

THE HOPKINS HIV REPORT

A bimonthly newsletter for health care providers

XIV International AIDS Conference in Barcelona

Antiretroviral Therapy: When to Start & What to Start With

By Timothy R. Sterling, M.D.

When to Start Therapy

There were several abstracts at the meeting on the controversial topic of when to start therapy in asymptomatic individuals. There appears to be a consensus that therapy should be initiated based primarily on CD4 count rather than viral load, and that the CD4 count should be between 200 and 350 cells/mm³. However, the optimal CD4 count and timing within this range remains unclear.

Concurrent with the meeting, two studies and the most recent International AIDS Society–USA recommendations for the initiation of therapy were published in the peer-reviewed literature (discussed below). These papers provided additional, though somewhat contradictory, information. Opravil and colleagues from the Swiss HIV Cohort Study found that initiation of therapy at CD4 counts >350 cells/mm³ improved survival compared to matched controls who delayed initiation of therapy for at least 12 months [*AIDS* 2002;16:1371]. However, the proportion of patients who developed toxicity and/or required a change in therapy was substantial. Interestingly, the IAS-USA guidelines, which had previously recommended starting therapy when the CD4 count was <350 cells/mm³, now recommend initiating therapy when the CD4 count is ≤200 cells/mm³ [Yeni PG, et al. *JAMA* 2002;288:222]. Thus, in spite of the Opravil paper, there are currently no recommendations to

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Drug Resistance and the Treatment of Experienced Patients

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

The most exciting and eagerly awaited data presented in Barcelona pertained to the treatment of naïve patients. Patients starting therapy for the first time can choose among a number of simple, well tolerated, and highly potent combinations, and those who adhere to therapy shouldn't have to worry about issues such as drug resistance and salvage therapy for a long time. Nevertheless, treatment failure and drug resistance remain a big concern, especially for highly experienced patients with diminishing options for therapy. A number of interesting presentations on drug resistance and approaches to the treatment of experienced patients were presented in Barcelona.

Resistance Testing

• Expert prediction of phenotype based on genotype reports

Zolopa from Stanford University presented results of the GUESS study, in which a panel of 12 international resistance experts were asked to predict phenotypic susceptibility based on genotype report [Abstract 1385]. The study involved 50 randomly selected samples with simultaneously collected genotype and phenotype analyses. Experts were asked to predict phenotypic susceptibility to all currently available antiretroviral agents using the following fold-change strata: <2.5, 2.5 to 3.9, 4 to 6.9, 7 to 9.9, 10 to 19.9, and >20. In addition, they rated the expected activity of each drug on a 6-point scale.



"La Pedera Chimneys, Antoni Gaudi, Barcelona," photograph by Joel Meneses

Susceptibility predictions varied considerably, both by class and by drug. For example, accuracy of predictions about NRTI susceptibility ranged from 25% for abacavir to 74% for 3TC. In general, susceptibility was underestimated for all NRTIs other than 3TC. Among the PIs, prediction accuracy ranged from 26% for nelfinavir to 30% for lopinavir/ritonavir. As one would expect, predictions were more accurate for NNRTIs, with about 2/3 of the predictions being accurate for the three drugs in this class. Predictions of drug activity followed similar patterns, although there was stronger agreement among the experts about drug activity than might be expected given the variation in phenotypic predictions.

• Prospective study of resistance testing

The CERT study is yet another prospective study evaluating the utility of resistance testing in patients failing therapy [Wegner SA, et al. Abstract 1389]. This study compared genotype testing, phenotype testing, and standard of care (or what

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start therapy in asymptomatic persons with CD4 counts >350 cells/mm³. It should be noted that this does not pertain to patients who are symptomatic, who should initiate therapy regardless of CD4 count.

A study by Kaplan and colleagues confirmed previous studies and was consistent with initiating therapy at CD4 counts <350 cells/mm³ [Abstract 4661; Adult and Adolescent Spectrum of HIV Disease study of the Centers for Disease Control and Prevention (CDC)]. This study included 2,478 persons who initiated HAART and had at least one CD4 count within 12 months of starting therapy. Clinical disease progression was assessed according to baseline CD4 count and viral load at initiation of HAART. Compared with patients with CD4 counts >350 cells/mm³, patients with CD4 counts 200-349 cells/mm³ and viral load $<55,000$ c/mL did not have a statistically significant different risk of clinical disease progression.

The largest study to date on the topic was presented at the meeting and concomitantly published in *The Lancet*. In an observational study that assessed data from 13 HIV cohort studies, Chene and colleagues assessed the prognosis of 12,574 antiretroviral-naïve patients who started potent antiretroviral therapy [Abstract 1140; *Lancet* 2002;360:119]. The median baseline CD4 count was 250 cells/mm³, and the median baseline viral load was 4.9 log₁₀; there were 24,310 person-years of follow-up. The authors assessed 80 different risk strata in determining the probability of progression to AIDS and/or death. Baseline CD4 count was the most important predictor of disease progression, but baseline viral load $>100,000$ c/mL, age >50 , and a history of injection drug use were also associated with an increased risk of disease progression. The risk of clinical disease progression was greatest among those with baseline CD4 count <100 cells/mm³, followed by those with CD4 count 100-199 cells/mm³. Although individuals initiating therapy at CD4 >350 cells/mm³ had a slower rate of disease progression than those who started at 200-350 cells/mm³, the difference was approximately 2% and was not statistically significant. Drug toxicity was not accounted for in this analysis. The authors did not make any specific suggestions regarding the CD4 count at which to initiate therapy, but provided data

on the risk of disease progression according to several different clinical categories. These categories were based on CD4 count, viral load, and clinical factors, such as a history of stage C disease. Although not a controlled clinical trial (to date, none have been published on this issue), this is probably the most definitive study because of its large sample size.

A study by Brooks and colleagues assessed the durability of virologic response according to the baseline CD4 count [Abstract 1141; Adult and Adolescent Spectrum of HIV Disease Working Group of the CDC]. Of the 583 persons studied, 525 (90%) had a virologic response. The authors assessed the 525 responders and found that a baseline CD4 count <200 cells/mm³ was associated with a significantly less durable virological response than a baseline CD4 >350 cells/mm³. Persons starting at 200-349 vs >350 cells/mm³ did not have a statistically significant difference in durable virologic suppression. This study was limited by the relatively small number of participants, the median observation time of 12 months, and the lack of data on prior antiretroviral therapy, adherence, and viral resistance.

In a study by Peterson and co-workers, the risk of clinical disease progression was assessed according to adherence to therapy and CD4 count prior to starting therapy [Abstract 4664]. There were 1,211 patients who started combination antiretroviral therapy between 1996 and 2001, with 3,583 person-years of follow-up. Adherence was defined as an adherence score of at least 90%. Rates of clinical disease progression after starting therapy were higher among individuals with lower baseline CD4 counts. Adherence of $<90\%$ was also associated with an increased risk of disease progression. Among adherent patients who started therapy at ≥ 200 CD4 cells/mm³, initial CD4 count did not predict subsequent disease progression. In a multivariate model, independent predictors of disease progression on HAART included a prior opportunistic infection, low CD4 count, non-adherence, and psychiatric illness. Adherence did not affect disease progression among persons with baseline CD4 count >350 or <50 cells/mm³.

In a study from the British Columbia Center for Excellence in HIV/AIDS, Wood and colleagues found that factors associated

with an increased risk of disease progression included a CD4 cell count <200 cells/mm³ prior to initiating HAART [Abstract 4672]. However, adherence to therapy and physician experience in the care of HIV infected patients also had a significant impact on survival. A total of 1,416 patients were included in this study. Adherent patients were defined as those who received at least 75% of their medications; physicians were considered experienced if they had previously treated at least five HIV infected patients.

In conclusion, disease progression may be slower in persons who start at CD4 >350 cells/mm³ than at 200-350 cells/mm³, but the difference is small. Adverse events from medications usually tip the balance in favor of not starting at >350 cells/mm³. Factors such as viral load $>100,000$ c/mL, age >50 , prior AIDS-defining conditions, and a history of injection drug use increase the risk of disease progression, and may influence the decision to start earlier rather than later. Durable virologic suppression is more likely in persons who initiate therapy at CD4 >200 cells/mm³, and as long as patients are $>90\%$ adherent, further stratification of CD4 above this level may not be necessary. Adherence decreases the risk of disease progression, particularly among persons who start at CD4 <200 cells/mm³; receiving care from a more experienced clinician also improves outcome.

What To Start With

This topic dovetails nicely with the issue of when to start therapy, since factors such as adherence, durable virologic suppression, and the class of therapy selected all influence the response to therapy. There were several important studies reported in Barcelona that addressed the issue of what to start with in chronically infected, antiretroviral-naïve patients.

In one of the more important studies presented, JA Bartlett reported preliminary (48 week) data on the CLASS study, which is comparing the nucleoside combination of abacavir + 3TC plus either efavirenz (EFV), amprenavir/ritonavir (APV/RTV) (1200/200 mg qd) or d4T in treatment-naïve patients with CD4 >50 cells/mm³ and viral load $>5,000$ c/mL [Abstract 1189]. Patients were allowed to make in-class substitutions if necessary (e.g., due to toxicity). In an intention-to-treat (missing=failure) analysis at 48 weeks, the proportion of patients



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achieving viral load <50 c/mL was 76%, 59%, and 62% among those receiving EFV, APV/r, and d4T, respectively ($p=0.047$ for EFV vs APV/r or d4T comparisons). Among those with baseline viral load >100,000 c/mL, 77% of the EFV group achieved viral load <50 c/mL, compared with 53% of the protease inhibitor group and 55% of the triple nucleoside group. Abacavir hypersensitivity occurred in 6% of patients. Thus, while all three regimens performed well, the EFV-based regimen appeared to be superior. An additional 48 months of follow-up is planned and will include analysis of sequencing strategies, in which patients failing the triple-NRTI regimen switch to EFV/APV/r, and patients failing the EFV or APV/r regimens switch to AZT/ddI plus APVr or EFV, respectively.

Forty-eight-week data were also presented for Gilead 903, an assessment of

the efficacy and safety of tenofovir DF vs d4T in combination with 3TC and EFV in naïve patients [Staszewski S, et al. Abstract LB17]. In an intention-to-treat (missing= failure) analysis after 48 weeks of follow-up, 82% of the patients in the tenofovir arm ($n=299$) had a viral load <50 c/mL, compared with 81% of the patients in the d4T arm ($n=301$) ($P=NS$). There were no differences in efficacy by baseline viral load. The drop out rate was low, and rates of adverse events and drug discontinuation were similar in both arms, though random cholesterol and triglycerides were significantly higher in d4T treated patients ($p<0.001$), and there was a suggestion of increased peripheral neuropathy in the d4T arm as well. The impressive efficacy seen in both arms of the study confirms the potency of EFV in previously naïve patients, and supports the use of tenofovir as first-line

therapy. While this was not specifically designed as a study of once-daily therapy, the implications are obvious, since both tenofovir and 3TC can be administered once a day, and d4T will also be a once daily drug when *Zerit XR* is approved.

ACTG 384 was also presented at the late-breaker session [Robbins G, et al. Abstract LB20a; Shafer R, et al. LB20b]. This trial, which included 980 patients among 6 study arms, was designed to answer three questions:

1. Which is the preferred dual-NRTI combination, AZT/3TC or ddI/d4T?
2. Which is the preferred third agent, EFV or nelfinavir (NFV)?
3. Which strategy is better, starting with a 4-drug, 3-class regimen, or using two sequential 3-drug, 2-class regimens?

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The first component presented assessed the following four strategies (n=155 in each arm; nelfinavir and efavirenz were blinded):

ddI/d4T/EFV → AZT/3TC/NFV

ddI/d4T/NFV → AZT/3TC/EFV

AZT/3TC/EFV → ddI/d4T/NFV

AZT/3TC/NFV → ddI/d4T/EFV

The primary endpoint was time to regimen failure of the second 3-drug regimen. Regimen failure included virologic failure, toxicity, or premature discontinuation. Secondary endpoints included time to first regimen failure or virologic failure. The median baseline CD4 was 278 cells/mm³ and the median baseline viral load was 4.9 log₁₀ c/mL. Median follow-up time was 28 months.

Compared with ddI/d4T, starting with AZT/3TC showed a strong trend toward delay in sequential regimen failure, and significantly delayed first regimen failure, when combined with EFV but not NFV. Compared with NFV, starting with EFV showed a strong trend to delayed sequential regimen failure and significantly delayed first regimen and virologic failure, when combined with AZT/3TC, but not ddI/d4T.

