these drugs, GS-9137/JTK-303, which was discovered by Japanese Tobacco but is being developed clinically by Gilead, was reported to have antiretroviral activity in another late breaking abstract [DeJesus E, et al. Abstract 160LB]. Fifteen treatment-naïve and 15 treatment-experienced patients were randomly assigned to 10 days of GS-9137 monotherapy at a dose of 200, 400, or 800 mg bid or 800 mg qd. Since this drug, unlike MK-0518, is a cytochrome P450 (CYP) 3A4 substrate, a regimen of 50 mg plus 100 mg ritonavir qd was also evaluated. Compared to 10 subjects who received placebo, all GS-9137 regimens produced a median reduction in viral load that ranged from 0.96 to 2.03 \log_{10} c/mL. However, the 800 mg unboosted qd regimen and the 200 mg bid regimen were statistically inferior to the other three regimens.

GS-9137 is chemically distinct from MK-0518, and would therefore be predicted to have little or no cross-resistance with the other integrase inhibitor. It is structurally related to the fluoroquinolones but has no antibacterial activity. The drug must be given with food and is reported to be a moderate P450 inducer but not an inhibitor. There were no significant drug-related toxicities in this short-term trial. This initial study suggests that the drug could be administered as a bid agent without ritonavir or as a qd agent with ritonavir.

Vicriviroc: Another Set-back for CCR5 Inhibitors

Last year was not good for the new CCR5 chemokine receptor antagonists. Aplavirac, the GSK CCR5 antagonist, was pulled from development in early 2005 because of unexpected severe liver toxicity [Gallant J, *HHR* 2006; 18(1):5]. Another case of liver toxicity requiring transplantation was reported with maraviroc, the Pfizer compound, but that case was attributed to other causes [ibid.] and the

drug continues in Phase 3 clinical trials. In October, 2005, the first Phase 2 trial of the Schering CCR5 antagonist, vicriviroc, was stopped because of low rates of virologic suppression compared to the control arm, efavirenz (EFV) plus zidovudine/lamivudine (AZT/3TC, *Combivir*) [Greaves W, et al. Abstract 161LB].

In that trial, 92 treatment-naïve subjects were randomized to receive placebo or vicriviroc at a dose of 25, 50, or 75 mg qd for a 14-day monotherapy run-in. At day 14, all patients added Combivir and the placebo was replaced by EFV. Designed as a 48-week treatment trial, the study was terminated by the Data Safety Monitoring Board after a mean follow-up of only 32 weeks. At that point, only one patient in the EFV control arm (4%) had suffered a virologic relapse (i.e., viral load >50 c/mL), while the relapse rates in the vicriviroc arms were 17, 41, and 56% for the 75, 50, and 25 mg regimens, respectively.

There was some good news – vicriviroc was well-tolerated with no discernible drug toxicity, hepatic or otherwise. It appears that the selected doses of vicriviroc may have been too low, allowing room for exploration of higher doses in future studies. There was also debate about whether the 14-day monotherapy period selected for drug resistance or co-receptor switching in some patients, although no phenotypic resistance to vicriviroc was noted in samples from those failing therapy. Most (96%) resistance was due to the M184V mutation, and coreceptor switching (to CXCR4 or mixed phenotype) occurred about as often with placebo as with vicriviroc.

A Phase 2 study of this drug at lower doses but in combination with ritonavir in treatment-experienced patients is continuing through the AIDS Clinical Trials Group, and is expected to be ready for analysis in late 2006 [Wilkin T, et al. Abstract 655].

PA-457: Update on a New Maturation Inhibitor

Another drug whose dose might still be too low is PA-457. This drug is the first in a new class of molecules called maturation inhibitors. These agents have the same effect on the virus as protease inhibitors, by blocking the processing of the gag precursor polypeptide that must be cleaved in order for the virus to become infectious. But unlike PIs, PA-457 achieves this by binding directly to the gag polyprotein; it does not bind to the protease [Flexner C, *HHR* 2005;17(2):8].

By applying a pharmacokinetic/pharmacodynamic model to data from the first PA-457 proof-of-concept studies, investigators from the



4 + 5 = 9: New Drug Targets Add Up

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University at Buffalo, NY (formerly SUNY Buffalo) found that higher concentrations of PA-457 continued to produce greater reductions in viral load without reaching a plateau in activity, even at the highest doses studied [Smith P, et al. Abstract 52]. They suggested that doses higher than the 200 mg qd maximum might produce viral load reductions greater than the mean 1.1 log₁₀ c/mL decline reported, and could produce monotherapy effects as great as that seen with the PIs and NNRTIs.

