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I ANTI-HIV AGENTS

A. Inflammation and HIV

At the beginning of the AIDS epidemic, complications and deaths from life-threatening infections were common. Now that potent anti-HIV therapy (commonly called ART or HAART) is widely available in most high-income countries, deaths from AIDS-related infections are no longer common.

ART has this amazing effect because it greatly reduces production of HIV. This allows the immune system to partially repair itself. However, while these repairs give the immune system the ability to resist common AIDS-related infections, other issues remain unresolved.

Because ART cannot cure HIV infection, HIV continues to be produced and this affects the immune system, keeping it in a state of continuous activation. Cells of the immune system can take up residence within other organ-systems—bones, brain, blood vessels, liver, lungs, kidneys and so on. There, activated immune cells release inflammatory chemical signals. Over the long-term, continuous production of these chemical signals can degrade and weaken these organ-systems.

Increased inflammation likely plays a role in some of the emerging complications that are being seen in HIV-positive people today in high-income countries, including:

- cardiovascular disease (heart attack and stroke)
- pulmonary hypertension and lung cancer
- dysfunctional liver and kidneys
- diabetes

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- thinning bones
- problems with memory and thinking clearly

Ways of reducing inflammation and assessing its effect on the health of HIV-positive people are being explored in clinical trials. For further information about HIV-related inflammation and some of these experiments, see *CATIE News*:

www.catie.ca/catienews.nsf/CATIE-NEWS

B. Cenicriviroc for inflammation and HIV

A company called Tobira Therapeutics is developing a drug called cenicriviroc (also known as TBR-652, formerly TAK-652). This drug has both anti-inflammatory and anti-HIV activity. Cenicriviroc works by blocking a receptor called CCR5, found on the surface of cells of the immune system. HIV needs this receptor to enter and infect cells. By masking CCR5, cenicriviroc makes it difficult for HIV to infect cells.

Cenicriviroc has another property—it can mask another receptor called CCR2. This other receptor plays a role in several inflammatory conditions, such as:

- cardiovascular disease
- Crohn's disease
- rheumatoid arthritis

In theory, blocking receptors such as CCR5 and CCR2 may interfere with the functioning of the immune system. This is why long-term monitoring of people who use the approved CCR5 inhibitor maraviroc (Celsentri) is important. However, after several years of monitoring, no increased risk for infections, cancer or immune dysfunction has been found in maraviroc users.

Because cenicriviroc also blocks CCR2 receptors, long-term monitoring of people who are exposed to this drug will be needed.

Cenicriviroc remains in the blood for prolonged periods; its half-life is 35 to 40 hours. As a result, it can be taken just once daily. Taking this drug with food enhances its absorption. An advantage of cencriviroc is that it generally does not interfere with enzymes in the liver that are used to process many other drugs.

Cenicriviroc has recently been tested in a Phase II study to explore preliminary safety and effectiveness. Specifically, researchers sought to understand the effect of different doses of cenicriviroc monotherapy in a randomized double-blind trial for 10 days. The drug was given in the following doses once daily to small groups of people:

- 25 mg
- 50 mg
- 75 mg
- 100 mg
- 150 mg

Between eight and 10 people received each dose of cenicriviroc, while a small number received placebo. The average profile of participants at the start of the study was as follows:

- 7 females, 47 males
- age – 40 years
- CD4+ count – 450 cells
- viral load – 15,000 copies/ml

The study team also assessed levels of the following chemical signals associated with inflammation in blood samples:

- MCP-1 (macrophage chemoattractant protein-1)
- hsCRP (high-sensitivity C-reactive protein)
- IL-6 (interleukin-6)

Results

Most doses of cenicriviroc—50, 75, 100 and 150 mg—were associated with a significant decrease in viral load, ranging from 1.4 to 1.8 log. By contrast, only a 0.3 log decrease in viral load occurred with placebo.

Although the drug was only given for 10 days, viral load continued to fall for several days after the study ended.

Levels of inflammatory markers such as hsCRP decreased during exposure to cencriviroc.

The following side effects associated with the drug were reported by some participants:

- fatigue
- diarrhea
- nausea

No one left the study prematurely because of side effects and no one died as a result of exposure to cenicriviroc.

Further studies are planned for 2011 to assess cencriviroc's impact on assessments of cardiovascular, immunologic and metabolic health.

