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I ANTI-HIV AGENTS

A. Cenicriviroc

In order to get inside and infect a cell, HIV needs access to certain proteins (called receptors) on the surface of the cell. The first receptor HIV needs is called CD4. In addition to this, it generally requires one of two co-receptors, as follows:

- CCR5
- CXCR4

Most strains of HIV require access to CCR5.

Cenicriviroc, an anti-HIV drug under development, blocks access to CCR5 and, in doing so, stops HIV from infecting cells with this co-receptor. In addition to blocking CCR5, cenicriviroc also interacts with another protein called CCR2. This protein plays a role in inflammation, and by interfering with it cenicriviroc helps reduce inflammation.

When tested in people, cenicriviroc taken by itself (monotherapy) in doses of 50 mg to 150 mg per day can significantly reduce the amount of HIV in the blood by 1.6 to 1.8 logs.

Cenicriviroc (CVC) can be taken once daily, as levels of this drug in the blood remain relatively high. The drug is broken down by enzymes in the liver, specifically CYP3A4 and CYP2C8. The first enzyme is particularly important because it breaks down many medicines in the liver and intestinal tract, including the following classes of anti-HIV drugs:

- non-nukes (NNRTIs)
- protease inhibitors (PIs)

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CVC has been tested in relatively small clinical trials with generally favourable results. It is likely to be co-formulated with 3TC (lamivudine) in the future and tested in many combinations, particularly against commonly used treatments such as the following:

- a fixed-dose formulation of abacavir + 3TC (sold as Kivexa)
- a fixed-dose formulation of tenofovir + FTC (sold as Truvada)

Comparing CVC to efavirenz

In one study, 143 participants were randomly assigned to receive one of the following regimens:

- CVC 100 mg + Truvada + placebo
- CVC 200 mg + Truvada + placebo
- efavirenz (Sustiva) + Truvada

All drugs were taken once daily.

The study lasted for 48 weeks and the average profile of participants at the start of the study was as follows:

- 94% men, 6% women
- age – 35 years
- viral load – 32,000 copies/ml (20% of participants had a viral load greater than 100,000 copies/ml)
- CD4+ count – 402 cells/ml

Results

Participants who completed the study were distributed as follows:

- 71% of participants assigned to receive CVC 100 mg
- 73% of participants assigned to receive CVC 200 mg
- 28% of participants assigned to receive efavirenz (Sustiva)

These results are suggestive of a high rate of people prematurely leaving the study, particularly those who were taking efavirenz. Below are some of the reasons that people prematurely left the study:

Confirmed virologic failure:
- CVC 100 mg – 12% of participants
- CVC 200 mg – 11% of participants
- efavirenz – 7% of participants

Adverse effects:
- CVC 100 mg – 0% of participants
- CVC 200 mg – 2% of participants
- efavirenz – 21% of participants

This suggests that efavirenz has far more bothersome side effects than cenicriviroc.

Effectiveness

The proportions of participants with a viral load less than 50 copies/ml in the blood at the 24th week of the study were as follows:

- CVC 100 mg – 76% of participants
- CVC 200 mg – 73% of participants
- efavirenz – 71% of participants

This result suggests that CVC is roughly equal in effectiveness to efavirenz. However, a larger study is needed to prove this finding.

At week 48, the proportions of participants with a viral load less than 50 copies/ml in the blood were distributed as follows:

- CVC 100 mg – 68% of participants
- CVC 200 mg – 64% of participants
- efavirenz – 50% of participants

Analysing failure

HIV resistance to therapy was detected in five participants taking CVC—three taking the 100-mg/day dose and two taking the 200-mg/day dose. Analysis of their HIV found that the virus was resistant to the nukes used in the regimen and not CVC.

No resistance to efavirenz was detected.

Changes in CD4+ cell counts

On average, participants who took CVC had their CD4+ counts increase by about 200 cells/ml. Efavirenz users had their CD4+ counts increase by 150 cells/ml.

Focus on side effects

In general, most side effects were of mild-to-moderate intensity. Side effects were reported by the following proportions of participants:

- CVC 100 mg – 50%
- CVC 200 mg – 44%
- efavirenz – 71%

Side effects of moderate intensity or greater were distributed as follows:

- CVC 100 mg – 9%
- CVC 200 mg – 9%
- efavirenz – 36%

Serious side effects were distributed as follows:

- CVC 100 mg – 2%
- CVC 200 mg – 2%
- efavirenz – 4%

There was no obvious pattern to the type of side effects seen in participants who received CVC.

Common side effects among efavirenz users included the following:

- abnormal dreams
- difficulty falling asleep
- rash
- nausea

Abnormal laboratory test results

Overall, abnormal lab test results of a severe or serious nature were not common. Increases in levels of certain blood tests occurred as follows:

CPK (creatine phosphokinase; elevated levels of this enzyme are suggestive of muscle injury):
- CVC 100 mg – 5% of participants had elevated levels
- CVC 200 mg – 16% of participants had elevated levels
- efavirenz – 7% of participants had elevated levels

Higher-than-normal levels of the liver enzyme AST (aspartate aminotransferase) occurred in the following participants:
- CVC 100 mg – 2%
- CVC 200 mg – 0%
- efavirenz – 0%

Decreased phosphorus (phosphate) levels in the blood (this mineral is needed to maintain bone health) were distributed in the following proportions of participants receiving the following drugs:
- CVC 100 mg – 3%
- CVC 200 mg – 4%
- efavirenz – 4%

Decreased levels of the protein fibrinogen (needed to help blood clot) occurred in the following proportions of participants:
- CVC 100 mg – 3%
- CVC 200 mg – 4%
- efavirenz – 4%

Changes in lipids (cholesterol and triglycerides) in the blood

Overall, levels of total cholesterol rose in efavirenz users and fell in CVC users. Levels of both bad and good cholesterol were elevated in efavirenz users compared to CVC users. A similar pattern was seen with triglyceride levels.

