Efficacy of Raltegravir Sustained at Nearly 2 Years

BY SUSAN LONDON
Contributing Writer

MEXICO CITY — When raltegravir (Isentress) is used as part of combination antiretroviral therapy in treatment-naive patients infected with HIV, its efficacy is sustained and similar to that of efavirenz (Sustiva) and it appears to have a better safety profile, according to updated results of a randomized trial.

Raltegravir is an oral inhibitor of the viral integrase enzyme and has been shown to be active against a variety of HIV isolates, Dr. Martin Markowitz, lead author, said at the International AIDS Conference. The aim of the phase II trial was to compare the drug's safety and efficacy with those of efavirenz.

In the trial, patients were treated with raltegravir (100, 200, 400, or 600 mg twice daily) or efavirenz, added to the backbone of tenofovir (Viread/TDF) plus lamivudine (Epivir/3TC), reported Dr. Markowitz, a staff investigator with the Aaron Diamond AIDS Research Center in New York. The results observed with raltegravir were indistinguishable across doses at the 48-week analysis, so all of the patients were treated with the 400-mg dose thereafter.

The updated, 96-week analysis was based on data from 160 patients who were treated with raltegravir and 38 patients who were treated with efavirenz, who had a mean age of 36 years. The low dropout rate of about 15% over 96 weeks of therapy "speaks to the tolerability of both regimens," Dr. Markowitz said.

The percentage of patients who had fewer than 400 copies/mL of viral RNA (the trial's primary end point) was identical in the raltegravir and efavirenz groups, at 84%. The percentage with fewer than 50 copies/mL was also similar, at 83% and 84%, respectively.

One patient in each trial arm experienced treatment failure in the second half of the 96-week period. Genotyping showed that the patient taking raltegravir had wild-type virus, whereas the patient taking efavirenz had resistance mutations consistent with exposure to that drug.

The rate of drug-related adverse events was 51% with raltegravir and 74% with efavirenz. The difference was driven mainly by a difference in neuropsychiatric events, Dr. Markowitz said, most of which occurred by 48 weeks. The rate for raltegravir was half of that for efavirenz at 96 weeks (16% vs. 32%).

Cancers occurred with nearly equal rates in the raltegravir and efavirenz arms (2% vs. 3%, respectively), and grade 3/4 laboratory abnormalities were uncommon for both drugs, with individual abnormalities occurring in 8% of patients at most.

However, efavirenz was associated with significantly greater unfavorable changes from baseline in levels of total cholesterol—an increase of 24%, compared with an increase of 1% with raltegravir—and low-density lipoprotein cholesterol—an increase of 4%, compared with a decrease of 6% with raltegravir.

Dr. Markowitz concluded that with the combination therapy used, raltegravir has a sustained antiretroviral efficacy similar to that at 48 weeks and to that achieved with efavirenz. In addition, it was generally well tolerated and seemed to be associated with a lower rate of adverse events.

An attendee asked if the earlier report of the more rapid virologic suppression achieved with raltegravir had any clinical importance now that the two drugs seem to have similar efficacy. Dr. Markowitz replied that differing antiviral mechanisms may explain that early finding, but the clinical importance of more rapid suppression remains uncertain.

Another attendee asked why all of the patients were put on the 400-mg dose of raltegravir if lower doses were equally efficacious, and whether a trial of once-daily dosing might not be reasonable. Dr. Markowitz replied that pharmacokinetic data show marked interpatient and intrapatient variability in drug levels, and exposure to this drug is reduced by some of the other drugs HIV-positive patients take.

The 400-mg dose was chosen in an effort to ensure that most of the patients were receiving exposures that would "appear to be consistent with a good virologic response," he explained.

Addressing the once-daily dosing issue, he noted that the development plan for raltegravir focused on previously treated patients, but that the drug is now being used in the treatment-naive population.

"It's rare in HIV that we have actually developed drugs with different dosing plans for different patient populations. However, I think that's an interesting thought and one that certainly should be [considered] for raltegravir perhaps and other drugs, particularly as we try to roll some of these drugs out to less developed areas," he said.

