HIV JournalView

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It's Official: Once-Daily Atazanavir Effective in Naive Patients

Squires K, Lazzarin A, Gatell JM, et al. *Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV*. ***J Acquir Defic Syndr. August 15, 2004;36(5):1011-1019.***

It's always good to see the publication of data that led to the approval of an HIV medication. This paper presents data from one of the major studies that led to the U.S. Food and Drug Administration's approval of the HIV-1 protease inhibitor (PI) atazanavir (ATV, Reyataz) on June 23, 2003.

This was an international, randomized, double-blind, 2-arm, comparative study in treatment-naive patients. The 2 arms of the study were efavirenz (EFV, Sustiva, Stocrin) 600 mg or atazanavir 400 mg given orally once daily plus fixed-dose zidovudine/lamivudine (AZT/3TC, Combivir) given orally twice daily for 48 weeks. The primary endpoint was the number of treated patients who achieved a plasma viral load < 400 copies/mL at 48 weeks. The secondary endpoint was the number of patients who achieved a plasma viral load < 50 copies/mL at 48 weeks. Patients were stratified 1:1 by baseline viral load (< 30,000 vs. > 30,000 copies/mL). Safety, tolerability and toxicity were also monitored throughout the study.

Of the 810 randomized patients, 805 began therapy (404 atazanavir, 401 efavirenz) and 144 discontinued therapy before week 48 (20% of the efavirenz arm and 16% of the atazanavir arm). The median patient age was 33, with two thirds being male and one third being white in both arms. Median viral load and CD4+ cell count were 4.88 $\log_{10}$/mL and 282 cells/mm^3, respectively, with no difference between arms.

The results revealed that serious adverse events were evenly distributed between arms -- except for jaundice, scleral icterus and hyperbilirubinemia, which were seen more frequently in the

atazanavir arm, and dizziness, which was seen more frequently in the efavirenz arm.

In general, total cholesterol, low-density lipoprotein cholesterol and fasting triglycerides were more significantly elevated in the efavirenz arm compared to the atazanavir arm. The CD4+ cell increases were similar in each arm (160 vs. 176 in the efavirenz and atazanavir arms, respectively). In addition, patient viral load responses were not significantly different between arms (64% vs. 70% in the efavirenz and atazanavir arms, respectively, achieved < 400 copies/mL, and 37% vs. 32% in the efavirenz and atazanavir arms, respectively, achieved < 50 copies/mL).

The surprisingly small number of patients who at 48 weeks achieved undetectable viral loads at the < 50 copies/mL level -- given the potency of these regimens -- prompted further investigation.

Blood had been collected in plasma preparation tubes (PPT) and standard EDTA Vacutainer blood collection tubes. The original viral load results were produced from blood plasma collected in PPT tubes. Reanalysis of the data from standard EDTA tubes revealed consistently lower viral loads than those from PPT tubes: 89% of the blood plasma collected with EDTA tubes, compared to 55% of the PPT samples, had viral loads that were < 50 copies/mL. The researchers theorize that part of this difference may be the result of different centrifugation parameters (time and g-force) used in the processing of each kind of tube type. EDTA tubes are spun twice as long (20 minutes) as PPT tubes and g-force can vary between 800-1600g. PPT tubes are spun for 10 minutes at 1100g. These factors can alter the amount of cellular debris and platelet-associated virus contained in presumably cell-free plasma, and could affect viral load quantitation. A considerable amount of discussion and reanalysis of the results was devoted to this phenomenon in this paper. For general practitioners it is a useful reminder that viral load results may be different depending on what kind of blood tube the sample was collected in.

Although unintended, this is the first published report highlighting the blood collection tube controversy. It has touched off a firestorm regarding what should be the appropriate blood collection for both future clinical trials and routine clinical practice. Further real-time comparative studies will be necessary to determine any actual differences in viral load results from plasma collected in the 2 tube types and whether these differences are truly clinically significant.