Inflammation

As mentioned earlier, CVC can interfere with a co-receptor called CCR2. This receptor plays a role in inflammatory diseases, including cardiovascular disease. In the present study, CVC reduced levels of a protein called soluble CD14, written as sCD14, found in the blood. This is an emerging marker (or protein) of inflammation, and elevated levels of sCD14 have been linked to an increased risk of cardiovascular disease and death. This change in sCD14 suggests that CVC has anti-inflammatory activity. However, the long-term effect of this change in sCD14 is not known and will require a longer clinical trial. In contrast, efavirenz raised levels of sCD14.

What's next?

Researchers involved in the study stated that CVC-containing combinations were generally safe and well tolerated. For the next stage of clinical trials with this drug—phase III—the 200-mg/day dose of CVC has been selected for testing. In the phase III study, the combination of CVC + 3TC will likely be tested against Truvada; all participants will be using these drugs as part of potent combination anti-HIV therapy.

Cenicriviroc is being developed by the San Francisco-based pharmaceutical company Tobira Therapeutics.

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B. GSK 1265744 moves further along

GSK 1265744 ('744) is an anti-HIV drug that interferes with an enzyme needed by HIV-infected cells. This enzyme is called integrase and drugs such as '744 are called integrase inhibitors. There are several integrase inhibitors licensed by regulatory authorities, including the following:

- raltegravir (sold as Isentress)
- elvitegravir (available in a fixed-dose combination called Stribild)
- dolutegravir (Tivicay)

'744 is under development by GlaxoSmithKline (GSK). The oral formulation of this drug can be taken once daily and relatively high levels of this drug remain in the blood for up to a couple of days. There is also a long-acting formulation of the drug designed to be injected into muscle or under the skin. In such cases, high concentrations of '744 remain in the blood for between 21 and 50 days.

Clinical trials with '744 are underway to do the following:

- assess the effectiveness of oral formulations of this drug
- test the effect of the oral combination of '744 and another anti-HIV drug, rilpivirine (Edurant and in Complera) as a form of maintenance therapy for people whose viral loads are less than 50 copies/ml
- test injectable formulations of '744 and rilpivirine

If '744 passes several future clinical trials, it will have potential for intermittent dosing—perhaps once monthly as part of treatment regimens. '744 will also have potential to be taken by HIV-negative people to protect them from becoming infected with HIV. This latter use of medicines is called PrEP (pre-exposure prophylaxis).

Latte—a study of different doses of '744

In a study called Latte, researchers randomly assigned participants to receive different doses of '744 (10, 30 and 60 mg/day) together with two nukes (nucleoside analogues) for 24 weeks. After this time, participants stopped taking nukes and replaced them with rilpivirine, 25 mg/day, and are being monitored for up to 18 months.

For comparison, another group of participants received the drug efavirenz (Sustiva and in Atripla) and two nukes from the start of the study. The nukes used in Latte were usually one of the following combinations:

- a fixed-dose combination of abacavir + 3TC (sold as Kivexa)
- a fixed-dose combination of tenofovir + FTC (sold as Truvada)

The average profile of the 243 participants was as follows:

- gender – 95% male. The reason for this huge imbalance in gender was that researchers have not yet studied the interaction between hormonal contraception ("the pill") and '744 so they did not recruit many women. Clinical trials often require women of childbearing age to take at least two forms of contraception, as regulatory agencies are concerned about the potential toxic effect that study drugs might have on a fetus.
- viral load – 20,000 copies/ml (between 12% and 20% of participants had a viral load greater than 100,000 copies/ml)
- distribution of nukes – 60% received Truvada, 40% received Kivexa
- hepatitis C virus (HCV) – 4% were co-infected with this virus

Results

Overall, the proportions of participants who prematurely left the study were as follows:

- '744 (all doses) – 12%
- efavirenz – 26%

The proportions of participants who left the study due to side effects and complications were as follows:

- '744 (all doses) – 2%
- efavirenz – 11%

Virologic success

The goal of therapy is to keep viral load in the blood as low as possible; usually that means below the 50 or 40 copies/ml mark, depending on the viral load assay used. In the present study, the proportions of participants with a viral load less than 50 copies/ml at week 24 of the study were as follows:

- '744 (all doses) – 87%
- efavirenz – 74%

Changes in CD4+ counts

At the 8th week of the study, increased CD4+ counts were distributed as follows:

- '744 (all doses) – 123 more CD4+ cells/ml
- efavirenz – 59 more CD4+ cells/ml

This difference arose because '744 and other integrase inhibitors tend to result in a relatively rapid decrease in HIV viral load and a similarly fast increase in CD4+ cell counts. But by the 24th week of the study, the situation was more balanced, with the following results:

- '744 (all doses) – 186 more CD4+ cells/ml
- efavirenz – 159 more CD4+ cells/ml

Side effects

Neuropsychiatric side effects (details were not released) were more common among users of efavirenz than '744. Headaches were more common in participants taking '744 (21%) than in participants taking efavirenz (11%). Most headaches were of mild-to-moderate intensity.

Less than 10% of participants who took '744 experienced nausea, fatigue or difficulty falling asleep.

The oral dose of '744 to be used in future studies will be 30 mg/day.

Our next issue of *TreatmentUpdate* will have further news on this compound.

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C. Simplification of therapy—caution needed

Since the early days of potent combination therapy for HIV (commonly called ART or HAART), doctors and their patients have wanted fewer and safer drugs in treatment regimens. There are many reasons for this but perhaps the main one is to reduce the potential for long-term side effects.