Unfortunately, some PA-457 recipients even at the highest doses showed little change in viral load, and an explanation for that observation is lacking. Although resistance to PA-457 occurs *in vitro* through specific amino acid changes at the capsid (CA)/SP1 binding site, no resistance has been detected in patients, even those who failed to respond to the drug in monotherapy studies [Adamson C, et al. Abstract 156]. The authors of the resistance study suggest that the PA-457 binding site is highly conserved, and resistance may occur with a substantial cost in terms of viral fitness.

TNX-355: An Anti-CD4 Monoclonal Antibody

TNX-355 is a humanized monoclonal antibody that binds to a part of the CD4 receptor that is essential for HIV entry. This antibody does not block the HIV outer envelope protein gp120 from binding to CD4; rather, it interferes with a conformational change in CD4 that is essential for access of gp120 to the chemokine receptors CCR5 or CXCR4. The antibody is equally active against CCR5- and CXCR4-tropic virus isolates.

The antiretroviral activity of this agent in patients was first reported in 2003 [Flexner C, *HHR* 2003;15(3):8]. Highly treatment-experienced patients who receive an injection of TNX-355 every 2 weeks have a sustained average drop in viral load of about 1.0 log₁₀ c/mL after 24 weeks. There has been hope that resistance would not develop with this agent, since it targets the host rather than a virus-encoded protein. However, some treated patients show little virologic benefit, suggesting the possibility of resistance.

Investigators from Tanox examined the TNX-355 sensitivity of baseline HIV isolates from 82 patients participating in an ongoing Phase 2 treatment trial [Duensing T, et al. Abstract 158LB]. They reported that TNX-355-resistant strains have modifications in their envelope proteins that result in altered envelope conformation. The gp120 trimers that normally form in the process of HIV entry are more open in these strains, allowing access to coreceptors

even in the presence of the antibody. Curiously, this open conformation makes these virus strains more susceptible to inhibition by recombinant soluble CD4 (rsCD4), an old agent from the annals of extinct antiretroviral compounds.

This remains an intriguing approach to therapy, whose main role would probably be in salvage. Although the compound is likely to be expensive and must be given by injection every two weeks, it is likely to have some advantages in cost and convenience over enfuvirtide. A big question is whether the resistance reported at CROI will become more widespread.

What's Next for Entry Inhibitors?

Enfuvirtide (ENF, T-20) is the only entry inhibitor approved for the treatment of HIV infection. This peptide has the drawbacks of high cost and the requirement for twice-daily injection, often resulting in painful subcutaneous nodules. A second generation entry inhibitor, T-1249, had better pharmacokinetic properties and could be given once daily, but was pulled from development in part for economic reasons. Although several oral entry inhibitors have been evaluated, none has made it past Phase 2.

Investigators from Trimeris reported the development of a third generation of ENF peptide analogs, designed for better antiviral potency and improved pharmacokinetics [Delmedico M, et al. Abstract 48]. One of these analogs, T-290999, is about 10-fold more potent *in vitro* against ENF-sensitive virus and >100-fold more potent against ENF-resistant virus than ENF. "T-999" and another analog called TR-291144 are modified by adding a fatty acid to a traditional ENF-like peptide. This not only appears to improve anti-HIV activity, but also to greatly slow elimination from the body after injection. In pharmacokinetic studies conducted in monkeys, both drugs had much longer half-lives than ENF, and sustained concentrations higher than the IC50 for HIV for more than a week after injection.

A new generation of entry inhibitors that could be injected once a week, or even less frequently, would be a major advance in HIV therapy. The recent approval by the FDA of an inhaled version of insulin, another small protein, raises the possibility of inhaled or perhaps even transdermal application of T-999 or T-1144. Although human studies have yet to begin with these two peptides, it appears we may be on the verge of developing drugs that not only improve the convenience of drug delivery, but may make concerns about adherence a thing of the past for some agents. This could be CROI's version of "Rocky Mountain High." ▲

HIV in Women

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statistical difference in the rates of vertical transmission between the sdNVP exposed and the NVP-naïve groups. Long-term follow-up of the infants continues.