In comparing the strategy of using a 4-drug regimen vs two sequential 3-drug regimens, the following regimens were studied:

ddI/d4T/NFV/EFV

AZT/3TC/NFV/EFV

ddI/d4T/EFV → AZT/3TC/NFV

ddI/d4T/NFV → AZT/3TC/EFV

AZT/3TC/EFV → ddI/d4T/NFV

AZT/3TC/NFV → ddI/d4T/EFV

The primary endpoint was time to regimen failure of a single 4-drug regimen or two sequential 3-drug regimens. There was no significant difference in the primary endpoint between single 4-drug regimens and two sequential 3-drug regimens. Four-drug regimens significantly delayed first regimen failure and virologic failure compared with NFV-containing 3-drug regimens. Four-drug regimens also significantly delayed first regimen and virologic failure compared to EFV-based 3-drug regimens that contained ddI/d4T, but not AZT/3TC.

It should be noted that the drop-out rate in this study was high and that less than one-third of the endpoints were due to virologic failure. Thus, in an intent-to-treat analysis, the differences among the

treatment arms may be more likely to reflect tolerability and toxicity than actual potency. On-treatment analyses will presumably be included in future presentations of the data.

Robert Hogg presented data from another study from the British Columbia Center for Excellence in HIV/AIDS, on the risk of clinical disease progression among patients who initiated therapy with a protease inhibitor-based vs NNRTI-based regimen [Abstract 1142]. Of note, 96% of the persons in the NNRTI group received nevirapine, and the protease inhibitor group received primarily indinavir (IDV). Very few people received either EFV or dual protease inhibitors; 431 persons (39%) received an NNRTI-based regimen. The primary endpoint was death. Although patients who received an NNRTI-based regimen had a slightly lower risk of progression to death (relative risk: 0.79), this was not statistically significant. Factors associated with an increased risk of death were baseline CD4 count <200 cells/mm³, increased age, and intermittent anti-retroviral therapy.

In a study that assessed the durability of first-line HAART regimens, NNRTI-based HAART was associated with a more durable response and significantly lower rates of adverse events and changes in therapy than PI-based regimens [Moreno A, et al. Abstract 4673]. The PI-based regimens included either IDV or NFV, and the NNRTI-based regimens included either NVP or EFV. In this study, 256 anti-retroviral-naïve patients started HAART after April 1998 and were followed up for at least one year. In a multivariate model that controlled for prior AIDS-defining illness, baseline CD4 count, and viral load, the relative risk of disease progression was 2.69 for persons on PI-based therapy compared with patients on NNRTI-based therapy (p<0.01).

In a retrospective study from Arribas and colleagues, EFV-based HAART regimens were more effective than PI-based regimens in patients who initiated therapy at CD4 counts <100 cells/mm³ [Abstract 4444]. There were 92 patients taking EFV-based regimens and 218 taking PIs; the median baseline CD4 counts were 34 and 39 cells/mm³ in the two arms, respectively, and median baseline viral load was 350,500 and 254,000 c/mL. At 24 months, 69% of patients taking EFV had a viral load of

<400 c/mL by ITT analysis (non-completer or change other than simplification=failure) vs 45% for patients taking PIs (p<0.05). While many clinicians have tended to prescribe protease inhibitors in patients with advanced HIV disease, this study supports the use of EFV in such patients. It should be noted, however, that 94% of the PI-treated patients in this study were taking single PIs, while the current trend is to use boosted PIs, especially in patients with high viral loads and/or low CD4 counts.

Fätkenheuer presented data from a similar study that assessed lopinavir/ritonavir (LPV/r, *Kaletra*) in 86 patients who initiated HAART at a CD4 count <100 cells/mm³, viral load >100,000 c/mL, or after having had an opportunistic infection [Abstract 4447]. The median baseline CD4 count was 90 cells/mm³, and the median baseline viral load was 321,561 c/mL. After six months of therapy, 13 of 15 (87%) who remained on the LPV/r-based regimen had a viral load <400 c/mL. In a study of 68 patients who had baseline CD4 count <200 cells/mm³ and who initiated HAART with an NNRTI based regimen, 84% of patients had viral load <200 c/mL at 12 months (N=49; intention to treat analysis) [Lonca M, et al. Abstract 4457].

Mallolas from Spain compared two HAART sequences in naïve patients with chronic infection [Abstract 1186]. In this multi-center, randomized, open-label study, patients with CD4 <500 cells/mm³ were randomized to receive either ddI/d4T/NFV, switching to AZT/3TC/NVP (group A; n=73), or ddI/d4T/NVP, switching to AZT/3TC/NFV (group B; n=85). The indication for switching regimens was virologic failure. The primary study endpoints were time to failure of the second regimen, and the proportion of patients with viral load <200 c/mL. After 18 months of follow-up, 65% of patients had failed (virologic failure or change in regimen). However, there were no statistically significant differences in the mean increase in CD4 count, or in the proportion of patients who had achieved viral load <200 c/mL, virologic failure, or had an adverse event. Thus, the two strategies had comparable efficacy and tolerability, though the study was under-powered to truly claim equivalence.

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used to be standard of care before the widespread use of these tests). Overall, there were no differences in virologic response among the three groups. However phenotype testing was associated with improved virologic outcome among those who were more heavily treatment experienced, those with prior NNRTI experience, and those with advanced disease. This is in contrast to some of the earlier prospective trials, in which resistance testing appeared to have the greatest utility in patients failing earlier regimens, presumably because they were more likely to have good options for fully suppressive therapy.

Drug Resistance

• Nucleoside Analog Resistance

Because thymidine analogs (AZT or d4T) have historically been a component of almost all antiretroviral regimens, we are used to thinking of the accumulation of thymidine analog mutations (TAMs) as the sole pathway to NRTI resistance. However, the availability of other NRTIs and concerns about thymidine analog toxicity have sparked interest in thymidine analog-sparing regimens, such as combinations of 3TC or emtricitabine (FTC) plus either tenofovir DF, abacavir, or ddI. As use of such combinations grows, we will undoubtedly begin to see the emergence of different NRTI resistance patterns. Of greatest concern is the K65R mutation, which confers resistance to abacavir, tenofovir, and ddI. K65R is infrequently seen, but data presented in Barcelona and at the preceding Resistance Workshop in Seville suggest that it will emerge more frequently in patients taking non-thymidine analog-containing regimens [Winston A, et al. Abstract 4600; Alt-Khaled M, et al. XI International Drug Resistance Workshop, Seville, 2002]. The inclusion of a thymidine analog in a regimen containing abacavir, tenofovir, or ddI appears to drive resistance toward the TAM pathway, while preventing the development of K65R. The unanswered question is whether there is an advantage to one pathway over another. Data from the dual-nucleoside era suggested that TAMs might emerge more slowly than K65R, allowing for modification of therapy before significant cross-resistance had developed. However, it is unclear whether these findings can be extrapolated to more suppressive regimens. Resistance data from studies like Gilead 903, where a thymidine

analog-containing regimen is being compared with a tenofovir-containing regimen, will be helpful in answering this question.

The M184V mutation confers high-level resistance to 3TC but is known to have a variable effect on the other NRTIs. It increases susceptibility to AZT, d4T, and tenofovir, while decreasing susceptibility to abacavir, ddI, and ddC. The clinical relevance of that loss of susceptibility is thought to be minimal for abacavir, and has been questioned for ddI. Gazzard [Abstract 3144] and Eron [Abstract 4486] presented reassuring data suggesting that the clinical impact of prior 3TC experience and/or M184V on ddI susceptibility is minimal.

• Further defining PI resistance

The next protease inhibitor to be approved will undoubtedly be atazanavir (ATV), which has the advantages of being administered once daily and of not raising lipid levels. Resistance patterns are beginning to be worked out for this drug. Colonna presented data on ATV resistance at the Resistance Workshop in Seville, demonstrating the emergence of a novel I50L mutation in 8 of 9 previously naïve patients failing ATV [*Antiviral Therapy* 2002;7:S4]. Of those, 5 also were found to have the A71V mutation. Interestingly, virus with the I50L mutation remained susceptible or even hypersusceptible to all other protease inhibitors, including amprenavir, for which another mutation at codon 50 (I50V as opposed to I50L) results in a marked decrease in susceptibility. I50L was also found to decrease replication capacity, though this was partially restored by A71V. When ATV is combined with saquinavir, however, 84V is selected rather than 50L.

The strategy of PI sequencing, once widely accepted, has taken yet another hit. It now appears that the I50V mutation, once thought to confer resistance *only* to amprenavir, is not so benign as it was once thought to be. Specifically, it results in a significant decrease in susceptibility to lopinavir (LPV). Other mutations associated with a decrease in LPV susceptibility are being identified, allowing genotype algorithms to be refined so that they are more predictive of phenotypic susceptibility to LPV [Parkin NT, et al. Abstract 4613].

• NNRTI Hypersusceptibility

It has been established that NRTI-resistant virus demonstrates phenotypic hyper-susceptibility (HS) to NNRTIs;

however, the clinical relevance of this finding has been controversial. Haubrich presented data on 177 patients enrolled in the California Collaborative Treatment Group (CCTG) studies and assessed the association between phenotypic susceptibility to NNRTIs and response to an NNRTI-containing regimen [Abstract 1388]. Patients were NNRTI-naïve and failing a stable regimen that included NRTIs. NNRTI-HS was defined as a fold-change of <0.4, and was seen in 24% of patients for efavirenz and 20% for nevirapine. It was more common in patients who had at least 3 NRTI mutations. Haubrich found that the mean decrease in viral load 6 months after starting the NNRTI-containing regimen was 1.2 log₁₀ c/mL for those with HS compared to 0.8 log₁₀ c/mL for those without HS (p=0.016), and the difference persisted through 12 months of therapy (p=0.023). CD4 response was also better in patients with HS. NNRTI-HS remained a significant predictor of virologic response in multivariate analyses after accounting for baseline viral load and the number of drugs used in the regimen to which the patient's virus was susceptible.

There is now little doubt that NNRTI-HS is more than just a number on a phenotype report. However, the clinical implications of these findings are still unclear. While some have argued that NNRTIs should be deferred in order to capitalize on the HS advantage, there are two problems with this approach. First, HS requires the presence of significant NRTI resistance, resistance that we should be trying to prevent by intervening early during failure of an initial regimen. Second, data presented in Barcelona from trials of EFV-based regimens in previously naïve patients [ACTG 384, Gilead 903, CLASS; see Sterling, *When to Start ART*, p. 1] demonstrate that such regimens are simple, well tolerated, and highly effective for initial therapy, perhaps the gold standard against which other regimens will be judged. If the "first shot" is still the "best shot," then it would probably be unwise to ignore the data on initial therapy in order to save these drugs for inclusion in subsequent regimens on the hope that HS will make them more potent than they already are.

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Treatment of Experienced Patients

• Tenofovir in experienced patients

Although the big news on tenofovir came from studies in naïve patients (Gilead 903) [see Sterling, *When to Start ART*, p. 3], follow-up data on the use of this drug in experienced patients were presented by Pozniak [Abstract 1266]. Gilead study 907 was a multicenter trial that enrolled 550 treatment-experienced patients who were randomized to continue current therapy or to add tenofovir DF (TDF) to their existing regimen. As noted in previous reports, addition of TDF was associated with a 0.6 log₁₀ c/mL reduction in viral load, both initially and after 24 weeks, when those randomized to continue current therapy were allowed to add TDF as well. In both the

907 and the 902 studies, the best responses to TDF were seen in those without thymidine analog mutations (TAMs), especially if the M184V mutation was present [Margot NA, et al. Abstract 1390]. Those with multiple TAMs that included the M41L and/or L210W mutation had a poor response to TDF. Because L210W is rarely seen with K70R or T215F but almost always found with T215Y and M41L, it is virtually diagnostic for the unfavorable resistance pattern associated with decreased TDF susceptibility.

This study was important in helping to define the resistance pattern of TDF as well as clinical cut-offs for phenotypic susceptibility. In addition, it supported the use of TDF in experienced patients and the strategy of intensification of failing regimens under certain circumstances. However, the success of TDF as a component of initial therapy reported in the Gilead 903 study [Staszewski S, et al. Abstract LB17], may cause clinicians to use this drug earlier, rather than waiting to use it for salvage or intensification, when its potency is likely to be lower and less predictable.

• IDV/r vs SQV/r

The MaxCmin1 trial compared two boosted PI regimens, IDV/RTV (800/100 mg bid) and SQV/RTV (1000/100 mg bid) in naïve and experienced patients [Cahn P, et al. Abstract 1265]. At 48 weeks, virologic suppression was similar in the two arms by treatment analysis and intent-to-treat (ITT), switch included analysis. However, by ITT switch=failure analysis, 68% of patients on SQV/r had viral loads <400 c/mL vs 53% on IDV/r. Treatment-related grade 3/4 adverse events were also significantly more common among IDV recipients, and lipid profiles were better in the SQV/r arm.