Some long-term side effects are thought to arise from exposure to nucleoside analogues, commonly called "nukes" by some doctors and patients. The basis for this concern about nukes arose in part from at least several experiences over different periods, as follows:

- Initial treatment for HIV was nuke based and one nuke in particular, AZT (zidovudine, Retrovir), was initially used at very high doses in the 1980s and injured the bone marrow.
- In the early 1990s, there were reports that other nukes, so-called "d" drugs—ddC (zalcitabine, Hivid), ddI (didanosine, Videx) and d4T (stavudine, Zerit)—could cause injury to the nerves in the hands, feet and legs. This type of toxicity is called peripheral neuropathy and can persist for years if it is not caught in the early stages and the use of d-drugs is discontinued.
- In the late 1990s another problem appeared—the HIV lipodystrophy syndrome. The most disturbing feature of this syndrome is the loss of the fatty layer just under the skin (subcutaneous fat). This could lead to distressing changes in the appearance of the face. It took several years after the appearance of the syndrome for researchers to determine that exposure to the nuke d4T, and to a lesser extent AZT, were the main culprits behind the loss of subcutaneous fat.

This legacy of bad news has tainted all nukes even though today the nukes recommended by treatment guidelines in high-income countries as part of the initial treatment of HIV are easier to

tolerate and do **not** cause injury to nerves, bone marrow or fat cells. These nukes are as follows:

- Kivexa – a fixed-dose combination of two nukes: abacavir + 3TC
- Truvada – a fixed-dose combination of two nukes: tenofovir + FTC

Kivexa and Truvada

Large randomized clinical trials have generally found that Kivexa and Truvada, when used as part of ART, are effective and generally safe for most patients. However, there can be exceptions to these general results and we discuss a few of them next.

Focus on abacavir

Abacavir, one of the drugs in Kivexa, can cause a hypersensitivity reaction. However, there is a simple blood test available that can predict the likelihood of such a reaction occurring with a relatively high degree of accuracy. By using this test to assess which patients are at risk for a hypersensitivity reaction **before** starting therapy, doctors can steer susceptible people away from abacavir.

In some cases, abacavir can also cause moderate increases in cholesterol levels.

Several years ago one large observational study suggested that the use of abacavir was associated with a temporarily increased risk of heart attacks. Bear in mind that observational studies, due to built-in limitations, can never prove cause and effect. That is, they can never prove that abacavir can temporarily cause an increased risk of heart attack. Another large observational study, the French Hospital Database also assessed the risk of heart attack among its participants who used abacavir. French researchers found that after adjusting for use of cocaine (a powerful stimulant that by itself can cause heart attacks), exposure to abacavir was not linked to an increased risk for heart attacks. Furthermore, a review by the U.S. Food and Drug Administration (FDA) of randomized clinical trials with abacavir has not found any such risk. Also, there have been recent randomized clinical trials with Kivexa and the new integrase inhibitor dolutegravir (Tivicay) in several thousand HIV-positive people and heart attacks have not been reported.

Abacavir does have advantages: It can be taken once daily, it does not harm bone cells and it penetrates the brain. This latter property is important, as HIV-infected cells can reside in the brain and not all anti-HIV drugs get into or can stay in the brain.

Focus on tenofovir

Large clinical trials have found that, like abacavir, tenofovir is generally safe and effective. However, in some cases, this drug, which is processed by the kidneys, has been linked to kidney injury. This is usually reversible when patients stop taking tenofovir. Its use has also been linked to thinning bones in some patients.

Tenofovir also has advantages: It can be taken once daily, in some cases it may help reduce cholesterol levels and it penetrates the kidneys well. Research has found that the kidneys are rich in HIV-infected cells.

Not approved

Despite the benefits of using nukes, some patients and their doctors may prefer to avoid nukes entirely, even if the risk of potential side effects is relatively low. Other doctors and patients wish to use simplified regimens and may jettison nukes (or other classes of drugs). However, so far such strategies are not recommended as routine therapy by leading treatment guidelines in North America. Also, bear in mind that some nuke-free regimens may not be able to suppress HIV replication in the brain.

Relatively small studies have been done with simplified therapy and in some cases they show beneficial effects. The problems with such trials are as follows:

- they are small
- they probably have highly selected patients who are very motivated and therefore likely to be highly adherent
- they have other factors that prevent results from being extended to everyday use in clinics and, most importantly, approval by regulatory authorities

Still, sometimes—because of prolonged toxicity or intolerance to some medicines in patients—doctors are forced to devise unusual regimens, some of which may be nuke free.

In this issue of *TreatmentUpdate* we provide readers with results from some clinical trials of simplified therapy should doctors and their patients wish to discuss this topic. In our next issue of *TreatmentUpdate* we will have further clinical trial results from a large study of simplified therapy.

Resources

Is protease inhibitor monotherapy sufficient to keep HIV under control in the brain? – *CATIE News* [http://www.catie.ca/en/catienews/2012-11-01/protease-inhibitor-monotherapy-sufficient-keep-hiv-under-control-brain]

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D. Kaletra + raltegravir—does sparing some nukes help bones?

Once potent combination therapy for HIV (commonly called ART or HAART) is initiated, several clinical trials have found that bone mineral density tends to decrease, usually between 2% and 6%, and then stabilize. The reasons for this initial decrease are not clear.

Some studies suggest that exposure to the anti-HIV drug tenofovir (Viread and in Truvada, Atripla, Complera and Stribild) may be linked to decreased bone mineral density (BMD) in some

people. However, it is important to bear in mind that most HIV-positive people who use tenofovir in prospective clinical trials have not developed decreased BMD and subsequent fractures.

The Progress study—a summary

Researchers in several countries conducted a pilot study called Progress to compare the effect of the following two regimens:

- lopinavir-ritonavir (Kaletra) + Truvada (a fixed-dose combination of tenofovir + FTC)
- lopinavir-ritonavir + raltegravir (sold as Isentress)

When it was first introduced in 1996, the drug ritonavir (sold as Norvir) was meant to be used at very high doses as part of ART. However, at such high doses ritonavir has many side effects. Today when ritonavir (Norvir) is used, it is generally taken in relatively small doses to help boost the level of another drug, usually an HIV protease inhibitor. When used in this way ritonavir does not have anti-HIV activity, as it is merely a boosting agent. The other drug that is boosted has powerful anti-HIV activity.

