



# Annual progress report

What was hot in 2009, what's coming in 2010

by Dr. Harold Dion

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**P**rogress doesn't seem to happen on all fronts at once. The year 2008 brought us remarkable advances in treatment choices. Almost every person with HIV can now expect to bring their viral load down to undetectable levels, regardless of their stage of disease or resistance to antiretrovirals (ARVs). However, little progress was made that year in preventing HIV, with vaccine trials showing dismal results.

The year 2009 saw the situation reversed: few new drugs made their way onto the market, but we saw the first encouraging signs of a vaccine against HIV.

## **New hope for preventive vaccine**

Last September, the US Military HIV Research Program and Thailand's Department of Public Health announced that, for the first time ever, a vaccine had demonstrated some efficacy in preventing HIV. The RV144 study, underway in Thailand since 2003,

involves some 16,000 HIV-negative men and women aged 16 to 30. They were given a dose of either the ALVAC-HIV vaccine or a placebo (sugar pill) at the start of the study, then one month, three months and six months later. A second vaccine, AIDSVAX/B/E, or placebo was also administered at three and six months. Participants were then tested for HIV every six months over three years and received counselling on HIV prevention.

Researchers found, when they analyzed the data, that HIV transmission was reduced by 31.2% in the group that was vaccinated compared to those who received the placebo. Both vaccines were well tolerated. However, neither had any effect on the viral load or on the CD4 cell counts of study participants who were infected with HIV during the study despite having received the vaccine.

These results, while not spectacular, are very encouraging because no other clinical trial in humans has ever been able to demonstrate that a vaccine can reduce transmission of HIV. The researchers are now trying to see precisely which aspect of the vaccine regimen was responsible for the observed effect. Is one vaccine better than the other? Was the combination beneficial?

## **More data to support early treatment**

Over the past few years, more and more large-scale **cohort studies** seem to suggest that starting antiretrovirals (ARVs) when CD4 levels are still higher than 350 cells/mm<sup>3</sup> can protect against the development of complications. In 2009, these

## **What's a cohort study?**

A cohort study follows groups of people over time to observe differences between those who are treated a certain way and those who are not. There may be underlying differences between the two groups that influence the way they are treated and their outcomes. This is unlike a randomized controlled study, in which similar people are randomly assigned one treatment course or another and we can say with greater certainty that the treatment choice caused the difference in outcome.

findings became impossible to ignore. The most convincing results came mainly from two studies.

The first study, called NA-ACCORD, followed 17,517 asymptomatic patients from 22 cohorts (groups of people) in the US and Canada between 1995 and 2006. People with CD4 counts between 350 and 500 cells/mm<sup>3</sup> who delayed starting ARVs until their CD4 counts were lower than 350 cells/mm<sup>3</sup> had a 69% greater chance of dying than those who started treatment earlier (i.e. if 1 in 100 people died starting treatment early, then 1.7 people in 100 would die starting treatment later). What's more, for people with CD4 counts greater than 500 cells/mm<sup>3</sup>, delaying treatment until counts were lower than 500 cells/mm<sup>3</sup> was associated with a risk of dying 94% higher than those who started treatment early (i.e. almost 2 people in 100 would die starting treatment later compared to 1 in 100 who started treatment early).

The second study analyzed data on more than 24,000 people living with HIV in North America and Europe. It showed that delaying ARV treatment until CD4 counts were between 251 and 350 cells/mm<sup>3</sup> was associated with a 28% higher risk of developing AIDS or dying than starting at a CD4 count above 350 cells/mm<sup>3</sup>.

Faced with this evidence, the US Department of Health and Human Services (DHHS), along with the World Health Organization (WHO) revised their clinical guidelines in 2009. The DHHS now recommends starting ARV treatment as soon as CD4 cell counts fall below 500 cells/mm<sup>3</sup>, while the WHO adopted a threshold of 350 cells/mm<sup>3</sup> as the recommended moment to start treatment.

### More one-pill-a-day regimens

In terms of new treatments, about a dozen new drugs are under development, though none have yet been submitted to Health Canada for approval. Among the most promising is a new integrase inhibitor (S/GSK 1439572) that has demonstrated remarkable activity at a dose of 50 mg, taken once a day. This drug has the added advantage of being effective against HIV that is resistant to first generation integrase inhibitors. It also remains in the bloodstream a long time, which means it can be taken just once a day. If Phase III studies are successful, it's expected that this new drug will be co-formulated with abacavir (Ziagen®) and lamivudine (3TC®) to produce a new pill containing three medications that can be taken once a day.

New booster drugs, similar to ritonavir but without any anti-HIV activity, are also being studied. In the first study, a new drug called GS-9350, co-formulated

in a new "quadruple pill," was analyzed. It contains elvitegravir (an integrase inhibitor expected to be approved by Health Canada in 2010), emtricitabine, tenofovir (Viread®) and GS-9350. GS-9350 increases the concentration of elvitegravir in the blood to 11 times its initial value. The treatment has been well tolerated and has no negative effects on lipid metabolism. Researchers are now proceeding to a Phase II study, where the new quadruple pill will be compared to Atripla® (which combines emtricitabine, tenofovir and efavirenz).

The second study looked at how well a new drug called SPI-452 was tolerated and how effectively it boosted blood levels of different protease inhibitors. Different doses of the drug (25, 50, 100, 200, 400 and 600 mg) were compared to placebo. Researchers were able to show that the new drug was safe and well tolerated and that it produced significant increases in the blood levels of saquinavir (Invirase®), atazanavir (Reyataz®) and darunavir (Prezista®). They concluded that this new protease inhibitor (PI) booster was promising and will continue to develop it.

Finally, rilpivirine, a new non-nucleoside reverse transcriptase inhibitor (NNRTI), is also in Phase III study. If the ECHO and THRIVE studies show that it's just as effective as efavirenz (Sustiva®), it will also be incorporated into a pill containing tenofovir (Viread®) and emtricitabine.

### What to expect in 2010?

Along with results of the studies mentioned above, we're waiting with great anticipation for results of studies on pre-exposure prophylaxis (PrEP, in which HIV-negative people take ARVs before exposure to HIV in the hope of lowering the risk of becoming infected). We can also expect to find out more about how HIV infection and ARVs affect people as they age.

Not a bad year in store! 