• T-20

The Barcelona conference was a debut of sorts for the investigational fusion inhibitor, T-20, as results of two nearly identical multicenter trials, TORO-1 and TORO-2, were presented in the late breaker session [Henry K, et al. Abstract LB19b; Clotet B, et al. Abstract LB19a]. The generic name for T-20 is “enfuvirtide,” and the trade name will be “Fuzeon.” (Under the circumstances, I think I’ll just call it “T-20.”) In the TORO trials, patients who had failed all three classes of antiretroviral agents were randomized in a 2:1 fashion to take optimized background

therapy (OBT) plus T-20 (90 mg sq bid) or OBT alone. There were approximately 500 patients in each study. At 24 weeks, patients taking T-20 had significantly better virologic responses to therapy (-1.7 and -1.43 log₁₀ c/mL in TORO-1 and TORO-2, respectively, vs -0.76 and -0.65 log₁₀ c/mL, p<0.0001). Viral load suppression to <400 c/mL was observed in 37% and 28% of T-20 recipients vs 16% and 14% of those taking only OBT (p<0.0001). These results clearly indicate that T-20 provides potent virologic activity despite multi-class resistance. However, a new drug used in salvage therapy is typically only as good as the regimen with which it is combined, and T-20 will probably be no exception. T-20 resistance, mediated by mutations in gp41, has been described in patients who fail therapy with this drug. Patients who wait to use T-20 until after they have become resistant to all available antiretroviral agents are unlikely to have a durable response.

• Switch Studies

Martinez presented data from the NEFA trial, in which patients with virologic suppression on PI-containing regimens were randomized to switch from PIs to nevirapine, efavirenz, or abacavir (hence the acronym) [Abstract 1262]. Overall, there were no significant differences among the three arms with respect to the proportion of patients who maintained viral loads <200 c/mL at 12 months by ITT analysis. However, an as-treated analysis revealed that patients switching to abacavir were less likely to maintain virologic suppression, due mostly to the use of pre-HAART nucleoside analog therapy with presumed NRTI resistance. Patients switching to abacavir had the largest reduction in cholesterol levels, though most patients had normal levels prior to switch. There were no significant differences in fat accumulation or lipoatrophy.

This and other switch studies support the safety of switching from PI-based regimens to NNRTI-based or triple NRTI regimens, but consistently demonstrate the rather unsurprising finding that patients with prior NRTI resistance don’t do well on triple NRTI regimens.

In other switch studies, a switch from nelfinavir to atazanavir was associated with a significant decline in total cholesterol, LDL cholesterol, and triglycerides, as well as an increase in HDL cholesterol [Murphy

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Drug Resistance and the Treatment of Experienced Patients

R, et al. Abstract 9013]. Moyle presented data supporting previous studies [see *HHR* 2002;14(2):4] that suggested reversibility of lipotrophy with NRTI switches [Abstract 7322]. In his study, patients switching from d4T to abacavir experienced a 36% increase in arm fat and a 17% increase in leg fat by DEXA. No increases in subcutaneous fat were observed in patients switching from PIs or EFV to ABC, or even in patients switching from d4T and a PI or EFV to abacavir and AZT.

Treatment Interruption

In the enthusiasm that followed the introduction of protease inhibitors and that ushered in the HAART era, treatment guidelines were aggressive, recommending antiretroviral therapy for patients with CD4 counts <500 cells/mm³ or modest elevations in viral load. In 2001 these guidelines were modified, reflecting a growing reluctance on the part of clinicians and patients to commit patients to life-long therapy prematurely with the accompanying risks of side effects, long-term toxicity, and resistance. As a result of these changes, many patients are now on therapy who were started during the “hit early, hit hard era,” but who would not have been treated based on guidelines in use today. In Barcelona, we heard reports on two studies addressing the issue of treatment interruption in such patients.

Krolewiecki from Buenos Aires presented data on patients treated with stable HAART for at least 6 months whose baseline CD4 counts were >350 cells/mm³ and whose maximum viral load was $<60,000$ c/mL [Abstract 1440]. Patients were randomized to continue or discontinue therapy. Patients who discontinued therapy appeared to do well. None developed HIV-related symptoms or AIDS-defining conditions, and the mean decrease in CD4 count was only 14 cells/mm³. Viral load after rebound was within 1 log₁₀ c/mL of the pre-treatment setpoint.

This author presented data from an observational cohort of patients who discontinued therapy with the intention of restarting based on laboratory or clinical parameters [Gallant JE, et al. Abstract 1439]. At the time of the most recent analysis, 67% the 101 patients in the cohort remained off therapy, after a mean interruption of 74 weeks. Mean CD4 count (most recent off therapy) was 508

cells/mm³. The remaining third resumed therapy after a mean interruption of 34 weeks. The best predictor of time off therapy was pre-treatment CD4 cell count. Using a baseline CD4 count of >500 cells/mm³ as a referent, those with a CD4 count below 200 cells/mm³ were 7 times more likely to resume therapy ($p=0.001$), and those with a baseline count of 200-350 cells/mm³ were 4 times more likely to resume therapy ($p=0.015$). There was no significant difference in time off therapy between those with baseline CD4 counts of 350-500 cells/mm³ and those with baseline counts over 500 cells/mm³. Patients who met *current* DHHS guidelines criteria at the time of treatment initiation were 2.9 times more likely to resume therapy than those who did not ($p=0.004$), a difference affected more strongly by the CD4 component of the guidelines than the viral load component.

Both studies provide support for an approach that many find intuitive: Patients who didn't need therapy when they started probably still don't need it now. There are also longer-term implications for strategies such as pulse therapy, where treatment is interrupted for prolonged periods of time, with the goal of therapy being to maintain the CD4 count above a pre-determined threshold. Clinical trials are in progress to evaluate this approach, though results may not be available for several years.

Another rationale for interruption of therapy is to allow re-emergence of wild-type virus and thereby improve response to salvage therapy. Katlama and colleagues presented data on their GigHAART trial (ANRS 097), a small open-label trial in which patients with advanced disease (CD4 <200 cells/mm³) who were failing therapy (viral load >50 c/mL) were randomized to switch immediately to a multi-drug “mega-HAART” regimen or to defer salvage therapy until after an 8-week treatment interruption [Abstract 263]. Patients who stopped therapy first were twice as likely to have a 1 log₁₀ c/mL drop in viral load or to achieve viral load reduction to <400 c/mL at 24 weeks. This is still a controversial strategy, however, in part because results have been inconsistent, in part because of the potential danger of treatment interruption in patients with advanced disease, and in part because of the lack of durability data [Clotet B, et al. Abstract 264]. Archived resistant mutants are

expected to reappear with reintroduction of selective pressure exerted by salvage therapy. Larger randomized controlled clinical trials are in progress to evaluate this approach.

The idea that a “structured treatment interruption” (STI) strategy might help to immunize infected patients against their own virus seems to have died due to lack of supportive data. However, this strategy may still be viable in patients treated during primary infection. Walker presented data on a select group of patients who were diagnosed and treated before Western blot seroconversion [Abstract 259]. Eight of 14 such patients maintained viral loads below 5000 c/mL after at least one STI. Controlled trials are being planned to assess the effectiveness of STI after early antiretroviral therapy.

Still another approach to intermittent therapy involves cycling therapy in order to decrease the cumulative time on treatment, and presumably toxicity as well. In a debate session on treatment interruption strategies, Dybul discussed his experience with the “structured intermittent therapy” (SIT) approach, in which patients with maximal virologic suppression are treated with a “7-days on/7-days off” schedule [Session 261]. Drug regimens have included d4T/3TC/IDV/r and ddiI/3TC/EFV. To date there has been no evidence of virologic rebound or drug resistance, though some “blips” have been observed during the off-treatment periods in the IDV/r-containing regimen. It should be noted that when the SIT strategy was studied using longer cycles (2 months on, 1 month off), resistance emerged to 3TC and NNRTIs in patients taking regimens containing those agents [Perrin, et al. *Antiviral Therapy* 2002;7:S59]. While no recommendations have been made with respect to discontinuation of NNRTI-containing regimens, clinicians should be cautious given the long half-lives and low genetic barrier to resistance with this class of drugs. Temporary substitution of the NNRTI with another agent (e.g. PI or TDF) prior to interruption may be advisable, though this approach has not been studied.

Conclusions

Patients lose treatment options each time they fail an antiretroviral regimen,

continued on page 16



Pharmacology and Drug Interactions: A Progress Report

By Adriana Andrade, M.D., M.P.H. and Charles Flexner, M.D.

At the XIV International AIDS Conference in Barcelona, there were only six oral presentations and approximately 30 posters on pharmacology and drug interactions. A number of the studies presented had potential relevance to resource poor countries, a theme that resonated throughout the conference.

A Cheaper Alternative to Saquinavir-Soft Gelatin Capsules?

Saquinavir was developed in two successive formulations, “hard gel” capsules (SQVhgc, *Invirase*) and “soft gel” capsules (SQVsgc, *Fortovase*). Because the soft gel capsules have three-fold greater bio-availability, this formulation has been favored for the treatment of HIV infected patients. While available pharmacokinetic data support the use of once-daily SQVsgc when boosted with ritonavir (SQVsgc/RTV 1600/100 mg), a direct comparison of the pharmacokinetics of once-daily hard gel capsules with soft gel capsules boosted with ritonavir has not been reported.

To address this issue, a team of investigators from Thailand and Australia (HIV-NAT) examined the effect of ritonavir on the pharmacokinetics of SQVhgc [Ananworanich J, et al. Abstract 2007]. Fourteen HIV infected subjects taking SQVsgc/RTV (1600/100 mg) once daily plus 2 NRTIs for 48 weeks had SQV pharmacokinetics assessed at steady-state and one week after switching to SQVhgc at the same dose. Subjects were then switched back to SQVsgc and continued on this formulation throughout the study. The authors found that the 24 hour area under the curve [AUC₍₀₋₂₄₎] of SQVhgc was significantly greater when compared to SQVsgc. The authors attributed this to the slower absorption of the hard gel formulation, resulting in a greater interaction with ritonavir. Other pharmacokinetic parameters (C_{max}, C_{min}) were equivalent for the two formulations. In the U.S. the hard gel capsule formulation is more expensive than its counterpart. However, according to the study authors, SQVhgc will be less costly to produce than SQVsgc and will also be available in Thailand at a lower cost. If that is the case, SQVhgc may be an attractive treatment option not only in Thailand but possibly in other resource poor countries where the

high cost of therapy limits access for most infected individuals.

Self-Reported Adherence and Therapeutic Drug Monitoring: Is there a Correlation?

Adherence to antiretroviral therapy is crucial for long term success of HAART. Though therapeutic drug monitoring (TDM) is available for a number of antiretroviral agents, this intervention is more expensive and less accessible than self-report as a measure of adherence. It is important to determine whether patient self-report is correlated with drug levels, since it is so much easier and cheaper to ask patients about their adherence than to draw serum levels.

A group of investigators from the United States explored this issue by obtaining antiretroviral trough levels and self-reported adherence data from 85 HIV infected women followed in the Women’s Interagency HIV Study [Gandhi M, et al. Abstract 2012]. From October 2000 to April 2001, study participants were asked to recall adherence to their antiretroviral medications over the past 24 hours, 3 days, and 6 months. Additionally, trough levels of PIs and NNRTIs were obtained from each subject. Expected trough levels for each drug were calculated based on the subject’s report of the time of the last dose and published pharmacokinetic data. Results revealed no correlation with 3 day and 6 month adherence by self report, and only a weak correlation with the reported time of last dose ($r=-0.28$).

It is important to point out that this study has several limitations: they measured only a single drug concentration, the sample included only female subjects, and there was large variability in trough concentrations. Nevertheless, these findings suggest that self-reported adherence is likely to be affected by recall bias: the more time has passed, the less likely it is that patients will be able to provide reliable adherence information.

Nelfinavir and Pharmacogenetics

The role played by pharmacogenetics in antiretroviral pharmacokinetics and response is a hot topic in HIV pharmacology. Genetic polymorphisms can affect enzymes involved in drug metabolism and

result in profound differences in drug exposure between patients. These genetic differences can result in higher drug concentrations and increased toxicity or excessive drug metabolism, leading to a decreased therapeutic effect.

A genetic polymorphism has been identified in the CYP450 isoenzyme, CYP2C19. This isoenzyme is responsible for the formation of M8, the major active metabolite of nelfinavir (NFV). Though a substantial proportion of Asians are poor metabolizers using CYP2C19, it has not been clear whether NFV and M8 concentrations are affected in this population.