In all cases in this study, Kaletra was taken twice daily, as was raltegravir. Truvada was taken once daily.

Researchers recruited 209 volunteers who had **not** been previously exposed to treatment and monitored them for up to two years.

On average, participants were about 40 years old and mostly male (85% men, 15% women).

Similar proportions of participants (71%) taking each regimen achieved a viral load less than 40 copies/ml at week 96, according to an assessment called the Food and Drug Administration's "snapshot" analysis.

Participants who experienced virologic failure were distributed as follows:

- Kaletra + Truvada – five cases; drug-resistant HIV was detected in one person
- Kaletra + raltegravir – eight cases; drug-resistant HIV was detected in three people

Participants had their CD4+ counts increase by 300 cells/ml by the end of the study.

Side effects

In general, side effects reported by patients were similar with each regimen. According to researchers, the most common side effect of "at least moderate severity was diarrhea," distributed as follows:

- Kaletra + Truvada – 16% of participants
- Kaletra + raltegravir – 8% of participants

They also stated that the following proportions of participants left the study prematurely due to side effects:

- Kaletra + Truvada – 4% of participants
- Kaletra + raltegravir – 5% of participants

Overall, two participants taking each regimen (for a total of four participants) left prematurely because of diarrhea. Thus, about 2% of participants taking each regimen left prematurely because of diarrhea.

The proportions of participants taking each regimen who took anti-diarrhea medicines were distributed as follows:

- Kaletra + Truvada – 29%
- Kaletra + raltegravir – 27%

Elevated levels of lipids (cholesterol and triglycerides) in the blood are common when protease inhibitors are used. Rates of severely elevated levels of total cholesterol were distributed as follows:

- Kaletra + Truvada – 14%
- Kaletra + raltegravir – 17%

Rates of severely elevated triglycerides were distributed as follows:

- Kaletra + Truvada – 5%
- Kaletra + raltegravir – 10%

Focus on overall changes in bone density and fractures

Among participants for whom bone mineral density scans were available, researchers noted that bone thickness was generally similar at the start of the study. However, at the 96-week mark, on average, BMD had changed as follows:

- Kaletra + Truvada – minus 2.5%
- Kaletra + raltegravir – + 0.7%

This difference was statistically significant; that is, not likely due to chance alone.

There were four fractures during the study that were distributed as follows:

- Kaletra + Truvada – one fracture each in the foot, arm and wrist
- Kaletra + raltegravir – one fracture in the hand

The study was not designed to assess the statistical importance of fractures so we cannot draw firm conclusions about their distribution and if that has any link to the regimens used in this pilot study. It is possible that the distribution of fractures may simply have been due to chance.

Researchers also assessed what they termed "clinically significant loss of bone mineral density." These were cases where participants lost BMD of 5% or more by the 96th week of the study. Overall, 12% (19 of 160 participants) had a large decrease in BMD during the study, distributed as follows:

- Kaletra + Tenofovir – 16 of 82 (20%) participants who had BMD X-ray scans taken at the start and end of the study
- Kaletra + raltegravir – 3 of 78 (4%) participants who had BMD X-ray scans taken at the start and end of the study

Factors that were statistically linked to having decreased BMD included the following:

- being 40 years or older
- being white
- having a CD4+ count less than 200 cells/ml when starting ART

Bone proteins

Although bone may feel stiff and hard, it is not dead. Bone tissue is dynamic—in adults small portions of bone are always being torn down and replaced. Researchers refer to this tearing down and building up of bone as "bone turnover." There are proteins in the blood and urine that are associated with bone turnover and can be assessed in research studies. In Progress, researchers assessed the following markers of bone turnover at several points throughout the study:

- CTx (C-terminal telopeptide of type 1 collagen)
- OC (Osteocalcin)
- P1NP (procollagen type I N-propeptide)
- BSAP (bone-specific alkaline phosphatase)

Bone turnover markers were, on average, elevated in all participants, reaching their highest level at week 48 of the study.

Early changes in some bone turnover markers were connected to a significant loss of BMD (at least 5%) at week 96, specifically these changes at week 4:

- elevated levels of CTx

Changes at week 4 in the following markers appeared to be protective from significant loss of bone density:

- elevated levels of OC and P1NP

These findings in bone markers seem novel and deserve further study in clinical trials with other medicines.

The Progress study and its sub-analyses provide important signals about changes that bones undergo once ART is initiated. Such changes should be studied with other commonly used regimens. Findings from Progress suggest that replacing Truvada with raltegravir may lead to very modest increases in BMD rather than significant loss of bone.

Bear in mind the following points:

1. The backbone of this study was the drug Kaletra. For much of the past decade in high-income countries, Kaletra was widely used both for the initiation of HIV treatment and in treatment-experienced patients. However, other treatment options became available in the past decade and Kaletra no longer holds the dominant position that it once did. Thus, while the Progress study has produced very interesting findings, it is unlikely that doctors will change the regimens of large numbers of patients to a combination of Kaletra (and raltegravir) based on the data from Progress.
2. Raltegravir costs more than Truvada. It is unlikely that formularies that subsidize the cost of HIV treatment would be willing or able to financially sustain a switch from Truvada to raltegravir among the majority of their patients over the long term.
3. The Progress study's results about bone mineral density in raltegravir users find some support from a study in Australia. There, researchers conducted a pilot study with 37 patients who had low BMD and who switched the tenofovir in their regimens for raltegravir.

Participants were monitored for 48 weeks. After the switch, researchers found that BMD increased by 2.5% to 3% in the hip and spine, respectively. Levels of bone turnover markers decreased at weeks 24 and 48 after the switch. However, the Australian study was small and of short duration and it was not randomized. As a result of these shortcomings, its findings can be at best considered suggestive not definitive. Still, it appears that for some HIV-positive patients, raltegravir is associated with modest increases in BMD when it has replaced tenofovir.

Overall, the findings from Progress and the Australian study are intriguing but require further larger randomized studies for confirmation.