This study clearly demonstrated the effectiveness of once-daily atazanavir-containing regimens in drug-naive patients. Atazanavir's side effect profile is limited primarily to the consequences of hyperbilirubinemia and does not appear to result in the hyperlipidemia that has been associated with other PIs. Atazanavir can also be used with low-dose ritonavir (RTV, Norvir) to boost atazanavir levels, particularly in patients with prior PI experience. Although not presented in this paper, atazanavir has a unique signature mutation (50L) in the protease gene in antiretroviral-naive patients who have failed atazanavir-containing regimens; this mutation does not appear to affect the activity of other PIs.

High Success for Sperm Washing in Preventing HIV, Hepatitis C

Garrido N, Meseguer M, Bellver J, Remohi J, Simon C, Pellicer A. *Report of the results of a 2 year programme of sperm wash and ICSI treatment for human immunodeficiency virus and hepatitis C virus serodiscordant couples****. Hum Reprod. 2004; epub- August 19, 2004.***

How does a man with HIV, hepatitis C (HCV) or both have a child with an uninfected woman? Many serodiscordant couples have been reluctant to reproduce because of the risk of transmitting these viruses to their partner or to the fetus. In the United States, liability issues have mostly steered reproductive specialists away from working with such couples, although in recent years there are a growing number of clinics offering help. In 2002, the Ethics Committee of the American Society for Reproductive Medicine[1] released new reproductive guidelines for HIV-infected people and discordant couples. The guidelines mention the use of sperm washing for HIV/HCV-infected men and HIV testing of the washed sperm.

Outside the United States, several groups have been using techniques for sperm washing in the hopes of reducing or eliminating the risk of HIV/HCV transmission through conception. This paper from a Spanish group in Valencia, Spain, reports on their in vitro fertilization (IVF) program in which men with HIV, HCV or both infections underwent sperm washing and harvested oocytes (eggs) underwent intracytoplasmic sperm injection (ICSI) before they were implanted.

Ninety-one seropositive males and seronegative female partners were included in this study. The

study was approved by the local institutional review board.

Oocytes were obtained from either the female partner or normal healthy young egg donors. Semen was obtained after sexual abstinence for 3-5 days. The sperm were pelletized after centrifugation and washed in media several times. The sperm were then allowed to "swim-up," a process by which sperm will swim up to the top of a liquid gradient. Half of this sample was stored in liquid nitrogen for subsequent ICSI and half was retained for PCR testing for the presence of HIV and HCV.

HIV RNA was found in 2/26 of the patient samples from the men who were infected only with HIV. No HIV DNA was found. HIV RNA and DNA were found in 4/52 and 2/52 HCV co-infected patient samples, respectively. Only samples that were PCR negative were subsequently used for ICSI. Injected oocytes were assessed for fertilization and embryos were then transferred to the uterine cavity 48-72 hours after ICSI.

Forty-one pregnancies were achieved, although only 23 babies were born. None of the infants or impregnated female partners has seroconverted for either HIV or HCV infection. Although still controversial in regards to U.S. government policy, etc., this study, as others have shown before, demonstrates that, through the process of sperm washing and ICSI, serodiscordant couples in which the male partner is infected can have uninfected children without infecting the mother. The question remains, when will most U.S. assisted reproduction clinics feel comfortable helping serodiscordant couples.

Long-Term Resistance Patterns on Enfuvirtide

Menzo S, Castagna A, Monachetti A, et al. *Genotype and phenotype patterns of human immunodeficiency virus type 1 resistance to enfuvirtide during long-term treatment****. Antimicrob Agents Chemother. September 2004;48(9):3253-3259.***

Enfuvirtide (T-20, Fuzeon) was approved March 13, 2003 as the first compound in the antiretroviral class known as fusion inhibitors. This synthetic peptide binds to the gp41 region of the HIV-1 envelope and prevents conformational changes in this envelope that are necessary for the virus to bind (fuse) with a cell.