Kuwahara and colleagues from Japan measured NFV and M8 concentrations in 48 HIV infected Japanese patients treated with NFV-containing regimens [Abstract 4550]. Plasma samples were obtained from subjects treated with NFV for at least two weeks who were not taking other drugs known to affect CYP2C19 or 3A4. Eight subjects were receiving NFV 750 mg tid and the remainder 1250 mg bid. Pharmacokinetic sampling was obtained at trough (49 samples) and 4 hours after the morning dose (50 samples). The table on page 8 shows the pharmacokinetic parameters obtained in this study compared to historical data. Overall, NFV concentrations were higher and M8 concentrations lower than those seen in predominantly Caucasian populations. The authors found that 22% of the patients had undetectable M8 levels. Ninety percent of the patients with undetectable M8 levels had higher NFV plasma concentrations than their counterparts with normal M8 concentrations. No patient discontinued NFV within one year of therapy because of toxicity. Reasons for discontinuing NFV therapy beyond one year were fatigue (2), diarrhea (2), lipodystrophy (12), and rash (14). No relationship was found between NFV-associated adverse events and NFV concentrations or M8/NFV ratios.

This is the first study to suggest that a genetic polymorphism might affect concentrations of an antiretroviral drug. Unfortunately, the authors failed to determine the enzyme genotype or phenotype of the participants to determine whether the poor metabolizer status was due to 2C19 deficiency. Still, this study introduces the potential role of pharmaco-



Table I. Plasma Concentrations of Nelfinavir and M8

Study Data	n	Trough Mean SD (ng/mL)	n	Four Hours Post Dose
750 mg tid	8	NFV 2009 ± 974 M8 381 ± 473	9	NFV 4546 ± 1521 M8 1136 ± 1034
1250 mg bid	41	NFV 2278 ± 1535 M8 461 ± 527	41	NFV 5001 ± 1237 M8 1237 ± 400
U.S. Data Nelfinavir (Viracept) Package Insert 750 mg tid		NFV 1400 ± 600		NFV 3000 ± 1600
1250 mg bid		NFV 2200 ± 1300		NFV 4000 ± 800

Adapted from Kuwahara, et al. In: Program and Abstracts of the XIV International AIDS Conference. Barcelona, Spain, July 7-12, 2002. Abstract 4550

genetics in antiretroviral metabolism and points out the potential importance of genetic polymorphisms as a cause of altered antiretroviral concentrations.

Drug Interactions

• **Didanosine EC–Methadone:** It is known that co-administration of the original buffered tablet formulation of didanosine (ddI) with methadone results in up to a 52% reduction in the ddI AUC without effecting methadone pharmacokinetics. One question that has been frequently asked is whether methadone would have a similar effect on the pharmacokinetics of the new enteric coated (EC) formulation of ddI. Gerry Friedland and colleagues presented results of an open-label randomized two-way crossover study in which HIV negative subjects on chronic methadone maintenance were randomized to receive ddI EC or the buffered formulation (400 mg PO qd) [Abstract 4548]. Each formulation was given for two days and then followed by pharmacokinetic sampling over 24 hours. At the end of the study, 15 subjects had completed both treatments. The authors reported a mean C_{max} that was 12% lower and an AUC that was 22% higher for the EC formulation compared with the buffered tablets. The relative bioavailability of the EC formulation was 122% higher than that of buffered tablets, possibly explaining this result. Subjects receiving the buffered tablets had a decreased ddI AUC (2633 ng-hr/mL) and C_{max} (1554 ng/mL) when compared to historical data obtained from patients treated with ddI who were not receiving methadone (AUC 3136-3489 ng-hr/mL and C_{max} 1838-2321 ng/mL),

confirming previous results. On the other hand, the pharmacokinetic parameters for study participants treated with the EC formulation (AUC 3062 ng-hr/mL and C_{max} 1196 ng/mL) were comparable to historical data in patients not taking methadone (AUC 2562-3578 ng-hr/mL and C_{max} 794-1427 ng/mL). Based on these results, the authors recommended that HIV infected patients on chronic methadone should be treated with the EC formulation of ddI.

• **Triple PIs: Lopinavir/Ritonavir Plus Saquinavir:** Stephan and colleagues assessed pharmacokinetic interactions at steady state between LPV/r (400/100 mg bid) combined with SQV_{sgc} (1000 mg bid) compared with SQV/RTV (1000/100 mg bid) [Abstract 4561]. The median C_{min} for LPV (5500 ng/mL) and SQV (181-216 ng/mL) was 2-fold greater than the IC₉₅ for susceptible HIV in all cases. The median RTV concentration was lower in subjects treated with LPV/r/SQV. However, the boosting effect of RTV was comparable in the two groups. LPV plasma concentrations were not affected by SQV. The authors concluded that LPV/r effectively boosts SQV concentrations, and that it is unnecessary to add RTV to this regimen.

• **Indinavir and Ritonavir: Comparison of Two Regimens:** Gerber and colleagues from the AIDS Clinical Trials Group presented results from a pharmacokinetic study comparing two indinavir/ritonavir (IDV/RTV) combination regimens [Abstract 4552]. Forty-four HIV infected subjects who had failed their first PI-containing regimen (amprenavir, nelfinavir, saquinavir, or saquinavir/nelfinavir), were randomized

to receive IDV/RTV at a dose of either 800/200 mg bid or 400/400 mg bid. Twelve hour pharmacokinetic sampling was obtained at steady-state (2 weeks). Two subjects were excluded from the final analysis due to incorrect dosing and undetectable IDV levels. The authors found that the AUC_{0-12h} and C_{max} of IDV was higher in the 800/200 mg arm (AUC_{0-12h} 38.2 µg/h/mL and C_{max} 6309.1 ng/mL) compared with the 400/400 mg arm (AUC_{0-12h} 23.0 µg/h/mL and C_{max} 3633.0 ng/mL). On the other hand, trough (C_{12hr}) was comparable in both groups. The authors conclude that if the trough concentration is the important pharmacokinetic parameter in suppressing HIV, then these two regimens should have comparable anti-HIV effect, but the risk of nephrolithiasis may be greater with the the 800/200 dosing regimen. The authors also observed that the concentrations of IDV and RTV were lower on average in the HIV infected subjects when compared with historical data from healthy volunteers. One possible explanation was a difference in medication adherence monitoring in the two populations. The healthy volunteer group received medications under direct supervision during the entire study, while in the current study observed doses only occurred during pharmacokinetic sampling. ▲

CORRECTIONS

- Please note that in the article, *Peripheral Neuropathy and HIV*, by Michael J. Polydefkis, M.D., which appeared in the July 2002 issue of the *HHR*, the key for the graph on page 7 was transposed. The graph was intended to show a rise in neuropathy, not dementia. We apologize for the error.
- The article, *Acute Neuromyopathy Syndrome*, by Justin McArthur, MBBS, M.P.H., which appeared in the July 2002 issue, contained an incomplete citation on page 5. The correct citation follows: Cote HC, et al. *N Engl J Med* 2002;**346(11):811**; Shikuma CM, et al. *AIDS* 2001;**15(14):1801**.



Antiretroviral Treatment in Developing Countries

By Jean Nachega, M.D., M.P.H.

HIV/AIDS Prevention vs Treatment

The debate over prevention versus treatment efforts took center stage at the XIV International AIDS Conference in Barcelona, Spain, July 7-12, 2002. In the background behind the debates were two controversial papers recently published by Marseille and colleagues [*Lancet* 2002; 359:1851] and Creese and colleagues [*Lancet* 2002; 359:1635], both of which used a narrow, cost-effectiveness analysis that suggested that prevention of HIV/AIDS should take priority over treatment in Africa. At the Barcelona conference, most attendees seemed to agree that this false dichotomy between prevention and treatment should be abandoned. Not only did the analyses by Marseille and Creese offer a static perspective on drug costs, which in reality are a rapidly moving target and may decline with time, but such analyses also fail to consider the impact of treatment on preventing transmission, or the positive impact treatment has on national economic development. Many delegates felt that the decision to treat is a humanitarian and ethical one that cannot be based solely on cost-effectiveness data. The prevailing sentiment, from eminent HIV/AIDS experts and activists, was that the lives of 28 million HIV infected Africans do matter and that debating prevention versus treatment misstates the problem. Although many African governments have focused almost exclusively on prevention, the HIV infection rate in these countries has continued to rise, and growing numbers of experts are saying that HIV/AIDS can only be fought effectively with programs that link prevention and treatment.

HAART Pilot Programs in the Public Sector

AIDS researchers in developing countries have started to report data on the feasibility of providing HAART in resource-limited settings. In a plenary session, Paul Farmer of Harvard University reported his experience in rural Haiti with a small (n=60) directly observed therapy-HAART pilot project at Clinic Bon Sauveur, which is located in one of the poorest parts of the poorest country in the Western Hemisphere [*Lancet* 2001; 358:404]. The treatment was directly observed therapy, given once or twice per day by community health workers (accompagnateurs, many of whom are HIV infected themselves). While Farmer noted that it is too early to

draw conclusions about mortality, so far, all patients enrolled have had a positive clinical response characterized by weight gain and abatement of AIDS-related symptoms, and the medications have been well tolerated. More objective data on immunologic, virologic and clinical responses are needed, but Farmer has shown that treatment and adherence are possible under very adverse conditions.

Another encouraging report about a pilot HAART project in a developing country came from South Africa. In May 2001, Médecins Sans Frontières added HAART with generic drugs imported from Brazil to the bundle of services available in dedicated HIV clinics at three government-run primary health care centers in Khayelitsha, a poor township of Cape Town [Kasper T, et al. Abstract 1095]. Patients with CD4 counts <200 cells/mm³ or with WHO stage 3 or 4 disease were enrolled in the program. In a primary analysis of the first 85 patients, presented by Kasper, the median CD4 cell count was 48 cells/mm³, and the median HIV RNA viral load was 5.20 log₁₀ c/mL (3.54-6.83). Fifty-eight patients were treated with AZT/3TC/nevirapine (NVP), and 27 received AZT/3TC/efavirenz (EFV). Incidence of opportunistic infections (OIs) was significantly decreased following initiation of HAART (4.4 new OIs per patient-year, prior to initiation of HAART vs 1.2 new OIs per patient-year following initiation). For patients who had been on HAART for >6 months, HIV RNA levels were <125 c/mL in 24/26 (92%) analyzed, the mean CD4 cell increase was 128 cells/mm³ (n=28), and the mean weight gain 8 kg (n=29). Side effects were limited, with 45% of patients reporting at least one, 87% of which were grade 1. Lab abnormalities of grade 1 were detected in 54%, and 8 patients switched therapy for drug intolerance.

HAART pilot programs conducted by the U.S. Centers for Disease Control and Prevention (CDC) in Kampala, Uganda, Abidjan (Ivory Coast), and Kisumu (Kenya) were reviewed by Lackritz [Abstract 1515]. The preliminary results of the UNAIDS/Uganda Ministry of Health HIV Drug Access Initiative in collaboration with the CDC have just been published [*Lancet* 2002; 360:34]. The clinical and laboratory data for 476 patients at three centers were assessed from August 1998 to July 2000. Of those, 399

started antiretroviral therapy: 204 (51%) received HAART, 189 (47%) received dual nucleoside therapy, and 6 received nucleoside analog monotherapy. The median baseline CD4 count was 73 cells/mm³, and the median viral load was 193,817 c/mL. A Cox proportional hazards model showed that a CD4 count less than 50 cells/mm³ was strongly associated with death (hazard ratio of 2.93 [1.51-5.58] p=0.001). In addition, among patients with a viral load >1,000 c/mL for more than 90 days after beginning therapy, phenotypic resistance to NRTIs was found in 47 (57%): 29 of 37 (78%) who received non-HAART regimens vs 18 of 45 (40%) who received HAART (p=.0005). An encouraging HAART pilot program was also reported by Laurent [Abstract 3279].

The Brazilian Ministry of Health has made PI and NNRTI-based HAART universally available to patients in Brazil since 1996. Teixeira presented a 6-year progress report, noting that by December 2001, 113,000 patients were included in the program [Abstract 1098]. The results are comparable to what has been experienced in the United States and Western Europe: mortality has been reduced by 60% to 80%, with a notable reduction in the number of OIs. It was estimated that 358,000 hospital admissions were avoided because of this program in 1997-2001, representing a savings of \$1 billion. It is worth knowing that today in Brazil, 63% of the antiretrovirals used are generics, and their prices have fallen by 82% over 5 years. In addition, the Ministry of Health negotiated a 60% cost reduction of imported drugs.

The HAART pilot programs described above demonstrate that HIV infected patients in developing countries can be managed successfully with HAART. When it comes to expanding or scaling up HAART access in countries with limited resources, however, much will depend on the local infrastructure and available resources. In addition, as recently reported by the WHO, there is an urgent need for the development and implementation of simplified, standardized treatment and monitoring algorithms that will facilitate such program expansion.