Cotrimoxazole and Birth Outcomes. HIV infected women with advanced disease, particularly in resource poor settings, may be at greater risk for poor pregnancy outcomes including preterm delivery, fetal growth restriction and neonatal mortality. Jan Walter and collaborators sought to examine the likelihood of improved fetal outcomes among HIV infected women in Zambia treated with cotrimoxazole during pregnancy [Abstract 126]. In this group of women with CD4 counts <200 cells/mm³ who were not on antiretrovirals, there was a reduction in the incidence of chorioamnionitis, prematurity and neonatal mortality. Though this has implications in settings where access to ART is limited, the extrapolation of these results to women on HAART would be inappropriate. ▲

Metabolic and Fat Complications

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antiretroviral therapy, specific antiretroviral agents, and HIV itself remain unclear. Clinicians are reminded that controlling traditional risk factors is still the best approach. At this meeting, we learned that interrupting therapy may be unwise, and that there is evidence supporting earlier initiation of therapy. Fat loss and fat accumulation, while often occurring together, are distinct phenomena with separate risk factors. We are also seeing that some promising therapies, such as metformin or testosterone for fat accumulation, are ineffective and may have unwanted side effects such as exacerbation of lipoatrophy. Even those with evidence of some benefit, such as "glitazones" for lipoatrophy, only yield a mild improvement. The task of the clinician remains complex: to select treatment regimens that will maximize the likelihood of a durable virologic response while minimizing the potential for side effects and long-term toxicity. ▲

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Antiretroviral Resistance Topics

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a retrospective analysis of data from BMS-045 [Abstract 634]. In the first 2 weeks of this trial in triple-class experienced patients, a subset of participants switched from a failing NNRTI or PI to ATV 300 mg and RTV 100 mg daily, without altering other drugs in their regimen. Coakley and colleagues examined 2-week virologic responses, defined as a decline in HIV RNA $>1 \log_{10}$ c/mL. They found that a 5.2-fold reduction in susceptibility to ATV at baseline best distinguished responders from non-responders. The virologic response rate was 89% in patients with baseline susceptibility below this cut-off, while the response rate was just 26% in those above the cut-off.

Does Antiretroviral Resistance Testing Improve Mortality?

Palella and coworkers from the HIV Outpatient Study (HOPS) presented data suggesting that having a resistance test (either genotype or phenotype) performed in clinical practice was associated with improved survival [Abstract 654]. Compared to 3,351 HAART-experienced patients in the cohort who had not had a resistance test, the 1,263 patients who had resistance testing were younger, were more likely to be white, and were more likely to have private

insurance, all factors that were also associated with longer survival. However, the tested group also had significantly lower CD4 cell counts and higher viral loads, factors associated with shorter survival. Adjusting for these variables, the authors found that resistance testing was associated with a 60% reduction in the risk of death.

They reached a similar conclusion in a separate analysis in which they compared mortality in triple-class-exposed, persistently viremic patients who had a resistance test performed with a comparison group (matched on injection drug use, insurance status, nadir CD4 cell count and calendar year of nadir CD4 cell count) that did not have resistance testing. Mortality in the tested group was 7.9% versus 21.8% in the untested group. The authors hypothesized that mortality differences were explained by more effective selection of antiretroviral drugs in patients in whom resistance testing had been obtained. However, they were not able to test this hypothesis directly. Additionally, it is also possible that failure to have resistance testing, particularly in situations where resistance testing is strongly recommended in clinical practice guidelines, was a marker for adverse patient characteristics (such as non-adherence) or poorer quality of overall HIV care.

Conclusion

Etravirine and darunavir are promising new additions to the NNRTI and PI classes, respectively, that appear to maintain good activity in heavily experienced patients. In each case, specific mutations have been identified that are associated with a poorer response to these drugs. The imminent availability of these agents underlines the importance of avoiding PIs and NNRTIs in “holding regimen” situations, where viral suppression is not possible but therapy is needed to delay clinical disease progression. Clearly, the new drugs lose their activity when an extensive number of resistance mutations have emerged due to prolonged exposure to non-suppressive therapy. Resistance mutations arise quickly when enfuvirtide is added as a single active drug to a failing regimen. Interestingly, however, some enfuvirtide resistance mutations appear to be associated with increases in CD4 cell counts, while other patterns are associated with declining CD4 cell counts. Finally, the clinical benefit of K65R-mediated hypersusceptibility to AZT was highlighted in a small case series, and a clinical phenotypic susceptibility cut-off was confirmed for RTV-boosted ATV. ▲

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