Gilead Sciences, the manufacturer of tenofovir, is testing a new form of tenofovir called TAF. Interim results from clinical trials have led Gilead Sciences to suggest that TAF may be safer for the bones and kidneys than tenofovir.

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E. Darunavir-ritonavir monotherapy—impact on fat and bones

Darunavir is a powerful protease inhibitor. In a previous trial called Monet, results showed that switching to darunavir-ritonavir monotherapy from standard triple therapy (ART) is roughly as effective as ART.

The Monarch study

In a substudy of a trial called Monarch, Italian researchers recruited 30 HIV-positive participants who were taking potent combination therapy for HIV (commonly called ART or HAART) and had low viral loads (less than 40 copies/ml) and randomly assigned them to change their regimens to one of the following:

- darunavir 800 mg + ritonavir 100 mg (all drugs once daily)
- darunavir 800 mg + ritonavir 100 mg + Truvada (a fixed-dose combination of tenofovir and FTC)

In the substudy, researchers conducted multiple blood tests and repeated low-dose X-ray scans of participants to assess changes in bone density and distribution of body fat.

Results

The study lasted for 48 weeks and at that time the amount of fat deep in the belly (visceral fat) did not change significantly from the start of the study (baseline). However, all participants saw improvements in the body's sensitivity to the hormone insulin, which helps to regulate blood sugar levels.

Among participants who received darunavir-ritonavir only, there were small increases in bone mineral density, between 1% and 2%. However, these changes could have arisen because at the start of the study more participants who received darunavir-ritonavir had been taking tenofovir (in Truvada).

Levels of fat in the limbs—a substitute or surrogate for assessing fat in the face (researchers do not want to X-ray the face, as the brain could be affected by radiation)—were stable in all participants during the study.

Among participants in the substudy, there was no mention of changes in viral load—presumably because there were none.

In context

The Monarch study should be considered a well-designed pilot study. Its findings are suggestive and can be used to design a larger and longer study.

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F. Dual therapy with etravirine and raltegravir

Researchers in Barcelona, Spain, reported results from a pilot study where volunteers who were taking ART were screened and then recruited. Once in the study their regimens were changed to the following combination of just two drugs:

- etravirine (Intelence) 200 mg every 12 hours and raltegravir (Isentress) 400 mg every 12 hours

Prior to entering the study, all participants had their viral loads below the 50-copy/ml mark for at least six months.

According to the researchers, in general, participants "were [in their mid-50s]…and had a long history of HIV infection and extensive treatment experience and changed to dual therapy mostly for tolerance and toxicity problems [with their prior treatments]."

Results

Researchers reported results from 25 participants (52% male, 48% women) after at least 48 weeks of observation. At the end of 48 weeks, 84% (21 out of 25 participants) continued to have viral loads less than 50 copies/ml.

At the start of the study, CD4+ counts were about 400 cells and at the 48th week they increased to about 500 cells/ml.

All 21 participants who reached week 48 of the study with a low viral load (less than 50 copies/ml) chose to continue with the study regimen, in some cases for up to a total of 194 weeks without any problems.

There were small but favourable improvements in levels of HDL-cholesterol, glucose (sugar) and triglycerides in the blood of participants at week 48.

Adverse events

The researchers stated that two participants quit the study after eight weeks because of "gastrointestinal intolerance."

Among participants who continued in the study there were no reports of rash.

One death was reported, due to overwhelming bacterial infection. This was not due to the study drugs.

Adherence

Technicians assessed blood samples for levels of etravirine and raltegravir and found them to be "adequate," including cases where treatment failure occurred.

Overall

These results, while interesting and hopeful, are not definitive. However, the study can serve as a guide when designing a more robust clinical trial to explore the effects of dual therapy with etravirine and raltegravir.

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G. Maraviroc + raltegravir— caution needed

Researchers in France conducted an exploratory study with 44 HIV-positive participants. Their average age was 55 years and they had been taking ART for 15 years. For the five years prior to the study, their viral loads were less than 50 copies/ml.

All participants were experiencing fat gain in their bodies (lipohypertrophy). On entering the study, participants had their regimens changed to the following:

- raltegravir (sold as Isentress) 400 mg twice daily
- maraviroc (sold as Celsentri) 300 mg twice daily

Premature ending

The study called "Roc 'n Ral" was expected to last for 48 weeks. However, an independent panel of doctors charged with monitoring the safety of participants recommended that the study be halted prematurely. The researchers said this recommendation arose because of an "excessive rate of treatment failure."

Results

In total, seven out of 44 enrolled participants (recruitment was supposed to have been 90 participants) experienced the following problems:

- virologic failure (viral load persisted above the 50-copy/ml log) – five cases
- adverse events – one case of hepatitis B virus (HBV) reactivation. This occurred because neither raltegravir nor maraviroc have anti-HBV activity and the participant's previous regimen included the drug 3TC (lamivudine), which has activity against both HIV and HBV. There was also one case of rash and diarrhea.

A closer look

In two of the five cases of virologic failure, analysis of blood samples from these participants suggested that levels of raltegravir and maraviroc were very low. It is therefore likely that these two participants were not taking their medicines as directed. Furthermore, in these participants, HIV was not resistant to either drug, which is also highly suggestive that they were not taking these drugs.

In the remaining three participants, HIV became resistant to at least one of the study drugs.

All five participants with virologic failure left the study and resumed their pre-study regimen and their viral load once more fell below the 50-copy/ml mark.

There were 22 other participants whose viral loads were suppressed at the end of the study. They chose to continue taking raltegravir + maraviroc.

Other data

Assessments of blood samples found decreased levels of total cholesterol, LDL-cholesterol and triglycerides over the course of the study for most participants.

In a subset of 24 men for whom low-dose X-ray scans (called DEXA) were available both before and at the 24th week of the study, bone mineral density increased by about 1%. Had the study continued for a year, researchers suggested that this would have increased to 2%.

There were no significant changes to the distribution of body fat.

