Treatment news from CROI

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The Conference on Retroviruses and Opportunistic Infections (CROI) brings together clinical [1]Pertaining to or founded on observation and treatment of participants, as distinguished from theoretical or basic science. investigators, scientists, researchers, educators and advocates from all over the world to share knowledge and develop a greater understanding of managing HIV and opportunistic infections. The 16th CROI, held in Montréal, Canada last month, was attended by close to 4200 delegates. John Daye, NAPWA's Health, Treatment and Research Co-Convenor, was amongst them.

Alternatives to ritonavir

In test tube studies, two new pharmacokinetic [2]Referring to the processes (in a living organism) of absorption, distribution, metabolism, and excretion of a drug or vaccine. In clinical trials, measurements are made of the rate at which a drug is absorbed into the bloodstream and then excreted via the kidneys or liver, to determine the optimum dose of the drug. enhancing agents — GS 9350 and SPI 425 — appear to boost protease inhibitor levels as well as ritonavir, but with fewer side effects.

Including ritonavir in current regimens is critical for maintaining effective therapeutic levels in the blood. It does this by slowing down the rate other protease inhibitors are metabolised so drug levels are sustained. However, ritonavir can cause side effects such as abnormal cholesterol [3]An essential component of cell membranes and nerve fibre insulation, cholesterol is important for the metabolism and transport of fatty acids and the production of hormones and Vitamin D. Cholesterol is manufactured by the liver, and is also present in certain foods. High blood cholesterol levels have been linked to heart disease and may be a side effect of some anti-HIV medications. and [4]A fat. levels and diabetes [5][Diabetes mellitus] A disorder in which sugars in the diet cannot be metabolised into energy due to a lack of the enzyme insulin. Late-onset diabetes mellitus may be a long-term side effect of some anti-HIV drugs.. These two new agents effectively boost protease inhibitors without causing these metabolic problems.

Gilead has created a fixed dose tablet containing GS 9350, tenofovir, emtricitabine and elvitegravir (an experimental [6](Of a drug) Not licensed for use in humans, or as a treatment for a particular condition. Experimental drugs are studied in clinical trials to determine their safety and efficacy, and are sometimes made available via Special Access Schemes prior to their approval. integrase inhibitor). In a safety study of 44 HIV negative volunteers the four-in-one pill was generally well tolerated. Further studies are planned in the coming months.

The other experimental enhancer, SPI 425, when taken with saquinavir was found to markedly increase the saquinavir levels. SPI 425 was also generally well tolerated, with mild headaches or sore throats being the most commonly reported side effects. The agent has also been effective in boosting darunavir and atazanavir levels. Further studies of this drug are planned.

HIV still present in semen when undetectable in blood

Two presentations at CROI showed that HIV is often detectable in semen despite being undetectable in blood. The two studies found measurable HIV RNA ('viral shedding') in 3% to 14% of semen samples taken from men with undetectable plasma viral loads.

The study also took single samples from 13 men in whom HIV had been suppressed for over four years and found detectable virus in the seminal fluid of 4 of them (31%).

Both presenters related their findings directly back to the controversial 'Swiss statement'. One noted that in all cases, blood plasma viral load had been undetectable for at least six months and no other STIs [7][Sexually Transmissible (or Transmitted) Infection] Infections spread by the transfer of organisms from person to person during sexual contact. Also called venereal disease (VD) (an older public health term) or sexually transmitted

diseases (STDs). were identified, the criteria specified for 'uninfectiousness' in that statement.

The level of seminal viral load necessary to pose a significant transmission risk is not known. One study did not see any cases of transmission from these men to their HIV negative partners, except in one non-adherent patient who had had plasma viral rebound. The conclusion: successful HAART [8]Highly Active AntiRetroviral Therapy ??? aggressive treatment of HIV infection using several different drugs together. does not reliably eradicate HIV in semen, and does not eliminate the risk of HIV transmission during unprotected intercourse.

When to start controversy

Conflicting presentations at CROI put a question mark over whether starting treatment above the currently recommended 350 T-cell mark is a good idea.