Enfuvirtide must be injected twice daily. All the major enfuvirtide studies show the drug to be effective in significantly lowering viral load in patients who have failed previous highly active antiretroviral therapy (HAART) regimens, provided that their practitioners were able to provide at least 1-2 other antiretroviral agents that still had activity in an optimized background (TORO 1 and 2 trials).

Genotypic and phenotypic resistance to enfuvirtide have been previously reported in vitro and in patient viral strains. Mutations located in the gp41 heptad repeat region have been associated with loss of enfuvirtide susceptibility. Other results, reported at the International AIDS Conference in Bangkok this summer, indicate that mutations found in other regions in the envelope gene are associated with a higher failure rate with enfuvirtide-containing regimens.

This study evaluated 11 patients who had been treated with enfuvirtide for over 1 year. These patients (4 responders and 7 virologic nonresponders) had been enrolled in the TORO 2 trial.

Population sequencing was performed in the gp41 region, evaluating codon 26 to 140. Infectious molecular clones from patient-derived sequences were then produced to evaluate susceptibility and replication capacity (RC). Most of the mutations clustered between amino acids 36 to 45, with mutations at codon 38 being more common. Single or multiple mutations in this region resulted in > 100 fold change increase in inhibitory concentration required to inhibit 50% viral growth. Mutations associated with the greatest reduction in susceptibility included V38A, Q41R, N42D/T, N43D, L44M and L45M.

Two patients stopped enfuvirtide and follow-up samples 2-3 months later demonstrated reversion of mutations back to wild type and return of phenotypic susceptibility. In a homebrew RC assay, 4 of 7 subject strains demonstrated a reduction of RC to varying degrees. However, the number of patients studied was too small to make any firm conclusions as to which codon changes affect RC to a greater degree.

This study confirms previous reports about the importance of changes at codons 36-45 in the gp41 in correlating with virologic failure and conferring phenotypic resistance to enfuvirtide. The

impact on RC needs to be further defined. It was also interesting to see reversion back to wild type after discontinuation of enfuvirtide. This is the first report of this with fusion inhibitors and mirrors what is seen with the RT and PR genes after a structured treatment interruption with conventional HAART.

Unfortunately, current genotypic and phenotypic assays used in clinical practice are not designed to evaluate enfuvirtide mutations or susceptibility. Thus, practitioners cannot evaluate baseline or subsequent samples in those patients who have failed enfuvirtide-containing regimens. However, research-associated assays currently being employed in studies such as the one reported here, will provide important background information regarding the significance of various gp41 mutations as clinically available enfuvirtide resistance assays come on line.

Primary Drug Resistance Can Persist a Year or More

Barbour JD, Hecht FM, Wrin T, et al. *Persistence of primary drug resistance among recently HIV-1 infected adults*. ***AIDS. August 20, 2004;18(12):1683-1689.***

As more patients fail successive HAART regimens and continue to practice unsafe sex or injection drug use, transmission of antiretroviral drug-resistant HIV-1 strains will continue to be an ever-increasing problem. Recent reports have indicated that the presence of antiretroviral resistance can persist at least for several months with some reversion to wild type in the absence of antiretroviral treatment. This is important because it has prompted changes in national guidelines for resistance testing -- namely, the indication for resistance testing has been modified to include that people who have been infected for up to 2 years should be required to undergo resistance testing prior to HAART initiation.

Using a detuned HIV-1 EIA assay, 22 patients with acute infection in the San Francisco, Calif. area were identified within about 60 days of infection. Resistance was assessed by population sequencing, phenotype (PhenoSense) and RC (using a modified PhenoSense assay). Six of the 22 patients had evidence of antiretroviral phenotypic resistance with the following results: 3/22 to PIs, 4/22 to nucleoside reverse transcriptase inhibitors (NRTIs) and 3/22 to non-nucleoside reverse transcriptase inhibitors (NNRTIs). All had corresponding evidence of genotypic resistance. Further evaluation revealed NNRTI resistance alone in 2/6, NRTI resistance alone in 1/6 and 3/6 had evidence of 2 or more classes of antiretroviral resistance.

