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The Seattle Treatment Education Project's (STEP) EZINE is an electronic treatment resource newsletter distributed monthly to case Managers, front-line workers, people affected by HIV/AIDS, physicians, other public health and allied health professionals and people living with HIV/AIDS.
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# More Once-Daily Antiretroviral Options

Numerous studies have now shown that very high levels of adherence are necessary for adequate HIV suppression. The ideal antiretroviral (ARV) regimen is simple, effective, and well tolerated. An increasing number of approved once-daily regimens are being used to minimize pill burden and optimize adherence. There is already data showing the efficacy of once-daily dosing of Videx, Epivir, Viread, Viramune, Sustiva, Fortovase/Norvir and Agenerase/Norvir.

Posters at the Ninth Retrovirus Conference supply data in support of once-daily dosing for a new formulation of Zerit (d4T) (Abstract 411, 416), additional support of once-daily Fortovase/Norvir (Abstract 441), and new data on once-daily dosing of Kaletra (Abstract 409). There were also several studies using newer, not yet approved, antiretrovirals such as atazanavir (a protease inhibitor) and DPC 083 (an investigational non-nucleoside reverse transcriptase inhibitor) as part of a once-daily highly active antiretroviral therapy (HAART) regimen.

A large, Phase II, placebo controlled, prospective study of 783 people compared an extended-release formulation of Zerit (d4T XR) dosed at 100 mg once daily to the currently available formulation of immediate-release Zerit (Zerit IR) dosed at 40 mg twice daily (Abstract 411). The Zerit was used as part of a HAART regimen of Epivir (150 mg twice daily) and Sustiva (600 mg once daily). At the start of the study, it was determined that Zerit XR blood levels were just as high as those seen with Zerit IR (Abstract 416). A 24-week interim analysis of the planned 48-week study was reported at the Retrovirus Conference. Virologic and immunologic responses were nearly identical in the Zerit XR and IR groups. The safety, tolerability and efficacy profiles of Zerit XR also appear comparable to that of Zerit IR. This data will likely result in the approval of once-daily Zerit XR in the next year if the results are maintained at the 48 week analysis.

Once-daily regimens using the combination of Fortovase and Norvir (at 1600 mg and 100 mg) have been previously studied with promising results. However, the combination of Fortovase with Sustiva once daily is discouraged because of the induction of Fortovase metabolism. L. López-Cortéz studied the safety, efficacy and blood levels of Fortovase (1200 mg) with Sustiva (600 mg) with the addition of Norvir (100 mg) to see if a once-daily nucleoside reverse transcriptase inhibitor (NRTI)-sparing regimen, using these drugs, was feasible in people in whom NRTIs were withdrawn because of adverse events (Abstract 441). All people were NRTI and protease inhibitor experienced. All 22 people who entered the study with an undetectable VL remained undetectable, and 13 of the 20 people with a high viral load became undetectable. At 52 weeks, a total of 71 percent of the people had a viral load below 50 copies with a median CD4 cell count increase of 215 cells.

Treatment had to be withdrawn in only one case, due to hepatitis. This regimen may be an effective once-daily alternative for people for whom NRTIs are no longer a good option.

Although once-daily regimens have been shown to be effective for the Fortovase with Norvir and Agenerase with Norvir combinations, additional once-daily protease inhibitor regimens are needed. Kaletra (Lopinavir and Norvir at 133 mg and 33 mg) is currently being prescribed at a dose of 400 mg/100 mg (3 pills) twice daily. In a pilot study of 38 people, a once-daily Kaletra dose of 800 mg/200 mg (6 pills) was compared with the standard twice-daily dose as part of a HAART regimen with Zerit and Epivir (Abstract 409). Comparable virologic responses were achieved in the once-daily and twice-daily arms and there were similar CD4+ cell count increases of approximately 240 cells, as well. Although the efficacy and safety results were similar in both groups, there were less consistent Kaletra drug levels with once-daily dosing (Abstract 126). Larger studies are needed before this once-daily regimen is accepted.

One major concern about once-a-day dosing is that if a person skips a dose, they go a whole day without sufficient drugs in the blood to suppress HIV replication, whereas if they miss one dose of a twice-a-day regimen, they go only 12 hours before the next dose. Additional data is needed to determine if missing one dose of a once-daily HAART regimen will allow HIV replication and more frequent failure rates.