HAART Pilot Programs in the Private Sector

The HIV/AIDS epidemic is having a catastrophic socioeconomic impact on the private sector and hence on economic



Antiretroviral Treatment in Developing Countries

productivity in sub-Saharan Africa. A growing number of private companies in the region are moving on an action plan to provide HIV/AIDS services that include HAART treatment to their employees. Several studies were presented in Barcelona highlighting this trend. Eholie and colleagues reported on a study from Cote d'Ivoire that was conducted in a private company with 3,500 employees [Abstract 1096]. He and his colleagues evaluated social costs (absenteeism, employee replacement) and economic costs (low productivity, cost of care, replacements and funerals) attributed to HIV infection among personnel over two periods of time, 1998-99 and 1999-2000. During the first period, they found that the main problems were absenteeism, employees' redeployment to other positions, and the social impact, which included fear and funerals. The economic effects included decreased productivity and an increased number of medical consultations and hospitalizations. During the first period the average cost for treatment of OIs was about U.S. \$26,154 per patient and for funeral expenses approximately \$107,692. Following the creation of a solidarity fund for HAART and aggressive promotion of voluntary counseling and testing services, the authors have been able to document significant decreases in healthcare costs and absenteeism.

In a taped plenary speech, South African AIDS activist Zachie Achmat sharply criticized the South African mining giant Anglo-American and challenged the company to create a program for providing AIDS treatment to its employees. It is estimated that 23% of the 90,000 people employed by Anglo in southern Africa (approximately 18,000 workers) are infected with HIV. In response, on August 6 the company announced that it would cover AIDS treatment of all its HIV-infected employees who do not have private medical coverage for HIV/AIDS.

Treatment Adherence

Preliminary data on HAART adherence in developing countries were presented at the XIV AIDS Conference in Barcelona. Pinheiro reported on a cross-sectional study of adherence to HAART in Southern Brazil [Abstract 5846]. Adherence was assessed by the self-report inventory method. There was a total of 195 patients, with 57% reporting 95% adherence in the previous two days; HIV RNA was <500 c/mL in 67.5% of this adherent group. Using a univariate analysis, the authors

found that the odds of adherence decreased with frequency of dosing (OR=4.4 95% CI 0.2-0.94) and perception of negative affect and physical condition (3.50, 1.90-6.55). Adherence increased with self-efficacy (3.5, 1.90-6.55) and education (2.28, 1.12-4.66).

In a study conducted in Botswana (n=112) that used patient self-report and clinician assessment, Weiser and colleagues found that 54% of patients were adherent by self-report, while 53% were adherent by clinician assessment [Abstract 5851]. Agreement between both methods was only 68%, however. The main barriers to adherence were financial constraints related to the cost of antiretrovirals (44%), stigma (15%), migration (10%), side effects (9%), and lack of food (7%).

Another HAART adherence study came from the Joint Clinical Research Center (JCRC) in Kampala, Uganda, where Kityo and colleagues conducted a retrospective chart review of 577 patients on antiretroviral therapy from January 1998 to June 2001 [Abstract 5848]. Adherence was assessed via patient self-report, and patients were then characterized as "adherent" or "non-adherent." An overall baseline adherence rate of 66% was reported.

Leandre and colleagues reported that their experience in rural Haiti showed DOT to be an effective way to maximize adherence to HAART and prevent the emergence of drug resistance [Abstract 3246]. This study was modeled after their experience with community-based treatment of multidrug-resistant TB in Haiti, Peru, and Russia, employing DOT twice daily. At the Clinic Bon Sauveur in Haiti, HIV-infected patients who begin HAART receive daily visits from a community health worker who observes only the first dose of the treatment. Of 40 patients tested, 88% had virologic suppression, and of the five without virologic suppression, only three had significant drug resistance.

Neonatal PEP with NVP and/or AZT for Prevention of Mother-to-Child-Transmission of HIV

In developing countries, a significant proportion of mothers do not have access to antenatal services until delivery. Therefore, studies evaluating the benefit of post-exposure prophylaxis (PEP) to prevent maternal-to-child transmission (MTCT) have been undertaken. Two studies with slightly different designs and conflicting results were presented

in Barcelona. Taha reported preliminary results from a randomized clinical trial from Malawi that included 1059 babies randomized to receive either NVP/AZT (n=531) or NVP alone (528) as post-exposure prophylaxis [Abstract 1427]. HIV PCR results were available for 809 at 6 weeks (408 in the NVP/AZT arm and 401 in the NVP arm). At 6 weeks, 14.7% were HIV positive in the NVP/AZT arm compared with 22.7% in the NVP arm (p=0.004). Among babies who were negative at birth but positive at 6 weeks, 7.2% were in the NVP/AZT arm, and 12.1% in the NVP arm. Serious adverse events were rare (2% in each arm). The authors concluded that compared with NVP alone, post-exposure prophylaxis with NVP/AZT was significantly more efficacious, reducing MTCT by 35%.

In another study conducted at Chris Hani Baragwanath Hospital in Soweto, South Africa, Gray and colleagues conducted a randomized controlled trial evaluating a single dose of NVP vs 6 weeks of AZT for PEP in an MTCT setting [Abstract LB13]. They found that babies who were given a single dose of NVP within 24 hours after birth were no more likely to become infected with HIV than babies given AZT for the first six weeks of life. Approximately 6% of infants were infected at birth; an additional 7% of NVP-treated children became infected at 6 weeks, vs 11% of AZT-treated children. Other factors associated with transmission were low maternal CD4 count, high maternal viral load, and breastfeeding.

Simple and Affordable Diagnostic and Monitoring Lab Tests

Several papers were presented that examined efforts to find alternative, affordable, and feasible laboratory tests for the diagnosis and monitoring of HIV/AIDS. Of interest is the *Dynabeads* assay, an alternative method for providing CD4 cell counts using anti-CD4 monoclonal antibody-coated magnetic beads. Diabougou reported on an international multicenter study conducted in six countries in West Africa that validates the *Dynabeads* method and then compared this assay with flow cytometry [Abstract 1342]. The correlation coefficient between the two techniques was 0.89, and the ability to consistently measure the CD4 count at clinically relevant thresholds was close to 95%.

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The Global HIV/AIDS Pandemic 2002: A Status Report

By Thomas C. Quinn, M.D.

On the eve of the XIV International AIDS Conference in Barcelona, UNAIDS released its "Report on the Global HIV/AIDS Epidemic, 2002." This is the most comprehensive and detailed report on the epidemic that has ever been released by either the World Health Organization or UNAIDS. The 226-page report, made available to every participant at the International AIDS Conference, is available on the web at <http://www.unaids.org>. This article will summarize some of the highlights from the UNAIDS report, which, according to Dr. Peter Piot, Executive Director of UNAIDS, "Provides positive proof that HIV, if left to run its natural course, will cause devastation on an unprecedented scale."

The report illustrates the stark reality of the status of the global HIV pandemic with the following estimates:

- 40 million people were living with HIV/AIDS at the end of 2001, including 37.1 million adults and 3 million children (Table 1, below).
- 5 million people became newly infected with HIV in 2001, a number similar to the last two years, and representing little abatement in the spread of HIV.
- Over 3 million AIDS deaths were estimated for 2001.
- 14 million children have been orphaned by AIDS since the beginning of the epidemic. According to Piot, "The scale of the AIDS crisis now outstrips even the worst case

scenarios of a decade ago." Without effective treatment and care, over the next decade millions more will join the ranks of the more than 20 million people who have died of AIDS since the first reported cases in 1981.

Sub-Saharan Africa

Africa remains by far the worst affected region in the world: 3.5 million new infections occurred in Africa in 2001, bringing to 28.5 million the total number of people living with HIV/AIDS in the region (Figure 1, p. 13). In contrast to the developed world, where up to 30% of all infected people receive antiretroviral therapy, fewer than 30,000 people (0.1%) of the 28.5 million infected Africans were estimated to have received antiretroviral therapy (Figure 2, p. 14). Of the 14 million children orphaned by AIDS worldwide, 11 million live in sub-Saharan Africa. The highest HIV prevalence rate worldwide for pregnant women stands at 44.9% in Botswana. In neighboring countries, HIV prevalence rates continue to rise among pregnant women: In Zimbabwe the rate rose from 29% in 1997 to 35% in 2000; in Namibia, it rose from 26% in 1998 to 30% in 2000. As startling as these prevalence levels are, they do not reflect the actual risk of acquiring HIV. For example, prevalence rates are higher among specific age groups. In Botswana, among 25 to 29-year-old women attending antenatal clinics in urban areas, 55.6% of pregnant women (one out

of two) were living with HIV/AIDS. In Swaziland, the corresponding prevalence was 33.9%, and in Zimbabwe, it was 40.1%. For South Africa, HIV prevalence rates may be now leveling off at 25%. One in nine South Africans (5 million people) is living with HIV/AIDS, an alarming statistic from a country that has been slow to respond to the epidemic. Increasing HIV prevalence is also being reported from West Africa. Nigeria, the most populous country in sub-Saharan Africa, has reported an increase in prevalence from 1.9% in 1993 to 5.8% in 2001 in the general population. Already more than 3 million Nigerians are estimated to be living with HIV/AIDS.

The report balances these harsh statistics with some good news from Uganda. Over the past eight years, seroprevalence has fallen from 29.5% to 11.2% among pregnant women in Kampala. Countrywide prevalence stands at 5%. However, despite efforts to expand treatment and care, the vast majority of Ugandans with HIV infection do not have access to antiretroviral therapy, and the Ugandan orphan crisis continues to strain the society's resources. Nevertheless, the experience in Uganda underscores the fact that a rampant HIV/AIDS epidemic can be brought under control with intensive prevention programs. Similar reports from Cote d'Ivoire and Senegal help provide further evidence of successful prevention programs that need to be replicated in many other countries.

Asia and the Pacific

Despite the well-documented and successful HIV prevention programs in Thailand, the HIV/AIDS epidemic continues to spread rapidly in Asia and the Pacific. This region serves as a reminder that no country is immune to the HIV epidemic. Low national prevalence rates conceal serious localized epidemics in several areas, including China, Indonesia, and India, where large numbers of people are infected and affected, proof that the national HIV prevalence figures in highly populous countries do not tell the full story of the epidemic. Currently, it is estimated that 6.6 million people in Asia are living with HIV/AIDS and that one million adults and children became newly infected last year (Figure 1, p. 13). Less than 30,000 (0.4%) people are on antiretroviral therapy (Figure 2, p. 14). In China, while the initial HIV outbreak occurred among

Table 1. Global Summary of the HIV/AIDS Epidemic, as of End 2001 [From UNAIDS, *Report on the Global HIV/AIDS Epidemic*; XIV International Conference on AIDS, Barcelona, 7/02; <http://www.unaids.org>]

Number of people living with HIV/AIDS	Total	40 million
	Adults	37.1 million
	Women	18.5 million
	Children under 15 years	3.0 million
People newly infected with HIV in 2001	Total	5 million
	Adults	4.2 million
	Women	2.0 million
	Children under 15 years	800,000
AIDS deaths in 2001	Total	3 million
	Adults	2.4 million
	Women	1.1 million
	Children under 15 years	580,000



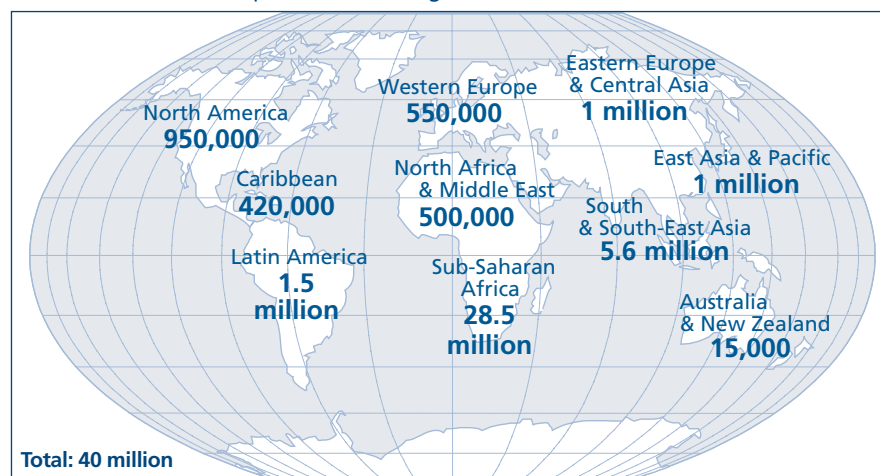
The Global HIV/AIDS Pandemic 2002: A Status Report

injecting drug users, with rates as high as 70% in Xinjiang and Yunnan Province, there are now signs of heterosexually transmitted HIV epidemics in at least three provinces. To compound the tragedy of the epidemic in China, recent reports in Henan Province in central China demonstrate that tens of thousands and possibly more rural villagers became infected by selling their blood to collecting centers that did not follow basic blood donation safety procedures. It has been estimated that 150,000 people have been infected through these practices. To further compound the epidemic in China, sexually transmitted infections have quadrupled in the last four years. Other neighboring countries are also witnessing the rapid expansion of HIV. India now estimates 4 million people living with HIV/AIDS, more than any other country after South Africa. Indonesia, the world's fourth most populous country, demonstrated how suddenly the HIV/AIDS epidemic could emerge. After more than a decade of negligible HIV prevalence rates, the country is now seeing infection rates increase rapidly among injecting drug users and sex workers, with rates as high as 40% in drug treatment centers in Jakarta. In contrast, Thailand and to some degree Cambodia have implemented strong prevention programs that have slowed the course of the epidemic within these countries.