Median baseline RC for the whole group was 85% of control, but tended to be lower in those with genotypic resistance (38% vs. 110%, $P = .07$). There was no loss of PI or NNRTI resistance during the 12-month observation period. Three patients showed a decline or loss of phenotypic resistance to NRTIs (1 to lamivudine [3TC, Epivir] and 2 to zidovudine [AZT, Retrovir]). In those patients without evidence of resistance, RC remained at high control levels.

This study further demonstrates that transmitted virus with evidence of antiretroviral resistance can persist for a year or longer after acute infection. The current U.S. Health and Human Services guidelines on antiretroviral treatment[2] suggest that resistance testing should be performed in treatment-naive patients even up to 2 years after acute infection. Longer observational studies are required to see whether detectable antiretroviral-resistant virus persists even longer. Many chronically infected patients who do not manifest evidence of antiretroviral-resistant virus may in fact have had a mixture of wild type and resistant virus transmitted to them. However, in the absence of antiretroviral drug pressure, wild type strains will out compete resistant virus, which will no longer be detectable by conventional resistance assays. There are isolated case reports, however, in which patients received only antiretroviral-resistant viral strains that demonstrated persistence up to 2 years after infection without evidence of wild-type virus emerging.

Many Patients Remain Stable Despite Persistent Low-Level Viremia

Re VL, Gasink L, Kostman JR, Leonard D, Gross R. *Natural history of patients with low-level HIV viremia on antiretroviral therapy*. ***AIDS Patient Care and STDs. August 2004;18(8):436-442.***

Most patients demonstrate significant virologic responses after initiating HAART and maintain undetectable HIV-1 viral loads (defined as < 50 copies/mL). Others experience virologic rebound that is correlated with the development of antiretroviral resistance.

For both groups of patients, we know how to respond. However, there remain 2 subsets of

patients for whom we're still not too sure what's going on and how to respond. These are patients who experience virologic blipping (intermittently detectable low viral loads) and patients who maintain stable low-level viremia (between 50-500 copies/mL). This study examines the later group. The concern has always been that this low level of viral load (and hence evidence of ongoing viral replication) would subsequently lead to the development of resistance and virologic failure. This study analyzes a cohort of patients who had low-level viral loads and takes a look at whether these patients demonstrated virologic failure at follow-up.

Patients were included if they were on a stable antiretroviral regimen and had a viral load between 50-500 copies/mL for at least 3 months prior to and at study entry. The main outcome of this study was the proportion of patients whose viral loads increased to over 1000 copies/mL over the study period.

Seventy-nine subjects were originally included. Five changed antiretroviral regimens during the course of the study. The median patient age was 47 years, 56% were African-American and 84% were male. The median viral load and CD4+ cell count at entry were 139 copies/mL and 455 cells/mm^3, respectively. The median follow-up was 693 days.

A virologic increase to > 1000 copies/mL was seen in 29/79 (37%) of the patients at a median time of 357 days. An additional 30/79 (38%) were undetectable (< 50 copies/mL) at their last follow-up visit. After 3 years of follow-up, 40% of the patients with detectable viral loads had still not reached a viral load of > 1000 copies/mL. To determine the risk factors associated with virologic rebound, Cox proportional hazard models were used and determined that the only factors associated with rebound were white race and viral load level at study entry. CD4+ cell count, whether patients were receiving HAART or non-HAART regimens, and other demographic factors did *not* appear to be associated with viral load rebound.

This small study indicates that there is a significant subset of patients with low, detectable viral loads that will either revert back to undetectable levels, or maintain low levels without rebound for at least as long as 3 years.