A North American study found that people who started treatment with a count below 500 had a 60% higher risk of death than people who started treatment above this level, but a collaborative study by European and North American cohorts failed to find any extra benefit to starting above 400 cells/mm3.

The second study found that while there was a clear benefit to starting treatment at a count in the 350–450 range when compared with a lower count, starting treatment at CD4 counts of 450–550 did not reduce the risk of disease progression.

A more definitive study is about to commence. The START study will randomise 900 patients across 22 countries to try to determine whether starting HAART before counts drop below 500 has any benefit in reducing mortality and serious morbidity.

Switching to raltegravir

A much-anticipated presentation was on SWITCHMRK – a study that encouraged enrolment [9]The act of signing up participants into a study. Generally this process involves evaluating a participant with respect to the eligibility criteria of the study and going through the informed consent process. from people who were on lopinavir/ritonavir and had some history of nucleoside resistance [10]HIV which has mutated and is less susceptible to the effects of one or more anti-HIV drugs is said to be resistant..

The theory being tested was that you could keep suppressing the virus while changing from lopinavir/ritonavir plus two nucleosides to raltegravir plus two nucleosides and that the change will have metabolic benefits such as a reduction in lipids.

The study did show these lipid reductions but a number of patients experienced virological failure. Of those who did, many had previously failed other regimens.

The study highlighted the need to use drugs carefully and the presenter concluded that 'one needs to be extremely cautious about making one drug substitutions to raltegravir'.

The findings also showed a range of nucleoside and non-nucleoside resistance mutations in people who failed raltegravir, a result which will require more analysis.

The reversible risk factors

A number of medical conditions can nearly double the risk of death in people with HIV. The good news is that most of these conditions are preventable or at least modifiable. The DAD study (Data collection on Adverse events of anti-HIV Drugs) has been collecting information on the risk factors affecting over 33,000 participants since 1999. Some of them, such as age and gender, are unavoidable. The others can at least be monitored and our lifestyles modified to reduce their effects.

These include (from most adverse to least): being underweight, diabetes, high blood pressure [11]Persistently high blood pressure, an outwardly symptomless condition which carries an increased risk of serious illnesses such as

stroke, heart disease and heart attack., infection with hepatitis C and (arguably, the most modifiable of all) being a smoker.

Not surprisingly a low CD4 cell count and a high viral load were also identified as risk factors.

IL-2 no benefit to people already on treatment

People already on antiretrovirals [12]A medication or other substance which is active against retroviruses such as HIV. who receive IL-2 may find it boosts their number of T-cells but it won't reduce the risk of advanced disease compared with combination anti- retroviral therapy alone. These are the findings of two large international clinical trials presented at CROI.

It is unclear why increased T-cell counts did not translate into better health outcomes.

James Neaton of the University of Minnesota, principal investigator of INSIGHT, the global clinical trials network that conducted ESPRIT, offered two possible explanations.

'It could be that the types of CD4+ T-cells induced by IL-2 play no role in protecting the HIV- infected patient, and therefore the administration of IL-2 has no benefit,' Dr. Neaton surmised.

'A second possibility is that the CD4+ T-cells are at least somewhat functional or that IL-2 has some modest benefit, but the side effects of IL-2 may neutralise any possible benefit.'

Cliff Lane, Director of Clinical Research at the National Institute of Allergy and Infectious Diseases (NIAID) and an executive committee member of INSIGHT, concluded: 'These clinical trials successfully reached a definitive answer about the utility of IL-2 therapy for treating HIV, and will have significant implications for the future development of immune- based therapies for HIV.'

Microbicide provides protection for women

The first successful clinical trial of a topical gel that can protect against vaginal infection of HIV has offered hope to a field that has been battered by numerous failures. The product, PRO 2000, works by blocking the binding mechanism of the virus to prevent entry. It is an exciting proposition because if proven effective, PRO 2000, will arm women with a personal protection from HIV.

- heart disease
- HIV prevention
- HIV treatments
- IL-2
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- ritonavir
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Links:
[1] http://www.napwa.org.au/glossary/term/475
[2] http://www.napwa.org.au/glossary/term/505
[3] http://www.napwa.org.au/glossary/term/88
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[9] http://www.napwa.org.au/glossary/term/489
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