Eastern Europe and Central Asia

Eastern Europe is experiencing the fastest growing epidemic in the world (Figure 1, above). Within three to four years, the number of HIV infected people rapidly rose from less than 100,000 to over 1 million, a ten-fold increase. Unfortunately, fewer than 1,000 people (0.1%) are estimated to be receiving antiretroviral therapy (Figure 2, p. 14). The Russian Federation remains at the forefront of the epidemic in this region. However, neighboring countries such as the Ukraine, Belarus, Moldova, Latvia, Estonia, and Kazakhstan, are following trends set by the Russian Federation for rapidly rising HIV rates (Figure 3, p. 14). Currently, the Ukraine remains the most affected country in the region, with an estimated adult HIV prevalence rate of 1%. Three-quarters of the HIV infections in Ukraine are related to injecting drug use, but the proportion of sexually transmitted HIV infection is

Figure 1. Adults and Children Estimated to be Living with HIV/AIDS as of End 2001
[From UNAIDS, *Report on the Global HIV/AIDS Epidemic*; XIV International Conference on AIDS, Barcelona, 7/02; <http://www.unaids.org>]



increasing. In China, the rates of other STDs, particularly syphilis, are increasing dramatically. The public health efforts to stem the tide of these epidemics are limited and in some cases nonexistent. In contrast to these countries, prevalence remains low in Poland, the Czech Republic, Hungary, and Slovenia, where well-designed national HIV/AIDS programs are in operation. If effective interventions are not implemented in the more severely affected countries, it is likely that the situation will become dramatically worse over the next five years.

Latin America and the Caribbean

An estimated 1.9 million adults and children are living with HIV in this region (Figure 1, above), and an estimated 170,000 (8-9%) people were receiving antiretroviral treatment (Figure 2, p. 14). Brazil has led the way with a nationalized antiretroviral therapy campaign that provides drugs for all eligible HIV-infected individuals. Prevention programs among injecting drug users have also featured strongly in the country's response, with a substantial decline in prevalence among IDUs in several large metropolitan areas. By reducing HIV/AIDS related morbidity through treatment, Brazil's treatment and care program is estimated to have avoided 234,000 hospitalizations in 1996 to 2000, thereby demonstrating a cost-effective approach to care.

Unfortunately, such aggressive campaigns in treatment and care are still not in place in many poorer countries. In the

Caribbean, adult HIV prevalence rates are the second highest in the world after sub-Saharan Africa. HIV/AIDS is the leading cause of death in some of these countries. Worst affected are Haiti, with a national prevalence rate over 6%, and the Bahamas with a prevalence of 4%.

High Income Countries

Western Europe, North America, and Australia have benefited from broad access to treatment for the nearly 1.5 million people living in these regions (Figure 1, above). For example, approximately 500,000 (33%) people are receiving antiretrovirals (Figure 2, p. 14). As noted in the report, a major concern is the high rate of sexually transmitted infections among men who have sex with men (MSM), signaling a rise in unsafe sex and highlighting the need for renewed prevention efforts, especially among young people. In addition, heterosexual transmission of HIV now accounts for a bigger share of new infections with young, disadvantaged people appearing to be at particular risk. The rise in new HIV infections among MSM is particularly striking (Figure 4, p. 15). Rising incidence of other STDs among MSM in Amsterdam, Sydney, London, San Francisco, Seattle, and Los Angeles confirms that widespread risk-taking is eclipsing the safer sex ethic promoted so effectively in the 1980s and 1990s.

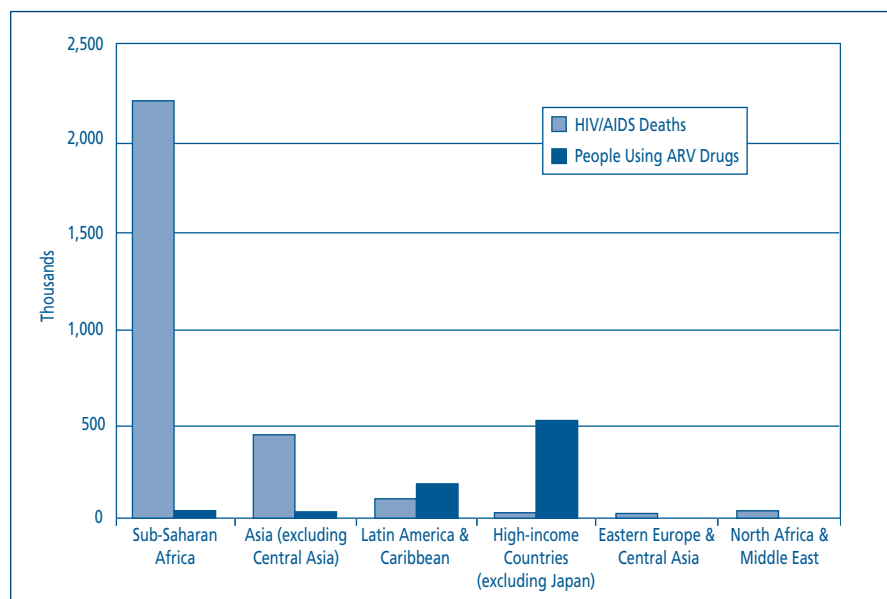
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Figure 2. HIV/AIDS Deaths in 2001 and Number of People Using Antiretroviral Drugs by End 2001: By Region [From UNAIDS, *Report on the Global HIV/AIDS Epidemic*; XIV International Conference on AIDS, Barcelona, 7/02; <http://www.unaids.org>]



Global Impact of AIDS

Other areas addressed in the report include the demographic, social, and economic impact of the HIV/AIDS epidemic. HIV/AIDS is now the leading cause of death in sub-Saharan Africa and the fourth largest global killer. Average life expectancy in sub-Saharan Africa is now 47 years, when it would have been 62 years without AIDS. Life expectancy at birth in Botswana has dropped to a level not seen in that country since the 1950s. Even in Haiti, life expectancy is nearly 6 years less than it would have been in the absence of AIDS. In Asia, Cambodia has also experienced a reduction in life expectancy of 4 years. Current HIV prevalence levels merely hint at the much greater lifetime probability of becoming infected with HIV. In Lesotho, it is estimated that a person who is 15 has a 74% chance of becoming infected with HIV by his or her fiftieth birthday.

According to a separate report from the U.S. Census Bureau, AIDS is expected to cause a decline in life expectancy in 51 countries over the next 20 years. Seven nations in sub-Saharan Africa now have life expectancies less than 40 years, and this number will increase to 11 countries over the next seven years. The declining life expectancies will soon reach levels that have not existed since the 19th century. In

Zimbabwe and South Africa, the infant mortality rate is higher than it was in 1990. Five African nations will experience more deaths than births by 2010 with a resultant decrease in population size. The Bureau predicted that life expectancy will drop to just 27 years in Botswana and Mozambique in the next eight years, while Swaziland will have an estimated life expectancy of 33, and

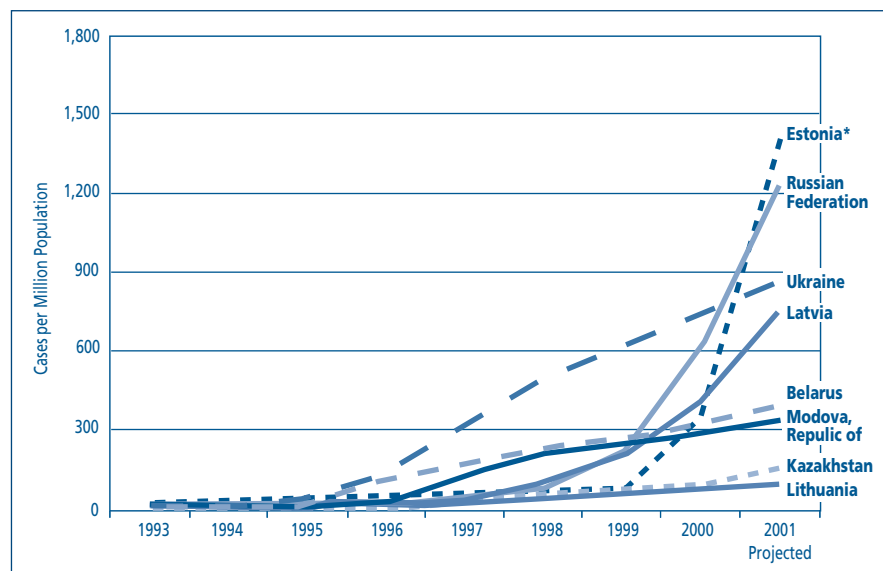
Zimbabwe, Zambia, and Namibia will have an expected lifespan of 34 years. In contrast, the Bureau estimated that without AIDS, the life expectancy in Africa would have been approximately 70 years by 2010.

Aside from the demographic impact, HIV is also having a dramatic impact on the health sector, the education sector, enterprises and workplaces, and on both micro- and macroeconomics. The report has much more detailed statistics that cannot be summarized here, but the reader is encouraged to review the report on the web.

Care, Treatment, and Support

This section of the UNAIDS report addresses the issues surrounding access to antiretroviral drugs, improvement of infrastructure in developing countries, and provision of medicines for opportunistic infections and tuberculosis. The report provides a balanced approach to both therapy and prevention by discussing the need for a continuum of care and support coupled with strong prevention programs. Unfortunately, financial resources are not available to meet this need. As of mid-2002, aggregate spending for HIV/AIDS was projected to approach \$3 billion in low and middle-income countries, much of it underwritten by international assistance. By 2005, an estimated \$9.2 billion will be required, three times greater than the

Figure 3. Cumulative Reported HIV Infections per Million Population in Eastern European Counties: 1993-2001 [From UNAIDS, *Report on the Global HIV/AIDS Epidemic*; XIV International Conference on AIDS, Barcelona, 7/02; <http://www.unaids.org>]

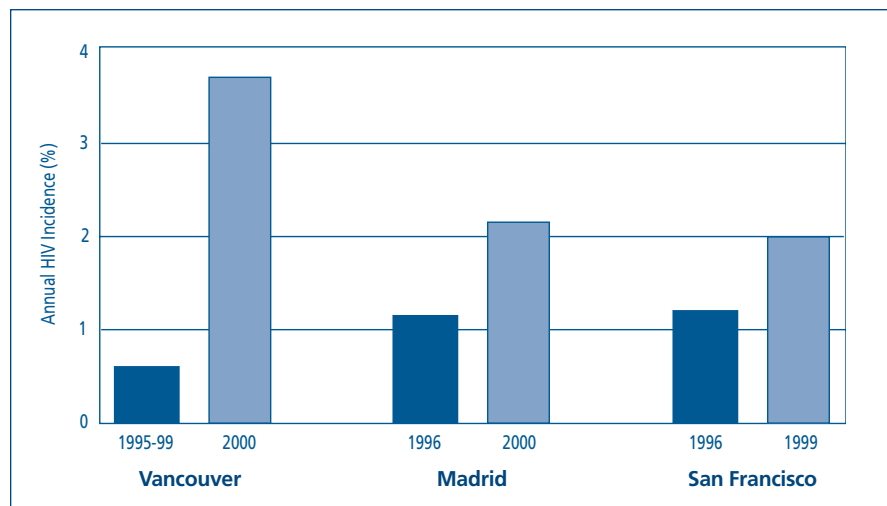


* Actual 2001 year-end data



The Global HIV/AIDS Pandemic 2002: A Status Report

Figure 4. HIV Incidence Among Men Who Have Sex With Men in Vancouver, Madrid and San Francisco: 1995-2000 [From UNAIDS, *Report on the Global HIV/AIDS Epidemic*; XIV International Conference on AIDS, Barcelona, 7/02; <http://www.unaids.org>]



current spending projections for this year. If expenditures on AIDS were to remain at current levels, the funding shortfall will be at least \$7 billion. The Global Fund for AIDS, Tuberculosis, and Malaria was established to help address this shortfall in current funding. Unfortunately, total pledges to the fund stood at just under \$2 billion in 2002, and only 60% of these funds are dedicated to support HIV/AIDS prevention and treatment programs. Consequently, other programs will be necessary to help address this shortfall in funding if the world is to support more comprehensive care and prevention programs. As stated in the report, "The evidence presented here could not be starker: Where care is most needed, it is least accessible." The agenda for building the capacity to extend care to those who need it is presented, but the resources to support this agenda remain severely limited and in short supply. The report tries to balance the good with the bad, but it is clear that without a significant increase in financial resources, the epidemic will continue unabated and will continue to "cause devastation on an unprecedented scale."