REFERENCES:

1. Zhao Q. Dual targeting of CCR2 and CCR5: therapeutic potential for immunologic and cardiovascular diseases. *Journal of Leukocyte Biology*. 2010 Jul;88(1):41-55.

2. Martin DE, Palleja S, Gathe J, et al. TBR-652, a potent dual chemokine receptor 5/chemokine receptor 2 (CCR5/CCR2) antagonist in phase 2 development for treatment of HIV infection. In: Program and abstracts of the *18th International Conference on AIDS*, 18–23 July 2010, Vienna, Austria. Abstract MOAB0104.

C. Integrase inhibitor '572 tested against raltegravir-resistant HIV

GlaxoSmithKline (GSK) has licensed an anti-HIV integrase inhibitor discovered by the Shionogi Corporation in Japan. Because of these arrangements, this drug has the complex code name S/GSK1349572 and for now is increasingly referred to simply as '572 by researchers.

In lab experiments '572 has activity against HIV that is resistant to raltegravir, the only currently approved integrase inhibitor.

Researchers tested '572 in HIV-positive volunteers who had HIV that was resistant to raltegravir. Participants either substituted '572 in place of raltegravir or started taking '572 if they had already quit raltegravir. All participants had HIV that was also resistant to drugs from the three commonly used groups of anti-HIV medicines:

- nukes
- non-nukes
- protease inhibitors

For the first 11 days of the study, participants received 50 mg once daily of '572 and no other drugs. After this period they also received an optimized background regimen based on resistance testing and medical history. This study is called Viking and so far only results from the first 11 days have been released.

The average profile of the 27 participants enrolled at the start of the study was as follows:

- 2 females, 25 males
- age – 45 years
- CD4+ count – 110 cells
- viral load – 30,000 copies/ml
- duration of taking ART – 14 years

Examples of prior ART used included these drugs, which were used by the following proportion of participants:

- etravirine (Intelence) – 70%
- T-20 (Fuzeon, enfurvirtide) – 81%
- darunavir (Prezista) – 85%
- maraviroc (Celsentri) – 37%

That most of these potent drugs were commonly used suggests that the study group represented heavily pre-treated patients.

Results

After 11 days, 21 out of 27 participants (78%) had their viral load fall to 400 copies/ml or less or had their viral load fall by 0.7 log.

Side effects

Participants in this study had weak immune systems and sometimes it is difficult to separate drug side effects from symptoms of HIV disease in this population. Despite this, investigators determined that the following side effects were caused by '572:

- mild diarrhea – one person
- mild nausea – one person
- moderate fatigue and problems falling asleep – one person
- moderate diarrhea – one person

Two participants had severely elevated levels of pancreatic enzymes; it is not yet certain if this is due to exposure to '572. However, no serious or life-threatening complications occurred after exposure to '572.

Long-term results from Viking are needed to assess the benefit of '572 in raltegravir-resistant people.

REFERENCE:

Eron J, Durant J, Poizot-Martin I, et al. Activity of a next generation integrase inhibitor (INI), S/GSK1349572, in subjects with HIV exhibiting raltegravir resistance: initial results of VIKING study (ING112961). In: Program and abstracts of the *18th International Conference on AIDS*, 18–23 July 2010, Vienna, Austria. Abstract MOAB0105.

D. Once-daily '572 as part of initial therapy for HIV

The investigational integrase inhibitor '572 can be taken once daily and does not need to be boosted with ritonavir (Norvir) or any other drug. '572 is being tested as part of the initial therapy for HIV infection in several hundred people in a trial called Spring. Preliminary results are very promising.

Study details

In Spring, participants were randomly assigned to receive one of three doses of '572 (10, 25 or 50 mg) taken once daily or efavirenz 600 mg also taken once daily. All participants also received two nukes. Spring has a complex design and is planned to continue for at least 48 weeks. So far results for the first 16 weeks have been released.

The average profile of the 205 volunteers enrolled at the start of the study was as follows:

- 14% females, 86% males
- age – 37 years
- CD4+ count – 324 cells
- viral load – 29,000 copies/ml
- 21% of participants had a viral load greater than 100,000 copies/ml
- 67% of participants took a combination of tenofovir and FTC (Truvada)
- 33% of participants took a combination of abacavir and 3TC (Kivexa)

Results—16 weeks later

All doses of '572 performed well, achieving viral suppression more rapidly than efavirenz. This is not surprising, as integrase inhibitors as a class rapidly suppress HIV levels.