## Viral Blips and Virologic Failure

Intermittent episodes of low-level viremia (viral load “blips”) are often observed in people on highly active anti-retroviral therapy (HAART) with a suppressed viral load (HIV RNA below 50 copies). An increased frequency of blips is associated with a slower fall in the viral load (VL) and an increase in the number of viral mutations, but as of yet viral blips have not been associated with subsequent virologic failure (Abstract 532).

Dr. Diane Havlir has previously published in JAMA that VL blips do not predict virologic failure in people with limited or no prior antiretroviral experience. At the Ninth Retrovirus Conference, Dr. Havlir analyzed two ACTG salvage therapy trials to determine whether blips in the VL are associated with virologic failure in antiretroviral-experienced people (Abstract 93). A viral blip was defined as a VL of more than 50 copies in a patient who was previously suppressed, followed by a subsequent VL of less than 50 copies. Virologic failure was defined as two consecutive measures of VL above 200 copies.

In ACTG 398, 25 percent of people who had a VL below 50 copies were observed to have at least one blip. The median blip was 81 copies, and only 7 of the 41 people had blips in their VL over 500 copies. The CD4+ cell count at 48 weeks was similar in subjects who did and did not experience blips. Viral blips also were not associated with baseline drug resistance or virologic failure. Virologic failure was, on the other hand, associated with the failure to suppress HIV DNA to below 50 copies and drug treatment interruptions. Similar results were observed in the other salvage therapy trial, ACTG 359. These two studies demonstrate that highly treatment-experienced subjects can tolerate blips without HIV progression. Treatment changes are, therefore, not always necessary for transient low-level viremia, since blips in the VL is not synonymous with virologic failure. However, trials with longer follow-up are necessary to better clarify the significance of these observed viral blips.

M. Di Mascio analyzed the dynamics of viral blips during HAART therapy in123 previously treatment-naïve people (Abstract 94). More than 75 percent of the participants had at least one blip during the period of observation, with a mean of 165 copies. People were found to have different tendencies to have viral blips and the frequency of an individual to blip over time remained constant. People who had more consecutive blips also had a higher frequency of blips overall. Two consecutive blips are

thought more likely to represent two independent episodes of incomplete viral suppression rather than one prolonged period with increased viremia.

In conclusion, the authors felt that viral blips were not associated with the amount of time on HAART and therefore could not be explained by a decrease in drug adherence rates as was originally thought. Although viral blips should probably still spark discussions about drug adherence, it appears that they represent a random process that can occur even if people are completely adherent to their HAART regimen. New theories behind the causes of these blips were subsequently proposed. These blips may be a result of variable drug concentrations in the blood over time or periods of immune activation that stimulate HIV replication. Di Mascio speculated that the "intermittent viremic episodes might reflect a random, massive release of HIV virions (viruses) from one compartment [within the body], followed by transport to another [compartment] where they are more quickly cleared."

**Dr. Lara Strick is a member of STEP's Board of Directors, and is completing her residency in internal medicine at the University of Washington.**

# POZ in the City

## a community meeting

### *A forum for HIV-positive men.*

STEP, POZ Seattle and Lifelong AIDS Alliance invite you to a community meeting with featured speaker Dr. Tony Mills, former International Mr. Leather and well-known physician from LA. Dr. Mills will share his experiences as and 'out' HIV-positive man.

He'll also facilitate discussions identifying the challenges and solutions for HIV-positive men who want a healthier and happier future in 2002 and beyond. Topics will include prevention strategies related to sex, drugs, hard bodies and everything else in between.

This community meeting will take place at the new LGBT Community Center on 1115 Pike Street, between 11 and 12 Ave. on May 23rd. Time: 6:30 to 9:00pm.

For more information call STEP at 206- 329-4857 or 329-0064 x 105

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- Please note that this is not a complete list of all HIV-related treatment information. STEP strives to provide the very latest in HIV treatment information, research and drug development information. The most current research directions and antiretroviral drug data are provided throughout the Ezine publications. You will find highlight reports as well as extensive follow-up reports from many of the AIDS research and science conferences on the Ezine. In addition, all STEP quarterly treatment journals are available on our Web site at http://www.thebody.com/step/steppage.html or by calling our Talkline at 1-877-597-STEP. STEP works hard to give unbiased treatment information to all interested parties. If you have comments, questions, suggestions or grievances, please contact robertog@stepproject.org or ezine@stepproject.org.

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