Overall

In this exploratory study, a combination of maraviroc and raltegravir was able to keep HIV suppressed in 79% of participants. Note that 100% of participants had a suppressed viral load on ART prior to entering this study.

The research team states that the combination of maraviroc and raltegravir as dual therapy "lacks virological robustness…and therefore cannot be recommended for further evaluation in a larger scale."

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II INFLAMMATION

A. A note on HIV and inflammation

It is normal for the body to respond to a viral infection by triggering inflammation within the immune system. People experience the resulting inflammation as fever, chills, sore throat, swollen lymph nodes, fatigue and so on. Inside the body much is going on as the immunological equivalent of red alert begins. Cells of the immune system are mobilized, activated and sent to sites of infection. Lymph nodes swell as the invading germ is captured, analysed, and in response the immune system makes cells with different functions—some to directly attack the virus and virus-infected cells, some to help coordinate the attack, and others to try to amplify the immune response against the virus.

In the short term, these are all generally useful steps against viruses such as those that cause the common cold or flu. However, continued inflammation and activation of the immune system over the long term carries the capacity to injure key organs and systems within the body.

Among HIV-negative people, chronic inflammation has been linked to an increased risk for cardiovascular disease, type-2 diabetes, lung disease and so on. It is very likely that the chronic inflammation detected in HIV-positive people also plays a role in these other conditions or co-morbidities.

Reducing inflammation

An essential part of keeping HIV-related inflammation low is to take potent combination therapy for HIV (commonly called ART or HAART). Taking ART exactly as directed should help people acquire virological control of HIV; that is, the production of new viruses should be kept as low as possible. This means that regular viral load measurements are below the threshold where they can be accurately counted; that is, less than 50, 40 or 20 copies/ml, depending on the viral load test that is available.

However, ART cannot completely eliminate HIV-related inflammation, as HIV-infected cells continue to produce small amounts of virus deep within the body: in the lymph nodes and lymphatic tissues, within the brain and possibly bone marrow, and occasionally in the genital tract.

This ongoing production of HIV, particularly within lymph nodes and tissues, likely causes low-level continuing dysfunction within the immune system, inflammation and prolonged activation of its cells. Therefore, additional measures are needed to help further suppress inflammation. These measures will of course differ from one HIV-positive person to another but generally include the following:

- quitting smoking
- treatment of co-infections such as hepatitis B and C viruses
- regular screening for sexually transmitted infections and treatment where necessary
- maintaining a healthy weight

Clinical trials to find ways of further suppressing HIV-related inflammation are being considered or are underway. In the future, *TreatmentUpdate* or *CATIE News* will bring results from these clinical trials.

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B. The importance of soluble CD14 and inflammation

Research suggests that one of the body's sensors to help detect invading bacteria is called soluble CD14, written as sCD14. Levels of this protein are elevated in HIV-negative people who are experiencing severe bacterial infections. Research suggests that sCD14 is released by a group of cells called monocytes. These are cells of the immune system that play multiple roles in helping to detect and fight infections.

Since the 1990s, researchers have found that sCD14 levels are higher than normal in HIV-positive people, including those with severe bacterial infections.

However, interest in sCD14 has resurged in recent years as scientists study HIV-related inflammation and its effect on the immune system and survival. Here is a summary of some findings related to sCD14 and HIV:

- Treatment with the HIV integrase inhibitor raltegravir (Isentress) as part of combination therapy can modestly reduce levels of sCD14 in the blood, particularly in HIV-positive women. However, note that levels of sCD14 even in raltegravir users remain relatively high compared to those in healthy HIV-negative people.
- High sCD14 levels in the blood are associated with an increased risk of death among HIV-positive people.
- In one study, HIV-positive women with elevated levels of sCD14 were at increased risk for cardiovascular disease.

Disagreement about lingering inflammation

Some researchers think that bacteria cause elevated levels of sCD14 in the blood. This seems to make sense because the initial work on understanding sCD14 in HIV-negative people linked this protein to bacterial infections.

The gut (or intestines) plays an important role in human health. The intestines not only absorb food but are surrounded by lymphatic tissues and lymph nodes that intercept any germs that get into our intestines. These parts of the immune system also contain many CD4+ cells. When HIV infection occurs, the immune system surrounding the gut loses many of its CD4+ cells. As a result, some scientists say that the intestines become immunologically weaker and are less able to fend off germs. A weakened intestine may allow more germs to pass through and get into the body. The intestines and their surrounding lymphatic tissue and lymph nodes may also produce more chemical signals that favour inflammation.

The leakage of bacteria from the gut into the blood is called "bacterial translocation" by researchers. Clinical trials are planned or underway to test supplements of gut-friendly bacteria (probiotics) to try to reduce HIV-related inflammation.

Beyond bacteria

Researchers in San Francisco have conducted elegant and sophisticated experiments to try to understand why monocytes produce sCD14 even in HIV-positive people who do not have bacterial infections. As part of this work, they took blood samples from both HIV-positive and HIV-negative people for analysis.

They found that monocytes from HIV-positive people seem to be activated because of exposure to interferon-alpha and not bacteria or bacterial proteins. Furthermore, activation of monocytes in their experiments resulted in the release of sCD14. The activation of monocytes in their experiments stemmed from exposure to HIV.

Other researchers in London, UK, have found that persistent activation of another group of cells—natural killer (NK) cells, which can help fight HIV-infected cells and cancers—occurs in people with HIV. This activation did not occur because of bacterial infections.

Back to the lymph nodes

What all of these studies of sCD14 have in common is that they have assessed blood for this protein. Most HIV (and most of the body's CD4+ cells) is not in the blood. Instead, most HIV and CD4+ cells are inside lymph nodes, lymphoid organs (such as the spleen and thymus) and lymphatic tissues around the gut, mouth, nose, anus and rectum.

Recently, researchers in the U.S. found that HIV-infected cells continue to produce HIV in the lymph nodes of ART users who are highly adherent and who had viral loads in their blood less than 50 copies/ml.