At 16 weeks, the proportion of participants in each dose group whose viral load was less than 50 copies/ml was as follows:

- 10 mg – 96%
- 25 mg – 92%
- 50 mg – 90%

These differences were not statistically significant.

The proportion of efavirenz users at week 16 who had a viral load less than 50 copies/ml was 60%. This difference was statistically significant.

One reason for the inability of efavirenz users to achieve undetectable viral loads by week 16 is that 30% were not able to suppress HIV by that time. In contrast, at week 16 only 10% of '572 users had not suppressed their viral load.

Lack of virologic suppression occurred as follows when analysed by the nuke regimen used:

- Truvada + '572 – 3 people
- Truvada + efavirenz – 11 people
- Kivexa + '572 – 4 people
- Kivexa + efavirenz – 4 people

Changes in CD4+ cell counts

In general, increases in CD4+ cell counts were greater by week 16 in users of '572 than in efavirenz users. Here is the combined analysis of '572 dose groups:

- '572 – 165 extra CD4+ cells
- efavirenz – 116 extra CD4+ cells

Side effects

About 8% of efavirenz users left the study prematurely because of severe side effects. Only 2% of people exposed to '572 left the study for such reasons.

The following proportion of participants reported the following side effects, which were graded as moderate to life-threatening among all '572 users:

- gastrointestinal – 2%
- psychiatric – 0%
- skin disorders – 0%
- general side effects – 1%

The proportion of efavirenz users who experienced the same intensity of side effects was as follows:

- gastrointestinal – 4%
- psychiatric – 6%
- skin disorders – 4%
- general side effects – 2%

While no serious side effects occurred among '572 users, one person taking efavirenz attempted to commit suicide.

One person left the study prematurely because of indigestion arising from '572. Four people left the study prematurely because of efavirenz-related side effects, such as:

- attempted suicide
- abnormal dreams
- drug intolerance
- hypersensitivity

Increased levels of so-called bad cholesterol (LDL-c) are associated with an increased risk for cardiovascular disease. In this study, changes in LDL associated with each drug were as follows:

- '572: +0.066 mmol/l
- efavirenz: +0.436 mmol/l

In summary, all doses of '572 showed potent anti-HIV activity with shorter times to undetectable viral load than efavirenz. The 50-mg once-daily dose of '572 has been selected for Phase III study, the final stage of large clinical trials before regulatory approval.

REFERENCE:

Arribas J, Lazzarin A, Raffi F, et al. Once-daily S/GSK1349572 as part of combination therapy in antiretroviral naïve adults: rapid and potent antiviral responses in the interim 16-week analysis from SPRING-1 (ING112276). In: Program and abstracts of the *18th International Conference on AIDS*, 18–23 July 2010, Vienna, Austria. Abstract THLBB205.

E. Rilpivirine vs. efavirenz

Rilpivirine, also called TMC278, is an anti-HIV drug chemically related to the non-nuke family of drugs, which includes efavirenz (Sustiva and in Atripla), nevirapine (Viramune) and etravirine (Intelence).

Rilpivirine is being tested as part of combination therapy for the initial therapy of HIV infection and is often compared against efavirenz-based combinations. Unlike efavirenz, rilpivirine does not appear to cause birth defects in animal experiments. Rilpivirine remains in the blood for prolonged periods, with a half-life of 45 hours. This means that it can be taken once daily. At doses of 25 mg per day, in short and small studies rilpivirine has similar efficacy as efavirenz but is better tolerated.

Now researchers have combined (or pooled) the results of two large comparative trials of rilpivirine vs. efavirenz—Echo and Thrive. Analysis of these two studies suggests that, overall, rilpivirine-based regimens are roughly equivalent to efavirenz-based regimens. However, results from each trial were slightly different and worth further scrutiny.