Dr. Markowitz reported that he received research grants and speaker fees from Merck Research Laboratories, which manufacturers raltegravir, and that he serves as a paid consultant for the company. ■

Mortality Gap Has Narrowed For HIV-Infected Patients

BY MARY ANN MOON
Contributing Writer

Mortality rates of people infected with HIV now approach those of the general population, at least for the first 5 years of the infection, according to a large multinational study.

The gap in mortality rates between people with HIV infection and the general population has narrowed every year since the introduction of highly active antiretroviral therapy (HAART) in 1996, the study investigators reported.

This represents a 94% reduction in excess mortality in recent years, as compared with the time before HAART was available.

However, there still appears to be an excess in mortality as the duration of HIV infection increases.

To compare mortality rates, the investigators used a large data set comprising 21 separate cohorts of HIV-infected subjects whose dates of seroconversion (defined as development of serum antibodies as a result of infection) had been pinned down relatively precisely.

These cohorts included 16,534 subjects who were followed for up to 23 years in 10 European countries, Australia, and Canada.

A total of 2,571 of the subjects had died as of the end of 2006, compared with an estimated 235 deaths that would be expected in a matched cohort of individuals from the general population.

The excess in mortality was most marked during the pre-HAART time period and declined dramatically from 1996 onward, said the investigators, led by Krishnan Bhaskaran of the Medical Research Council Clinical Trials Unit, London.

By the end of the study period in 2006, "there was no evidence of any excess mortality to 5 years from seroconversion in any age group," Mr. Bhaskaran and his associates reported (JAMA 2008; 300:51-9).

However, some excess mortality was still evident as the duration of HIV infection in the subjects lengthened to 10 years or more.

"It is likely that, even with current standards of HIV management, some long-term excess mortality would remain because problems of toxicity, resistance, and therapy adherence are likely to increase with time receiving HAART," they noted.

Mortality was four times as high among subjects who acquired HIV through intravenous drug use than among those who acquired it through sexual contact.

This difference in mortality likely reflects the fact that intravenous drug users are at higher risk than nonusers for mental health–related illness and coinfections, and often have poorer access to and adherence to treatment, the investigators added. ■

HIV/AIDS Diagnoses Rising in Young Black Men in Most States

BY ELIZABETH MECHCATIE
Senior Writer

From 2001 through 2006, the number of HIV/AIDS diagnoses among men who have sex with men increased by nearly 9% in 33 states, with particularly high increases among black men and Asian/Pacific Islanders under the age of 25 years, according to the Centers for Disease Control and Prevention.

Diagnoses among black MSM aged 13-24 years increased by 93%, a rate about twofold greater than the rate among white MSM in the same age group.

The CDC analysis of trends in HIV/AIDS diagnoses among men who have sex with men (MSM) estimated that of the 214,379 people who were diagnosed with HIV/AIDS, 46% occurred among MSM and 4% occurred among MSM who also injected illicit drugs.

Diagnoses during this time period dropped in all transmission categories except for MSM (MMWR 2007;57:681-6).

Of the cases diagnosed among MSM, 64% were in men aged 25-44 years.

There was a 12% increase in diagnoses among all black MSM.

Diagnoses among black MSM aged 13-24 years increased by 93%, a rate that was about twofold greater than the rate of increase among white MSM in the same age group.

Asian/Pacific Islanders aged 13-24 years saw the largest proportionate increase.

In this group, HIV/AIDS diagnoses increased by 256% (an estimated annual increase of almost 31%).

Among MSM in this younger age group, the annual percentage increases in diagnoses were statistically significant in all racial/ethnic populations, with the exception of American Indian and Alaska Natives.

"These findings underscore the need for continued effective testing and risk reduction interventions for MSM," particularly for those younger than age 25 years, according to the report.

As an example, the report cites an intervention targeted to young black MSM in North Carolina (one of the 33 states), implemented by the CDC, in collaboration with the state health department and local organizations, that successfully reduced their high-risk sexual behavior and the number of sex partners with whom they engaged in high-risk sexual behaviors.

Among the limitations of the report, the patients in the included 33 states are not representative of all HIV-positive people in the United States.

However, the racial and ethnic disparities observed are similar to those observed for AIDS patients in all of the states. ■