CCR5 antagonism

This month’s ATU focuses on the newest class of antiretrovirals, CCR5 antagonists. Three drug companies, all hoping to produce the first oral entry inhibitor, currently have major trials enrolling worldwide.

It is a concern that these drugs, which have only been tested so far in Phase I, dose-finding studies, are now being offered to thousands of HIV-positive trial participants all over the globe, in combined Phase II/III trials. This fast-tracking pleases some US treatment advocates, who are, rightfully, dissatisfied with currently approved antiretrovirals, and are eager to see how well this exciting new class performs in both treatment-naïve and treatment-experienced people.

However, some European treatment advocates, the EATG, after being asked to consult on the design of these trials, have gone public with their concerns that people new to treatment with low CD4 counts and high viral loads may fall through the cracks and needlessly suffer if the drugs don't work for them.

The CCR5 controversy is similar to concerns about protease inhibitors (PIs) exactly a decade ago. Some were desperate to get on them; others warned there could be unforeseen problems ahead. In hindsight, PIs have saved many lives in the short- and mid-term, but long-term issues of cross-resistance, lipodystrophy and heart attacks have since been discovered.

Can we learn any lessons from the development of PIs to ensure that this new class of drugs doesn't produce winners and losers all over again?
what we know (and don't know) about the next class of antiretrovirals, by gus cairns

The newest class of antiretrovirals on the development fast-track, CCR5 antagonists, promise to be the first oral anti-HIV drugs that prevent HIV from entering cells. If all goes well, they may become widely available by 2007-8; they are currently only available in clinical trials that are enrolling in the UK and worldwide. Since they can be made into pills, these entry inhibitors will be easier to take than the one currently approved fusion inhibitor, T-20 (enfuvirtide, Fuzeon), which has to be self-injected. It is hoped that, since CCR5 antagonists do their work outside of cells, they may produce fewer side-effects than most of the currently available anti-HIV drugs, although elsewhere in this newsletter, we question that assumption. Here we explain how CCR5 antagonists were discovered, what they are and how they work.

Summary
- CCR5 antagonists are the latest class of anti-HIV drugs to have reached the stage of widespread testing.
- They work by blocking the way some types of HIV attach themselves to cells.
- They have the potential to cause fewer side-effects.
- They also have the potential to make people sicker.
- Due to the fact that they have so far only been tested in small numbers of HIV-positive people for very short periods we don't know yet if taking them will make people better or sicker in the medium- or long-term.

What are CCR5 antagonists?
In 1995, the co-discoverer of HIV, Robert Gallo, discovered that three naturally occurring body chemicals called chemokines could inhibit HIV replication. Chemokines are a type of cytokine - chemicals that allow communication between different parts of the immune system. Gallo's discovery led to the realisation that, in order to enter a cell, HIV needs to latch on to two molecules on the surface of a cell in a particular order, in a complex three-stage entry process. CCR5 inhibitors interfere with the second stage of this process, by stopping HIV attaching itself to the chemokine co-receptors. At first it was thought that HIV targeted just one co-receptor molecule, which was called fusin. But it was quickly discovered that there were, in fact, two - CXCR4 (sometimes still called fusin) and CCR5. The 'C' in each of these terms stands for an amino acid called cysteine, a component of all proteins. CCR5 has two cysteine molecules in a row - so it's Cysteine-Cysteine Receptor 5 (there are four other CCRs, to which HIV doesn't seem to be attracted). CXCR4 inserts another amino acid (the 'X') in between its cysteine pairs.
When a nasty virus turns nastier
It has been known since the early 1990s that an ominous sign that an individual was progressing to AIDS was when their CD4 cells began to merge into big, baggy, useless clumps called syncitia (which can also be spelled, confusingly, as synctia or syncitia). When syncitia formed, the individual’s CD4 count would rapidly start to fall.