Study details

In the Echo trial, 690 HIV-positive people who had not previously used anti-HIV therapy were randomly assigned to receive one of the following regimens:

- rilpivirine 25 mg once daily with Truvada (tenofovir + FTC) also once daily
- efavirenz 600 mg once daily with Truvada

In the Thrive trial, the overall design was similar except that doctors were allowed to use any of the following nuke combinations with either rilpivirine or efavirenz:

- Truvada
- AZT + 3TC in one pill (Combivir)
- abacavir + 3TC in one pill (Kivexa)

The average profile of participants when they entered the Echo and Thrive studies were as follows:

- 25% females, 75% males
- age – 36 years
- CD4+ count – 250 cells
- viral load – 100,000 copies/ml
- 8% were co-infected with hepatitis B or C virus

These trials lasted two years but so far only the results from the first year have been released.

Results—Suppression of HIV

When the results of Echo and Thrive were combined, the proportion of participants with a viral load less than 50 copies/ml at 48 weeks was as follows:

- rilpivirine – 84%
- efavirenz – 82%

This difference was not statistically significant

CD4+ cell counts increased in both groups as follows:

- rilpivirine – 192 extra CD4+ cells
- efavirenz – 176 extra CD4+ cells

Again, this difference was not statistically significant.

In examining the results of the studies individually, rilpivirine was found to be roughly equivalent to efavirenz in anti-HIV activity. The technical statistical term for this is non-inferior.

In the combined analysis, 9% of rilpivirine users developed virologic failure compared to 5% of efavirenz users. This difference was driven by

results from the Echo study, where differences in virologic failure were as follows:

- rilpivirine – 11% developed virologic failure
- efavirenz – 4% developed virologic failure

This occurred despite 83% of participants who received rilpivirine or efavirenz achieving a viral load less than 50 copies/ml. Clues to possibly explain the differences between the two drugs and the two trials may be found below.

In assessing differences in outcomes, the proportion of participants in Echo whose baseline (starting) viral load was greater than 100,000 copies/ml and who later achieved a viral load less than 50 copies/ml was as follows:

- rilpivirine – 76% achieved a viral load less than 50 copies/ml
- efavirenz – 82% achieved a viral load less than 50 copies/ml

Yet this difference was not statistically significant.

In Thrive, the results in participants with high baseline viral loads (more than 100,000) were as follows:

- rilpivirine – 79% achieved a viral load less than 50 copies/ml
- efavirenz – 80% achieved a viral load less than 50 copies/ml

This difference was not statistically significant. Nonetheless, the reason(s) for the slightly different results of Echo and Thrive are not clear at this time.

Results—Side effects

The proportion of participants who had side effects judged as moderate to life-threatening and possibly related to exposure to treatment were as follows:

- rilpivirine – 16%
- efavirenz – 31%

This difference was not statistically significant.

Common differences in side effects highlighted by the Echo and Thrive investigators were as follows:

Any neurological side effect:
- rilpivirine – 17%
- efavirenz – 38%

Dizziness:
- rilpivirine – 8%
- efavirenz – 26%

Any psychiatric side effects:
- rilpivirine – 15%
- efavirenz – 23%

Abnormal dreams or nightmares:
- rilpivirine – 8%
- efavirenz – 13%

Rash:
- rilpivirine – 3%
- efavirenz – 14%

These differences were all statistically significant.

When researchers assessed lab tests of blood samples for signals of toxicity they found these differences between the two drugs:

Any severe or life-threatening value in all lab tests:
- rilpivirine – 11%
- efavirenz – 18%

This difference was statistically significant.

Any severe or life-threatening value in the following lab tests:

Liver enzyme ALT:
- rilpivirine – 2%
- efavirenz – 3%

Fasting levels of LDL-cholesterol:
- rilpivirine – 1%
- efavirenz – 3%

Fasting total cholesterol:
- rilpivirine – 0.1%
- efavirenz – 3%

All of these differences were statistically significant.

Overall, rilpivirine appears to be as effective as efavirenz. Rilpivirine also appears to be better tolerated, with fewer rash, lipid and neurologic problems than efavirenz.

REFERENCE:

Cohen C, Molina J-M, Cahn P, et al. Pooled week 48 efficacy and safety results from ECHO and THRIVE, two double-blind randomized Phase III trials comparing TMC278 versus efavirenz in treatment-naïve HIV-1-infected patients. In: Program and abstracts of the *18th International Conference on AIDS*, 18–23 July 2010, Vienna, Austria. Abstract THLBB206.

II CO-INFECTIONS

A. Factors affecting early discontinuation of hepatitis C therapy

Hepatitis C virus (HCV) can invade the liver, damaging this organ. Prolonged liver damage can cause severe complications. In cases of co-infection with HIV the pace of this damage speeds up. HCV infection can also lead to the development of liver cancer.

