national

Treatment, Interrupted

Conference focuses on strategies for reducing the drug burden in anti-HIV therapy

by Bob Roehr

Anti-HIV therapy has been spectacularly successful at dramatically reducing progression and death from the disease during the past decade. But the downside to therapy can be side effects, the selection of resistant virus and the high cost, particularly in the developing world.

So it is no surprise that as treatment practices have matured, patients and physicians have sought ways to possibly minimize use of those therapies while at the same time retaining their benefits. Strategic interruptions of therapy were a major focus of discussion at the 13th Conference on Retroviruses and Opportunistic Infections meeting Feb. 5 to 8 in Denver.

Much of the attention focused on the Strategies for Management of Anti-Retroviral Therapy (SMART) trial. As the largest HIV treatment trial ever, it had enrolled 5,472 of its planned 6,000 patients before being stopped Jan. 11. An interim analysis revealed that those in the arm that interrupted therapy had more than twice the risk of disease progression as those who continued on therapy.

The trial design had patients start treatment when their CD4 cell count dropped below 250. Half continued therapy uninterrupted, while half were randomized to stop therapy once their CD4 count climbed above 350.

"The study showed that there was an increased risk of HIV complications and death in patients who used anti-HIV treatment intermittently. But even more surprisingly, they also had more complications," said Wafaa El-Sadr, a researcher at Columbia University and a leader of the SMART study.

"A lot of the complications and deaths were not due to what we call HIV-related complications," she added. They were related to increased risk for heart, liver and kidney disease. "We don't understand why. We have a lot to learn about what starting and stopping does."

When asked what parameters she would be comfortable with for an interruption trial, El-Sadr said: "Clearly, we would like to go to a higher [CD4] threshold for restarting. In the SMART study, those who had depressed viral loads at baseline, they did the worst, they had the highest risk of progression" with interruption.

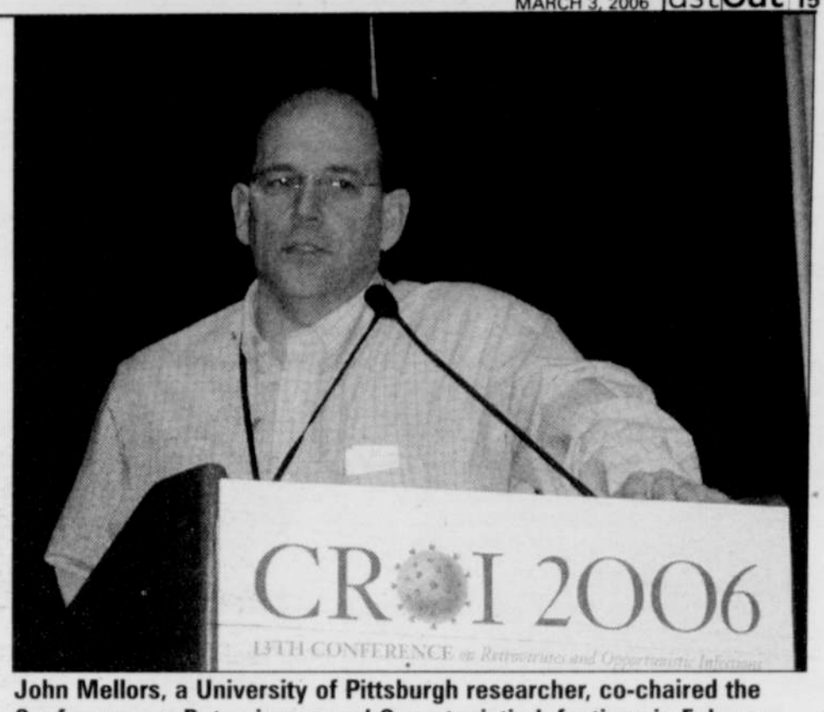
Mixed signals on interruptions came from a smaller trial in the Ivory Coast in West Africa that randomized patients to three arms: continuous therapy; the same CD4 start/stop criteria of the SMART trial; or a rotation of two months off and four months on therapy.

AIDS researcher Wafaa El-Sadr describes her findings about the ineffectiveness of intermittent HIV treatment.

It also stopped the SMART-like arm of the trial when "it found a 2.6 times higher rate of serious morbidity in the guided treatment arm, largely because of bacterial infections," said investigator Christine Danel. The fixed rotation of two months off and four months on therapy is continuing, as researchers did not see the same type or number of events, at least not so far.

In contrast, an interruption trial in Thailand that reinitiated therapy whenever CD4 counts fell below 350 saw no significant differences between that group and those who were on continuous therapy.

"The general themes are, the more time you are on therapy the better; the lower the reinitiation threshold, the higher the risk; the shorter the discontinuation the better," said John Mellors, a University of Pittsburgh researcher and vice chairman of the conference. Interruptions are "something that no one would advocate for patients with a low CD4 count, somewhere below 300."



John Mellors, a University of Pittsburgh researcher, co-chaired the Conference on Retroviruses and Opportunistic Infections in February.

He added: "There needs to be dialogue as to whether we can even move forward with any of these interruption strategies. The downside of starting/stopping, starting/stopping, even for brief periods of time…with another study we see 30 percent drug resistance. That's not a good thing."

Mike Youle is a researcher at the Royal Free Hospital in London who writes for the National AIDS Treatment Advocacy Project. In reviewing data on the handful of interruption trials, he acknowledged that the issue is far from simple. It often might depend upon a patient's coinfections and exposure to other pathogens.

He also noted that as anti-HIV regimens have become safe and easier to use, there is a greater willingness to remain on them and less pressure to develop strategies such as interruptions to reduce use of those drugs.

Another possible strategy for reducing the drug burden is a simplification approach that uses a standard cocktail of therapy to knock down the virus and, once viral load is undetectable, to withdraw part of the regimen.

The theory is that a single drug might be powerful enough to destroy the small number of virus that emerge from sanctuary resting cells and tissue compartments without giving resistance a chance to emerge. It would work best with a drug that requires several mutations for resistance to develop to that drug.

Susan Swindells described a small pilot study at University of Nebraska Medical Center. The patients had to be on a regimen containing a protease inhibitor, with undetectable viral load for at least a year and no previous drug failure. If they were not on it already, they were switched to a regimen of atazanavir/ritonavir (Reyataz) and Combivir, then stopped taking the Combivir.

According to Swindells, after a year on the single drug, only three of the 34 patients had a detectable viral load, though none showed resistance to atazanavir. Why did those three patients develop detectable levels of virus? Monitoring found periodic low levels of the drug in two of the three patients with detectable virus, suggesting they did not regularly take their medicine.

Swindells said the findings "are extremely similar" to a pilot study using Kaletra monotherapy. She does not believe nucleoside drugs are powerful enough to maintain sufficient suppression of the virus, while a non-nucleoside reverse transcriptase inhibitor can be rendered impotent with a single viral mutation, so at this point, any single drug strategy would have to be based upon a protease inhibitor.

However, one risk of this strategy in using atazanavir is that it does not appear to penetrate blood-brain barriers very well. One poster presentation found that concentrations of the drug in the cerebrospinal fluid "are highly variable and are 100-fold lower than plasma concentrations, even with ritonavir boosting." It warned that these concentrations might not protect against HIV replication in the fluid.

That raises the possibility of virus replicating behind those "walls" in the central nervous system and brain, the eyes and the testes. That is a significant issue for both individual and public health. Mellors acknowledged, "That has to be evaluated very carefully."

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