It is understandable that those patients with viral loads closer to 500 copies/mL would be more likely to demonstrate further viral load increases above 1000 copies/mL (only a 2-fold increase) than those closer to 50 copies/mL. What role white race plays in the increased frequency of viral load rebound is not clear.

Many practitioners have patients in this situation. It is always a dilemma about whether to change an antiretroviral regimen or continue to observe without changing antiretrovirals in this situation. Most commercial laboratories will not perform resistance testing on samples with such low viral loads, so it is difficult to assess whether resistance development is a major issue here. Although this study gives some comfort in knowing that some patients will remain stable on their current regimen, more studies are needed to better predict what variables are associated with those who will rebound and those who will not.

Using Suction-Assisted Lipectomy to Treat Buffalo Hump

Connolly N, Manders E, Riddler S. *Short communication: suction-assisted lipectomy for lipodystrophy*. ***AIDS Res Hum Retroviruses. August 2004;20(8):813-815.***

One of the most disfiguring of all the HAART-related side effects is lipodystrophy, which can manifest as lipoatrophy or lipoaccumulation in different regions of the body. Since there are few treatments for this adverse effect, the only solution has been to switch patients off the drug causing it.

This report is on a small case series of 6 patients who all had evidence of lipohypertrophy, manifested as cervicodorsal fat accumulation or "buffalo hump." This manifestation, although not as common as visceral fat accumulation, can result in localized pain and clearly can affect a patient's sense of well-being.

The 6 patients underwent suction-assisted lipectomy (SAL) of the affected region. These patients were all male, ranging in age from 35 to 53, were all receiving HAART, had very low or undetectable viral loads and had CD4+ cell counts ranging from 258 to 1130 cells/mm^3.

No complications were associated with the SAL procedure, and none of the patients have had a recurrence of their buffalo hump after 12 months of follow-up.

Thus, in addition to surgical resection of excess adipose tissue, which has previously been reported to successfully eliminate fat as a result of lipodystrophy, SAL may prove to be a useful alternative procedure in those patients with significant lipohypertrophy.

Exogenous Growth Hormone, an Expensive (and Questionable) Fat Accumulation Treatment

Lo JC, Mulligan K, Noor MA, et al. *The effects of low-dose growth hormone in HIV-infected men with fat accumulation: a pilot study*. ***Clin Infect Dis. September 1, 2004;39(5):732-735.***

Other strategies have also been explored to reduce the amount of visceral adipose tissue (VAT) resulting from lipoaccumulation in those patients with HAART-associated lipodystrophy. Administration of exogenous growth hormone (GH) has been reported in several case series and in randomized trials to result in a significant reduction in VAT. However, doses of 3-6 mg/day result in significant problems associated with glucose metabolism. The current pilot study was designed to determine if smaller doses of GH could achieve the desired VAT effect while not disturbing glucose regulation.

Five patients on stable HAART regimens, with manifestations of increased abdominal girth and buffalo hump, were enrolled to receive 1 mg per day subcutaneously of GH for 6 months. Patients with diabetes were excluded.

Numerous metabolic studies and anthropometric and imaging studies were conducted at baseline, 1 month and 6 months. As a group, total body fat and truncal fat decreased and lean body mass increased significantly as measured by dual energy x-ray absorptiometry scanning. VAT decreased in 3 patients and increased slightly in 2 patients as measured by abdominal computerized tomography. Although insulin growth factor 1 levels increased significantly and there was a trend toward decreased glucose tolerance, there were no significant changes in fasting lipids, glucose and HbA1C levels, or insulin sensitivity. Based on historical control patients, there appears to be a dose response to the amount of GH given versus loss of VAT. This pilot study demonstrated the potential utility of using low-dose GH in reducing truncal fat and minimizing the effects on glucose metabolism in at least some patients. Whether this will be a useful long-term strategy for treating HAART-associated VAT accumulation remains to be seen. It's extremely expensive, was not as successful as higher doses and still caused glucose problems in some patients.

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