Standard treatment for HCV infection is a combination of long-lasting interferon and the nuke ribavirin. However, because of side effects these drugs can be difficult to tolerate and may not always work.

Over the next several years less toxic and more effective anti-HCV drugs should become available, at least in high-income countries, and, in theory, this should mean more treatment options for co-infected people. Bear in mind that it will take several additional years for researchers to understand how best to use these new drugs. Moreover, they will likely have to be taken in addition to a backbone of interferon and ribavirin. This could potentially increase the likelihood of side effects or add to the burden of adherence.

Researchers in several high-income countries have found that some co-infected people who should receive therapy for HCV infection do not. It also appears that co-infected people seem to be more likely to discontinue HCV therapy prematurely. It is worth trying to resolve these issues before newer treatments become available. To investigate the issue of premature discontinuation of HCV therapy, researchers in New York City conducted a clinical trial. Their findings revealed some surprising results.

Study details

The research team recruited 102 people; 41 were co-infected and the remainder HCV monoinfected. None of these volunteers had previously received therapy for HCV infection and their average profile at the start of the study was as follows:

- 24% females, 76% males
- age – 51 years
- 78% had the difficult-to-treat strains of HCV called genotypes 1 and 4
- 90% of co-infected people had an HIV viral load less than 50 copies/ml thanks to anti-HIV therapy
- CD4+ cell count of co-infected people – 480 cells
- co-infected people had higher HCV viral loads (5.7 million IU/ml) than mono-infected people (3 million IU/ml)

Results

Overall, 78 participants began HCV therapy and 51 completed their course of therapy.

Researchers provided the following reasons for 26 participants who didn't complete their therapy:

- doctor's decision to stop therapy because of severe side effects – 12 participants
- participant's decision to stop therapy because of severe side effects – 9 participants
- lack of virologic response – 5 participants

Taking many factors into account, the researchers arrived at the following key factors based on statistical analysis which influence premature treatment discontinuation:

- having a diagnosis of mental health problems any time in the past
- having difficulty concentrating and being slow at processing information
- being a person of colour

Importantly, being co-infected with HIV and HCV was not associated with premature discontinuation of HCV therapy.

What to do?

About 68% of participants in this study had previously been diagnosed with mental health problems. The New York researchers suggest that in the future patients should be assessed for psychiatric and neurocognitive issues prior to initiating HCV therapy. If these are detected, patients should be given the support that they need. Such assessments should also be done while patients are receiving HCV therapy. The research team hopes that such steps would help to reduce premature discontinuation of HCV treatment and help more patients recover from this infection.

The research team also calls for more study of HCV-positive people of colour to determine what factors affect premature discontinuation of therapy in this population.

REFERENCE:

Weiss J, Brau N, Head C, et al. Early discontinuation of HCV treatment is not predicted by HIV status but by lifetime psychiatric diagnosis, poorer attention/psychomotor speed, and non-white race/ethnicity. In: Program and abstracts of the *18th International Conference on AIDS*, 18–23 July 2010, Vienna, Austria. Abstract MOPE0177.

B. Treatment of co-infection despite very low CD4+ cell counts

In general, treatment guidelines for HCV-HIV co-infection encourage the initiation of HCV therapy at counts well above the 200 CD4+ cell level. The reason for this is that HCV therapy can temporarily reduce CD4+ cell counts, and if these fall too low there is a risk that life-threatening infections could develop.

Researchers in Barcelona and elsewhere in Spain conducted a pilot study to evaluate the safety of HCV therapy in co-infected people with low CD4+ cell counts. Their results are surprising and may incite the initiation of larger studies to explore the issue of HCV therapy in people with low CD4+ cell counts.

Study details

Researchers recruited 11 co-infected volunteers, all who had HCV genotype 1 and who were taking anti-HIV therapy. None had hepatitis A or B or any other significant health condition. They were divided into two groups as follows:

- Group A: 5 participants with an average of 150 CD4+ cells
- Group B: 6 participants with an average of 450 CD4+ cells

All participants received standard treatment for HCV—interferon and ribavirin adjusted according to body weight.