Just prior to the release of the UNAIDS report, the WHO and the International AIDS Society formally launched new international guidelines for public health response to treatment of AIDS in resource-poor settings. Lisa Spacek, M.D., has previously reported these guidelines in the *Hopkins HIV Report* [see *HHR* 2002;

14(4):1]. The WHO believes that using appropriate resources, at least 3 million people needing care could be treated with antiretroviral therapy by 2005—a more than ten-fold increase in the developing world.

A Call to Action

In the opening ceremonies UNAIDS Director Dr. Peter Piot "openly challenged" political leaders to follow through on previous commitments by allocating the estimated \$10 billion needed annually to fight HIV/AIDS on an international scale. Piot also advocated for treatment in developing nations saying, "Treatment is technically feasible in every part of the world. It is political will that is required."

This plea for increased support was repeatedly echoed in the closing ceremony by two former presidents: Bill Clinton and Nelson Mandela, co-chairs of the International AIDS Trust. Both individuals called AIDS a threat to the world's economic well-being and said it was the job of the rich nations to live up to their promise to contribute to the global fund. Mandela called HIV/AIDS a "war against humanity" that requires the mobilization of entire populations and stated that antiretroviral drugs need to be made available for all those who need them, wherever they may be in the world, regardless of whether they can afford them, and that it is the job of the rich nations to live up to this ideal. ▲

Drug Resistance and the Treatment of Experienced Patients

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The cost per assay was estimated to be less than U.S. \$10.00. Low-tech assays like this will make monitoring therapy much more feasible in Africa and other developing regions.

Rodriguez presented preliminary studies in progress suggesting that microchip-based assays for HIV antibodies, p24 Ag, RNA, and CD4 counts could be feasible and affordable in resource-poor settings [Abstract 1343].

An AIDS Activist's Voice

As at previous World AIDS Conferences, the Barcelona conference provided an opportunity for AIDS activists to raise their voices against the inequalities in access to care between the South and the North. Zachie Achmat, the South African AIDS activist who in 1998 co-founded South Africa's Treatment Action Campaign (TAC), delivered a dramatic and touching pre-taped speech at the plenary session, as an acute lung infection prevented him from attending the conference in Barcelona. Achmat called on drug companies to waive patent restrictions and open the doors to a competitive market in generic drugs in the developing world as a way to deal with the epidemic in a sustainable manner. He noted that pilot HAART projects using generic drugs that combine prevention and treatment, such as the one conducted by Médecins Sans Frontières in Kyaletisha township [Abstracts 1095 and 3685], have proved that HAART can be feasible in limited-resource settings and should be expanded. Achmat lives with HIV and has free access to antiretrovirals, and yet he declared he would not take the lifesaving drugs until the South African Government agreed to an action plan to provide HAART in the public hospitals in South Africa.

Conclusion

The XIV International AIDS Conference will be remembered as the meeting that emphasized the need for both prevention and treatment of HIV/AIDS. It will also be remembered for the presentation of the first reports of pilot HAART projects that demonstrated the feasibility and effectiveness of such interventions in developing countries.

Dr. Nachega is Assistant Scientist in the Department of International Health, Johns Hopkins Bloomberg School of Public Health and conducts HIV clinical research in South Africa. ▲



Drug Resistance and the Treatment of Experienced Patients

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eventually running out of regimens that can be expected to provide durable virologic suppression. The best way to deal with treatment failure is to prevent it, by carefully preparing and educating patients prior to initiation of therapy, by using potent regimens that patients can take, and by reinforcing adherence at every visit. When failure does occur, it is now clear that allowing continued failure without intervention is a recipe for viral evolution and worsening drug resistance. Intensification is an option for patients experiencing low-level virologic rebound despite good adherence, as was indicated in the Gilead 907 study. For patients with higher viral loads, the standard of care is to perform resistance testing before selecting the next regimen.

There are a number of new drugs in the pipeline that may be effective in patients who have developed resistance to currently available agents. Some of these drugs have novel mechanisms of action, including T-20 and other agents that inhibit viral entry. Others inhibit reverse transcriptase or protease but have unique resistance profiles, such as tipranavir or some of the second generation NNRTIs. Initial therapy for untreated patients continues to improve, and our hope is that we'll see begin to see fewer failures and less drug resistance as a result. However, we must continue to search for more effective options and strategies for those experienced patients who do fail. ▲

Antiretroviral Therapy: When to Start & What to Start With

continued from page 4

In a retrospective cohort study, Pulido and colleagues assessed virological, immunological, and clinical outcomes among patients with CD4 counts <100 cells/mm³ who were treated with either an EFV-based or protease inhibitor-based HAART regimen [Abstract 1187]. The median baseline CD4 count was 34 cells/mm³ in the EFV group and 39 cells/mm³ in the PI group; median baseline viral loads were 351,000 and 254,000 c/mL, respectively. The mortality rate was 4% in the EFV group and 2% in the PI group (p=0.5). However, the time to failure (defined as either 2 consecutive viral loads >400 c/mL or a change in regimen) was delayed in the EFV group (p=0.001). There was no difference in the increase in CD4 count, except at 24 months, at which time it was higher in persons treated with EFV. Although this summary pertains primarily to the treatment of chronically-infected persons, there was one study of short-course antiretroviral therapy (SCART) in primary HIV infection [Fidler SJ, et al. Abstract 1185]. Although therapy is currently recommended for persons with primary HIV infection, the duration of such therapy is unknown. These investigators from the United Kingdom identified 60 persons with primary HIV infection, of whom 52 agreed to take SCART. They all achieved a viral load of <50 c/mL after a median duration of treatment of 12 weeks (range: 4 to 32 weeks). Up to 48 weeks after discontinuation

of therapy, the average viral load was lower than at baseline. Four of 52 discontinued therapy due to toxicity; 6/52 progressed to a CD4 count <300 cells/mm³, at which point therapy was resumed. SCART was also associated with preservation of HIV-specific immune responses.

In conclusion, for initial therapy in the antiretroviral-naïve patient, EFV-based regimens appear to be superior to the protease inhibitor-based regimens tested in these studies. A 3-drug regimen is sufficient, particularly if it contains EFV. If protease inhibitors are used, dual or boosted therapy now appears to be preferred over a single agent. Tenofovir appears to be a reasonable component of initial therapy, though it remains to be seen whether there will be differences in toxicity and/or resistance in tenofovir- compared to thymidine analog-based combinations. Longer-term follow-up, during which both efficacy and tolerability are assessed, will be helpful in determining the optimal regimens for initial therapy. ▲

Look for more coverage of the World AIDS Conference in the November issue of the *HHR* and on the web (<http://hopkins-aids.edu>), including: *Women's Health Issues* by J. Keller, PA.C., J. Lee, M.D., and J. Anderson, M.D. and a report on *Adherence* by B. Perdue Sabandayo, Pharm.D., M.P.H.

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Management of Hepatitis C: A Review of the NIH Consensus Development Conference

By Kelly A. Gebo, M.D., M.P.H. and John G. Bartlett, M.D.

The National Institutes of Health (NIH) convened a Consensus Development Conference June 10-12, 2002. The primary sponsors of the meeting were the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Office of Medical Applications of Research (OMAR) of the NIH. The event was co-sponsored by several different agencies within the Federal Government that have an interest in hepatitis C, particularly the National Institute of Child Health and Human Development (NICHD); the National Cancer Institute (NCI); the National Center for Complementary and Alternative Medicine (NCCAM); the National Institute on Alcohol Abuse and Alcoholism (NIAAA); the National Institute on Drug Abuse (NIDA); the National Institute of Allergy and Infectious Diseases (NIAID); the National Heart, Lung, and Blood Institute (NHLBI); the Centers for Medicare & Medicaid Services (CMS); the Centers for Disease Control and Prevention (CDC); the U.S. Food and Drug Administration (FDA); and the U.S. Department of Veterans Affairs (VA). The Agency for Healthcare Research and Quality (AHRQ) provided support to the Conference through its Evidence Based Practice Center Program. Under contract to AHRQ, the Johns Hopkins University Evidence Based Practice Center developed a systematic review of the literature and analysis that served as a reference for discussion at the conference and is available at <http://www.ahrq.gov/clinic/epcsums/hepcsum.htm>.

This 2-1/2 day conference examined the current state of the art regarding management for hepatitis C and identified directions for future research. During the first day and a half, experts presented the latest hepatitis C research findings to an independent non-federal panel. After weighing all of the scientific evidence, the panel drafted a statement, which addressed the following questions:

1. What is that natural history of hepatitis C?
2. What is the most appropriate approach to diagnosing and monitoring infected patients?

3. What is the most effective therapy for hepatitis C?
4. Which patients with hepatitis C should be treated?
5. What recommendations can be made to patients to prevent transmission of hepatitis C?
6. What are the most important areas for future research?

On the final day of the conference, Dr. James Boyer, the panel chair, read the draft statement and invited the audience to comment. A press conference followed to allow the panel and chair to respond to questions from the media. The draft statement was posted on the consensus website <http://consensus.nih.gov> on Wednesday June 12, 2002, and the final draft will be posted on or about September 9, 2002.

Natural History of Hepatitis C

Hepatitis C is an RNA virus of the flaviviridae family. There are 6 HCV genotypes and more than 50 subtypes. The genotypes can differ by as much as 30% to 50% in their nucleotide sequences. The virus also has a high propensity to mutate. The lack of a vigorous T cell response appears to promote a high rate of chronic infection. Genotype 1 accounts for 70% to 75% in the U.S. and has a poorer response to treatment. During acute infection the viral load can range from 10^5 to 10^7 [IU/mL]. Chronic HCV levels are variable and can range from 50,000-5,000,000 IU/mL; however, within the same person, they are generally stable.

According to the National Health and Nutrition Examination Study (NHANES), conducted by the Center for Health Statistics (NCHS) at the CDC, it is estimated that there are over 2.7 million people in the U.S. living with chronic HCV infection. This may be an under-estimate, however, since the NHANES household survey did not include high prevalence populations such as incarcerated, homeless, or institutionalized persons. There are an estimated 35,000 new infections per year, and the prevalence in the U.S. is 1.8%. The highest prevalence is seen among adults aged 40 to 59 years and among African

Americans, who have a prevalence of 6.1%. Seroprevalence among inmates, the homeless, and hemophiliacs is 15% to 50%; among IDUs, it is 70% to 90%.

After initial exposure, HCV RNA can be detected in the blood at 1 to 3 weeks. Antibodies to HCV are detected by enzyme immunoassay (EIA) in approximately 50% to 80% of patients at the onset of symptoms, and this increases to 90% at three months. ALT levels are elevated at 2 to 8 weeks. Acute infection can be severe but is rarely fulminant.

Chronic HCV is defined by the detection of HCV RNA for at least 6 months. In general, prospective studies have suggested that approximately 80% of HCV infected patients develop chronic infection. Factors associated with spontaneous clearance of the infection include younger age, female gender, and certain histocompatibility complexes. African-Americans appear to be least likely to spontaneously clear the infection.

The major late sequelae of chronic infection is cirrhosis, which is seen in 20% to 25% after 20 years (in retrospective studies) and in 2% to 4% (in prospective studies). This risk is not influenced by viral load, viral genotype, or quasi species diversity. However, host risks for cirrhosis include longer duration of infection, older age, male gender, immunosuppression (HIV infection), HBV co-infection and alcohol use (defined as 40-60 g/day). Other factors include iron overload, nonalcoholic fatty liver disease, and hepatotoxic medications. One-third of patients with hepatocellular cancer (HCC) have HCV as a risk factor. HCC rarely occurs without cirrhosis or advanced fibrosis. The incidence of HCC is continuing to rise in the U.S. and worldwide. Extra hepatic manifestations of HCV include rheumatoid symptoms, keratoconjunctivitis sicca, lichen planus, glomerulonephritis, and essential mixed cryoglobulinemia and are thought to be of immunologic origin. Cryoglobulins have been found in up to one-half of patients with chronic HCV infection, but symptoms occur significantly less frequently.

continued on supplement page ii



Management of Hepatitis C: A Review of the NIH Consensus Development Conference

continued from page i

What is the Most Appropriate Approach to Diagnosis and Monitoring?