This discovery will likely stimulate much research to explore the impact of HIV and related inflammation. Such research may provide more clues about how to reduce HIV-related inflammation, including levels of sCD14.

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C. Raltegravir in women and reduced soluble CD14

Researchers are studying the impact of raltegravir (sold as Isentress) as part of combination therapy in HIV-positive women. In one Canadian-U.S. study, researchers enrolled women who were taking potent combination therapy for HIV (commonly called ART or HAART) and exchanged the protease inhibitor or non-nuke in their regimen for the integrase inhibitor raltegravir. Prior to this change in their regimens, all women had viral loads in their blood below the 50-copy/ml mark.

There were 36 women in total and their average age was about 43 years; most were overweight and had about 560 CD4+ cells.

For this 48-week study, half the women immediately changed their regimens and the other half delayed this change for 24 weeks.

Overall, after 24 weeks, levels of sCD14 in the women decreased significantly—by 21% among women who made the regimen change immediately. Among women who made the regimen change later, sCD14 levels fell by 10%.

Assessing inflammation

There are many potential blood tests that doctors can use to try to assess inflammation, such as the following:

- high-sensitivity C-reactive protein (written as hsCRP)
- interleukin-6 (IL-6)
- tumour necrosis factor (TNF)
- D-dimer
- soluble CD163 (sCD163)
- soluble CD14 (sCD14)

Many of these proteins and others are being studied in research laboratories and testing for them may not always be available from local labs routinely used by clinics. The ideal protein, or group of proteins, to use to assess inflammation in HIV-positive people is not known.

Back to raltegravir

What is important about the raltegravir study in women mentioned earlier is that it reported on one measure of inflammation—sCD14—and how this decreased once raltegravir was used in treatment. Future studies need to be done to confirm this effect of raltegravir in HIV-positive women.

Another study found that HIV treatment regimens that used other classes of drugs, such as protease inhibitors and non-nukes, did not significantly reduce levels of sCD14 over the long-term.

Researchers are not certain why raltegravir was associated with a reduction in sCD14, but this may arise because of its generally neutral effect on cholesterol or perhaps because of its potent anti-HIV activity.

Raltegravir belongs to a class of drugs called integrase inhibitors. Other licensed members of this class include the following:

- elvitegravir (in Stribild)
- dolutegravir (in Tivicay)

Clinical trials with these two other integrase inhibitors are underway in HIV-positive women and hopefully will also demonstrate decreases in sCD14.

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III CARE AND SUPPORT

A. Email service for patients saves time, money and clinic visits

Many HIV-positive people who are taking potent combination therapy for HIV (commonly called ART or HAART) and who do not have co-existing conditions are generally otherwise healthy. They may therefore need to see a doctor less frequently. Doctors at a major clinic in Brighton, UK, have found that the number of HIV-positive patients in their care has been increasing by 5% to 7% per year for the past 10 years. However, staffing has not increased in proportion to the growth in the patient population at the Brighton clinic.

In general, patients at their clinic fit this profile:

- 88% are taking ART
- 95% of ART users have a viral load less than 50 copies/ml
- 68% get home delivery of their medicines

The standard of care at the Brighton and Sussex University hospital clinic is to have an HIV specialist see medically stable HIV-positive patients every four months. Two weeks prior to each of these clinic visits, patients go to a lab to have their blood drawn and analysed.

In 2008 the Brighton clinic established an email service for patients with the following profile:

- have been under the care of a clinic physician for more than one year
- have stable viral load test results (at least two consecutive test results less than 40 copies/ml) or more than 350 CD4+ cells
- have no other health conditions
- have Internet access
- have a family physician

Prospective patients were told about the service and had to sign a consent form to become enrolled. Under the new system, routine visits to an HIV specialist were limited to once a year.

Out of the several thousand patients at the clinic, initially 33% (674) signed up for the email service and reduced visits. The average profile of participants who enrolled was as follows:

- 91% men, 9% women
- 88% were white
- 83% were men who have sex with men (MSM)
- participants ranged in age from 21 to 81 years with the mid-point being 47 years
- all had stable HIV infection with 93% on ART and 97% of ART users had a viral load less than 40 copies/ml
- diagnosed with HIV for 11 years

However, eventually 33 participants chose to leave the email service for these reasons:

- preferred to be seen every six months – 10 patients
- missed more frequent visits to the doctor – 7 patients
- moved out of the area – 2 patients
- problems with home delivery of medicines – 2 patients

- computer problems – 2 patients
- other, unspecified reasons – 10 patients

Temporary stops

At present, 117 patients have temporarily stopped using the new system because of the need for more intensive medical care, such as the following:

- medical issues (including HCV co-infection) – 60 patients
- entered research studies – 26 patients
- decided to initiate or change ART – 26 patients
- other reasons – 5 patients

Satisfaction

Overall, 90% of participants rated the service "good" or "excellent."

Participants particularly like the following aspects of the service:

- fewer hospital clinic visits
- access to blood test results via email
- the ability to go to the lab early (7:30 am) and how it does not interfere with their job

96% of participants would recommend the service to a friend who was HIV positive.

Patients left comments such as these:

- "for busy people the service is excellent"
- "fabulous service, roll it out for the whole country"
- "…modern patient-centred approach to chronic disease management that other services should be copying"

The Brighton researchers have found a way to save money and keep patients satisfied at the same time. Other clinics serving people with HIV and other chronic health conditions may find a similar service useful.

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B. Some HIV-positive women in Canada have poorer responses to therapy

Potent combination therapy for HIV (commonly called ART or HAART) can improve and maintain the health of people who use it. In Canada and similar countries researchers have found that the benefits of ART are so tremendous that rates of AIDS-related infections and deaths associated with AIDS have significantly declined since 1996. Furthermore, researchers predict that a young adult who is infected today and is diagnosed and initiates treatment shortly thereafter *and* who is engaged in their care and treatment *and* does not have co-morbidities (such as untreated or poorly managed depression, schizophrenia, addiction or co-infections) is likely to survive for several decades.