Results

Preliminary results of 12 weeks of therapy were made available:

- Decreases in HCV viral load occurred and were similar in both groups.
- Although the CD4+ count fell to an average of 133 cells among those in group A, no life-threatening infections occurred.
- The CD4+ count among participants in group B (who began HCV therapy with higher CD4+ counts) fell to an average of 383 cells

Since no serious AIDS-related infections occurred and significant reductions in HCV viral load were seen, at least over the short-term, the Spanish researchers say that larger and longer studies are warranted in co-infected people with low CD4+ cell counts.

REFERENCE:

von Wichmann MA, Crespo M, Rodriguez-Arrondo F, et al. Pilot study to evaluate safety and HCV kinetics in HCV/HIV co-infected patients with less than 200 CD4+, treated with peginterferon alfa-2b and ribavirin (P04675 study). In: Program and abstracts of the *18th International Conference on AIDS*, 18–23 July 2010, Vienna, Austria. Abstract MOPE0178.

III NUTRITION

A. Antioxidants to the rescue

Both HIV infection and exposure to medicines, including anti-HIV medicines, can affect mitochondria, the parts of a cell that produce energy. Impaired mitochondria produce less energy and so cells do not function properly. At the level of tissues or organs this can lead to organ dysfunction and perhaps even affect the immune system.

Researchers at the University of Miami and elsewhere in the U.S. collaborated on a pilot study to assess the impact of antioxidants and nutrients used by the body to make antioxidants on the functioning of mitochondria. Their preliminary findings suggest that a mix of nutrients is helpful in improving the functioning of mitochondria, at least in the short term. There were also hints of favourable changes to the immune system.

Study details

Researchers enrolled 25 HIV-positive adults who were on stable ART regimens and whose viral loads were less than 50 copies/ml. They were randomly assigned to one of the following interventions for eight consecutive weeks:

- nutrients: B-complex vitamins, vitamins C and E, selenium, zinc, N-acetyl cysteine (NAC) and alpha-lipoic acid, all co-formulated into one pill
- placebo

To test for damage to mitochondria, participants' blood was analysed using an assay called Oxphos activity from the MitoSciences Corporation in Eugene, Oregon.

The average profile of participants at the start of the study was as follows:

- 44% females, 56% males
- age – 50 years
- CD4+ count – 506 cells
- 100% of participants had a viral load less than 50 copies/ml

Results

Over the eight weeks of this pilot study there were trends that approached but did not achieve statistical significance with the following metrics:

- absolute CD4+ counts
- CD4/CD8 ratio
- decreased insulin resistance

Bear in mind that this was a small study and it can take several months for new CD4+ cells to be produced and complete their maturation cycle before becoming fully functional. So, any increased cell numbers seen before this time likely arise from cells that were either redistributed from lymph nodes and tissues (where 98% of the body's lymphocytes are found) into blood or from cells that were rescued from death by antioxidants. Had this study enrolled many more participants and continued for up to two years, they might have found statistically significant changes.

Statistically significant differences in mitochondria function were seen between the two interventions, with improvements in the group that received nutrients. And a trend toward decreased insulin resistance was seen in the group that received nutrients. This is not surprising because in animal experiments alpha-lipoic acid has been found to decrease insulin resistance. HIV infection appears to increase the risk for diabetes by increasing inflammation, and antioxidants such as alpha-lipoic acid have the potential to improve insulin resistance.

Maintained in Canada

The present pilot study shows some encouraging trends that need to be better understood in further controlled clinical trials. One such trial, the Maintain study (CTN 238), is underway across Canada. This study explores the impact of a more complex mix of antioxidants and micronutrients in HIV-positive people. For more information about the Maintain study, see this link:

www.hivnet.ubc.ca/clinical-studies/canadian-hiv-trials-database/ctn-238/

For more information about nutrition and HIV, see CATIE's *Practical Guide to Nutrition*, available at:

www.catie.ca/ng_e.nsf/table+of+contents

REFERENCE:

Baum M, Marlink R, Jayaweera D, et al. Effect of antioxidant supplementation on immune reconstitution and mitochondrial damage. In: Program and abstracts of the *18th International Conference on AIDS*, 18–23 July 2010, Vienna, Austria. Abstract MOPE0102.

Disclaimer

Decisions about particular medical treatments should *always* be made in consultation with a qualified medical practitioner knowledgeable about HIV-related illness and the treatments in question.

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