EIA tests are reproducible, inexpensive, and are approved by the FDA for the diagnosis of HCV. They are suitable for screening at risk populations, as they have a very high sensitivity and specificity (exceeding 99%). A negative EIA excludes the diagnosis in immunocompetent patients, but not in immunodeficient patients. False positives occur with autoimmune disorders, and these cases require HCV RNA for confirmation with RIBA.

Persistent HCV infection in a patient with a positive EIA should be confirmed with a PCR. The FDA-approved qualitative HCV PCR has a threshold detection of 50 IU/mL. Transcription-mediated amplification (TMA) has a lower threshold for detection, but is not approved by the FDA. Sensitivity of these assays is over 98%. Testing for HCV RNA can provide an accurate assessment of the HCV viral titer. Viral load (HCV RNA level) is measured by quantitative PCR (qPCR) or branched DNA (bDNA) and reported in international units (IU). Significant variability exists between available assays. While there is little correlation between disease severity or progression with the absolute titer of HCV RNA, determination of the quantitative HCV titer can provide important information in assessing the response to treatment.

Serum alanine aminotransferase (ALT) is the least expensive test to measure disease activity, but it does not correlate with severity of histopathology by liver biopsy. Serial measurements are recommended for monitoring, but do not assess progression to cirrhosis.

Liver biopsy provides information on fibrosis and histology assessment and information about concurrent liver disease due to other causes. It may help guide the decision regarding therapy: Absent or minimal fibrosis may encourage deferral, though the response with genotypes 2 or 3 is so good (80%) that routine pretreatment biopsy is sometimes considered unnecessary.

Hepatocellular cancer screening is not well studied in HCV patients. While the incidence of HCC is 0% to 3% per year after the onset of cirrhosis, no study

has been able to identify a screening or surveillance protocol that improved long-term survival. One study evaluating alpha-fetoprotein and ultrasound every six months in patients with HCV showed earlier detection of HCC, but no survival analysis was performed. Therefore, further studies are needed to identify the most appropriate HCC screening protocols.

What is the Most Effective Therapy for Hepatitis C?

Since the 1997 NIH Consensus Development Conference on Management of Hepatitis C, many new therapies have been identified. Combination therapy results in better treatment responses than monotherapy. The highest response rates have been found with pegylated (PEG) interferon in combination with ribavirin. Genotype determinations influence treatment decisions as genotypes 2 and 3 have much higher response rates than genotypes 1 and 4.

The best indicator of effective therapy is "sustained virological response" (SVR), defined as the absence of qualitative HCV RNA by RT-PCR after 24 weeks of treatment. The highest response rates have been demonstrated in the trials with PEG-interferon plus ribavirin. Of note, these trials excluded patients with decompensated liver disease, cirrhosis, and other medical co-morbidities.

• **Initial Treatment:** SVR results are similar for PEG-interferon alpha 2A or alpha 2B when each is combined with ribavirin. Results of three large pivotal studies are summarized below:

	SVR
Genotype 1	42-51%
Genotype 2-3	76-82%

In all three trials, the SVR for genotype 1 was based on higher doses of PEG-IFN and ribavirin for 48 weeks.

Treatment for 24 weeks with lower dose ribavirin appears adequate for genotypes 2 and 3. Early viral response (EVR) is defined as a two-log decrease in viral load. EVR at 12 to 24 weeks of treatment predicts SVR, and those who fail to achieve EVR have little probability of achieving SVR even if therapy

is continued a full year. Of note, SVR has not yet been correlated with improved survival. However, longer-term follow-up of these patients is currently in progress.

• **Re-treatment:** Decisions regarding re-treatment should be based on the following:

1. Previous type of response.
2. Previous therapy and the difference in potency of new therapies.
3. Severity of underlying liver disease.
4. Viral genotype and factors predictive of response.
5. Tolerance of and adherence to prior therapies.

Definition of Previous Treatment Response

1. Relapsers are defined as patients who achieved an "end of treatment response" (ETR) that is not sustained over time. In these patients, re-treatment with standard interferon using the same regimen is generally unsuccessful. The use of PEG-interferon plus ribavirin in a patient previously treated with interferon monotherapy has not been evaluated. When a new regimen of the standard drugs (such as higher dose or longer duration of standard interferon plus ribavirin) is used in a patient previously treated with interferon alone, re-treatment is more effective in those who have relapsed compared with those who failed to respond.

2. Non-responders are defined as those who fail to achieve EVR, ETR or SVR. Preliminary data suggest that 15% to 20% of these patients who have received treatment with standard interferon and ribavirin will achieve SVR with re-treatment with PEG-IFN and ribavirin. Patients with genotypes 2 or 3 have better response rates to re-treatment than those with genotype 1.

3. Partial responders are a subset of non-responders who have a viral load reduction of 1-2 \log_{10} c/mL during treatment. Re-treatment of these patients may be associated with improved histology despite absence of SVR.

Other factors in the decision for re-treatment include the severity of liver disease, since those with advanced fibrosis or cirrhosis should be considered a higher priority for re-treatment. The possible role of maintenance therapy using PEG-interferon monotherapy in patients with advanced fibrosis or cirrhosis is



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currently being studied in the HALT-C trial; however, this strategy is considered experimental until these results are available.

Side effects are severe enough to require discontinuation in 20% of patients in the PEG-interferon and ribavirin registration trials. The most common side effects are influenza-like symptoms, bone marrow suppression, and neuropsychiatric symptoms. Often these side effects can be adequately treated with growth factors and antidepressants.

Indications For Treatment

All patients with chronic hepatitis C are potential candidates for antiviral therapy. The major indication for treatment is the risk for progression to cirrhosis based on measurable HCV RNA and liver biopsy showing portal or bridging fibrosis and at least moderate inflammation and necrosis. Age and prior behavior should not be factors in the decision to treat. Modifying circumstances include:

- **Normal ALT:** Thirty percent of patients with chronic HCV have a normal ALT, and an additional 40% have elevated levels that are less than two times the upper limit of normal (ULN). Currently, “experts differ on the indications for biopsy and treatment” and studies are underway to identify patients most likely to benefit from treatment. Notably, studies of PEG-interferon and ribavirin have not been completed in patients with normal ALT levels.

- **Biopsy results:** In patients with elevated ALT and no fibrosis plus minimal inflammation, the current recommendation is to monitor liver function tests and potentially to repeat the liver biopsy in 3 to 5 years. In patients with advanced liver disease (advanced fibrosis or compensated cirrhosis), sub-group analysis of studies to date have shown lower rates of SVR. However, this group of patients is being evaluated in the HALT-C trial, which should provide recommendations on re-treatment. In patients with decompensated cirrhosis, the main treatment is transplantation. Although re-treatment should be considered, this approach may be limited by potentially life-threatening side effects of antiviral therapy.

- **Acute HCV:** Currently the data available are inadequate for making a recommendation.

- **Injection drug users:** Data are available for treatment of HCV-infected IDUs who are in drug treatment programs. These studies show success even with continued drug use or with concurrent methadone treatment. Therefore, efforts should be made to promote collaboration between HCV experts and substance abuse providers. It should be noted that there are few data available on HCV treatment in active IDUs who are not in drug treatment programs.

- **HIV coinfection:** All HIV infected patients should be screened for HCV. Coinfection accelerates the course of HCV and HIV. Although there are no HCV therapies specifically approved for patients with HIV, these patients should be considered for treatment. Thus far, studies have only enrolled patients with stable HIV infection and well compensated liver diseases. However, in these patients, SVR can be achieved, and preliminary data suggest better responses to PEG-interferon with ribavirin than to standard interferon and ribavirin. Although treatment of HCV has not jeopardized control of HIV infection, additional studies are needed to further evaluate this possibility.

- **Alcohol:** Continued use of alcohol adversely affects outcome of treatment. Currently, treatment of HCV should be performed in conjunction with efforts to treat alcohol dependence. Heavy alcohol use (>80 g/day) seriously compromises HCV treatment; therefore, HCV treatment should be combined with abstinence whenever possible.

Reduction In Transmission

Injection drug use accounts for over two-thirds of new infections; therefore, it is assumed that drug rehabilitation and needle exchange programs should reduce transmission. Sexual transmission appears to be infrequent based on a seroprevalence of only 2% to 3% in partners of HCV-infected persons in long-term monogamous relationships and 4% to 6% among persons with multiple sex partners, sex workers and those at risk for sexually transmitted diseases. For heterosexual discordant couples, the estimated risk of

transmission in this setting is 0% to 0.6% per year, with the risk to females being three-fold greater than to male partners. Use of condoms may decrease HCV transmission and should be encouraged, especially for those at risk for other sexually transmitted diseases. The risk of occupational exposure with a needle stick injury from an HCV-infected source is about 2% and currently postexposure antiviral therapy is not recommended. Perinatal transmission is approximately 2% for infants from an HIV infected mother and is higher with high maternal viral load, injection drug use (10%), and with HIV co-infection (20%). Ribavirin and interferon are contraindicated during pregnancy and there are no data on Caesarean section and the risk of transmission. Breastfeeding does not appear to transmit HCV. Low transmission rates (less than 1%) are associated with body piercing and tattooing.

Conclusions

The panel recommended that the NIH establish a Hepatitis Clinical Research Network. The goal of this network should be to conduct research related to the natural history, prevention, and treatment of hepatitis C. In addition, they recommended organizing randomized controlled trials to extend treatment to special populations not represented in current trials to determine the applicability of current antiviral combinations in those with acute hepatitis, hemophilia, stabilized depression, and HIV co-infection, as well as in IDUs and alcoholics. Such an effort should lead to decreased HCV related morbidity and mortality as well as a decrease in the reservoir of disease.

Comment from authors: This summary is based on the draft guidelines. There may be changes to the final version, but we expect that they will be minor, particularly with regard to treatment issues. Issues of particular interest and controversy are diagnostic testing and the proper duration of treatment for genotype 1 infections. Many of the initial trials used 48 weeks if the EVR showed good viral response at 12 to 24 weeks; however, the ideal treatment duration has not been defined. ▲



Drug Profile

By Paul Pham, Pharm.D., BCPS

PEG-interferon 2b (PEG-Intron)

Manufacturer: Schering Corporation

Formulation/Price (AWP): \$240 to \$278 per week. 50 mcg/0.5 mL @ \$240; 80 mcg/0.5 mL @ \$253; 120 mcg/0.5 mL @ \$265; 150 mcg/0.5 mL @ \$279.

FDA Indication: PEG-interferon b monotherapy is indicated for the treatment of compensated chronic hepatitis C not previously treated with interferon alpha.

Pharmacology and Pharmacokinetics:

- **Absorption:** Approximately 20 hours after a subcutaneous injection
- **C_{max}:** 554 pg/mL after peginterferon 1mcg/kg SQ. C_{max} occurs between 15 to 44 hours post-dose and is sustained for up to 48 to 72 hours.
- **C_{min}:** 94 pg/mL at week 4 and 320 pg/mL at week 48.
- **Volume of distribution:** Approximately 1 L/kg (similar to non-pegylated interferon). PEG-interferon has approximately 10-fold greater C_{max} and 50-fold greater AUC compared to non-pegylated interferon 2b.
- **Half-life:** 40 hours (range 22 to 60 hours), 5-fold greater mean half-life due to decreased clearance compared to non-pegylated interferon.
- **Renal elimination:** Approximately 30%
- **Dose reduction** to 0.5 mcg/kg recommended for absolute neutrophil count (ANC) <750/mL or platelet count <80,000/mL.

Usual Dose: 1 mcg/kg q week

- **Weight based dosage recommendation*:**

37-45 kg	40 mcg per week
46-56 kg	50 mcg per week
57-72 kg	64 mcg per week
73-88 kg	80 mcg per week
89-106 kg	96 mcg per week
107-136 kg	120 mcg per week
137-160 kg	150 mcg per week

Dosage in Renal Failure: Consider reducing dose to 0.5 mcg/kg in patients with creatinine clearance less than 50 mL/min (Recommendation based on pharmacokinetic studies with limited clinical data).

Drug Interactions: None known.

Side Effects:

- **Common:** Flu-like symptoms, headache, dizziness, fatigue, fever, rigor, injection site inflammation, depression (29%), insomnia, alopecia, GI (abdominal pain, anorexia, nausea/vomiting/diarrhea).
- **Occasional:** Thrombocytopenia, neutropenia, hypo and hyperthyroidism, elevation of liver enzyme 2- to 5-fold above baseline.
- **Rare:** Hallucination, hyperglycemia, cardiovascular events, ulcerative and hemorrhagic colitis, pancreatitis, pneumonitis, retinal hemorrhage, cotton wool spots and hypersensitivity reaction.

Pregnancy Risk: Category C. Abortifacient in rhesus monkeys. No human data. Recommend that patients use an effective form of contraception during treatment with interferon. Breastfeeding: No data.