Focus on women

Although there have been massive reductions in AIDS-related illnesses and deaths, other troubling trends exist. For instance, in the past decade thousands of new HIV infections have occurred in Canada and women now make up nearly 25% of the population with this infection. As a comparison, in the first two decades of the HIV epidemic in Canada, women comprised 12% of cases.

In three provinces—A summary

Researchers in three provinces—British Columbia, Ontario and Quebec—recently analysed health-related information collected from 5,442 HIV-positive people since the year 2000. The researchers found that women generally began ART at an earlier age than men and that women were more likely than men to disclose that they injected street drugs. However, regardless of their history of injecting drugs, women in this study were less likely than men to achieve an HIV viral load less than 50 copies/ml. Furthermore, even if they did manage to get their viral load below the 50-copy threshold, women were more likely to have this degree of virologic control as a temporary event, as their viral loads would eventually rise above the 1,000 copies/ml level.

Reducing the amount of HIV in the blood (viral load) to the lowest possible level and keeping it there is a key goal of ART. This decrease in the production of HIV allows the immune system

to partially repair itself and usually results in improved overall health.

Study details

Researchers analysed health-related information collected from 5,442 HIV-positive people distributed as follows:

- men – 4,322
- women – 1,120

Participants entered the database when they began to take ART. This particular database, called CANOC, collects health-related information from major HIV clinics in BC, Ontario and Quebec.

Researchers working with the CANOC database sought differences in responses to ART between men and women.

Results

In general, prior to starting ART women tended to be younger (36 years) than men (41 years) and had lower viral loads (40,000 copies/ml in women vs. 79,000 copies in men). Also, more women (44%) than men (29%) disclosed a history of injecting street drugs. Women were more likely to be co-infected with hepatitis C virus (HCV) than men.

Regardless of drug use

Whether or not women in the study had a history of injecting street drugs, they were more likely than men to have poorer responses to ART. That is, their viral loads were less likely to fall below the limit of detection (50 copies/ml).

Furthermore, women who were able to suppress their viral load below the 50-copy/ml mark were more likely to eventually have it rise above 1,000 copies/ml compared to men.

Despite all this, researchers could not detect any significant differences in survival between men and women.

Reasons for differences

The CANOC researchers based their study on medical records stored in a database. Such records are relatively incomplete and so they are unable to give a precise reason for the differences that were found. Nevertheless, there are several possible reasons that could explain the study's findings, such as the following:

1. There are relatively high rates of women with a history of injecting street drugs in this study. This is probably due to the recruitment of many women from BC, where generally there are higher rates of drug use among HIV-positive patients than in other provinces.
2. The CANOC study has limitations—data were collected and analysed from three provinces. Moreover, the data from BC consisted of all HIV-positive people who were taking treatment in that province. In contrast, data from the other provinces were from selected clinics.
3. Information on participants' ability to take ART every day exactly as directed was not available.
4. Some medical records might have been incomplete, specifically about whether or not patients had a history of injecting street drugs.
5. Not all deaths that occurred among participants were captured in medical records.

The big picture

Despite these potential shortcomings, it is clear that some HIV-positive women in care do not achieve the best possible outcome when using ART. There are likely many factors that affect the health of HIV-positive women who were in this study, including factors such as domestic violence, prioritizing the care of other family members, social isolation and its consequences (anxiety and depression). Whatever the underlying reasons for the differences between genders found in this analysis, the findings have uncovered a troubling issue. Other studies are needed at the local clinic level in at least the three provinces that contributed to this study to assess the reasons for the poorer virological response among women. Such studies could be used as a starting point for improving the health of HIV-positive women in Canada.

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Disclaimer

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

CATIE (Canadian AIDS Treatment Information Exchange) in good faith provides information resources to help people living with HIV/AIDS and/or hepatitis C who wish to manage their own health care in partnership with their care providers. Information accessed through or published or provided by CATIE, however, is not to be considered medical advice. We do not recommend or advocate particular treatments and we urge users to consult as broad a range of sources as possible. We strongly urge users to consult with a qualified medical practitioner prior to undertaking any decision, use or action of a medical nature.

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Credits

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What CATIE Does

CATIE is Canada's source for up-to-date, unbiased information about HIV and hepatitis C. We connect people living with HIV or hepatitis C, at-risk communities, healthcare providers and community organizations with the knowledge, resources and expertise to reduce transmission and improve quality of life.

For more than 20 years, CATIE has been there to provide information that enables people to make informed choices about their health and enhances the ability of healthcare providers and other frontline organizations to respond to their clients' needs.

CATIE provides such information through a comprehensive website (www.catie.ca), electronic and print resources, webinars and other online learning, a national reference library, regional conferences, subscriptions to e-newsletters and a confidential phone inquiry service.

CATIE Publications

TreatmentUpdate
CATIE's flagship treatment digest on cutting-edge developments in HIV/AIDS and hepatitis C research and treatment. Subscribe to *TreatmentUpdate* and automatically receive an email notifying you the moment a new issue is available online or contact us at 1.800.263.1638 to receive a print subscription.

CATIE News
CATIE's bite-sized HIV and hepatitis C news bulletins.

HepCInfo Updates
CATIE's bi-weekly electronic newsletter highlighting key hepatitis C prevention, treatment and epidemiology information.

A Practical Guide to HIV Drug Treatment
The latest on what is known about the various aspects of treatment, including a description of the virus and the immune system, the stages of HIV disease, the tests used to assess health status, and anti-HIV medications.

A Practical Guide to HIV Drug Side Effects
The latest on what is known about various side effects related to treatment, from appetite loss to sexual difficulties, and tips for countering or preventing them.

***The Positive Side* magazine**
Holistic health information and views written by and for people living with HIV.

Fact Sheets
Concise overviews of conditions, symptoms, medications, side effects, complementary therapies, vitamins, herbs and other treatment issues.

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