It was also known that only certain strains of HIV caused these syncitia to form, and those strains became known as SI (for-syncitium-inducing) strains, as opposed to NSI (non-syncitium-inducing) strains. The discovery of the two different co-receptors explained the difference between SI and NSI virus. SI viruses are the ones that like to latch on to the CXCR4 chemokine receptor, while NSI viruses latch on to the CCR5 receptor.

This explained the very different behaviour of the two viral strains. The CCR5 molecule develops on cells that patrol the body’s boundaries, such as the skin and mucous membranes, and in particular cells called macrophages. In contrast, the CXCR4 receptor is found mainly on CD4 and CD8 cells. These tend to lurk deep inside the internal organs and recesses of the immune system - for example, in lymph nodes - until called upon by the immune system.

Navigating the tropics
What this means is that more than 99% of the HIV that gets passed from person to person is attracted to CCR5. These strains of virus are known as 'R5-tropic'. The term 'tropic' means having an affinity for a particular target or stimulus, or simply 'attracted to'. Confusingly, again, R5-tropic virus is also known as 'M-tropic' because it likes to link to macrophages.

The chemokines that link to CCR5 are the very ones that Robert Gallo found prevented HIV infecting cells in the test-tube. That’s because they occupy the CCR5 receptors - so HIV doesn’t get a look-in. Gallo realised that if you could make a compound that blocked the CCR5 receptor but had no other biological function, you would have a new kind of anti-HIV drug.

Importantly, it seemed that blocking the CCR5 receptor was not likely to have any disastrous biological effects, because one-in-fifty Caucasians have a genetic mutation which means their body can’t make the CCR5 receptor. This makes them almost completely immune to HIV infection (see ‘CCR5 antagonists: the long run’ on pages 8 and 9 for more on this). However, a CCR5 blocker would only stop R5-tropic viruses. What about the X4-tropic viruses (also called 'T-tropic' because they latch on to T-cells)?
What we don't know
There is a lot we don't yet know about the switch from CCR5 to CXCR4 virus, which is called 'tropism' or 'receptor' switch.

We don't know exactly what proportion of viruses in a person's body are capable of locking on to CXCR4. It used to be thought that only a tiny minority of people were initially infected with X4-tropic virus, and that for most people, as HIV infection developed, the virus spontaneously mutated and the proportion of X4-tropic virus increased. It now looks as if this is a difficult shift for HIV to perform, and that, in fact, a much higher proportion of people are infected with a 'bit' of X4-tropic virus, which begins to predominate in the long term.

Two studies of newly-infected people3,4 have found that while virtually no-one is infected with 'pure' X4-tropic virus, a significant minority (12% in one study, 17% in another) are infected with a mixture of X4- and R5-tropic virus and/or with dual-tropic virus (which can infect cells using both the CCR5 and CXCR4 receptors). And the TORO studies of T-20 (Fuzeon)5 showed that in treatment-experienced people, that proportion goes up to between a third and one half.

We also don't know exactly what changes HIV has to make to its surface envelope, including its gp120 protein, in order to turn from R5-tropic to X4-tropic. Preliminary studies6,7 suggest that the kind of HIV that is easily transmitted has fewer components to a part of the protein backbone of its gp120 molecule called the V1 and V2 loops than do the majority of viruses in infected people. It's also less heavily 'glycosylated'. (As HIV 'matures' within the body, new generations of the virus tend to coat their gp120 molecules with sticky sugar molecules. This is called glycosylation.)

The theory is that it's the change in shape caused by glycosylation that enables HIV to lock on to the CXCR4 receptor and directly invade T-cells. But it's the added sugars that make the resultant X4-tropic virus more harmful, because they block the limited containment of HIV that the body is initially able to make. This is because they stop anti-HIV antibodies (the very ones that are picked up in HIV tests) from getting in the way of gp120's 'docking mechanism'.

Importantly, we don't yet know whether the appearance of X4-tropic viruses is the cause of the accelerated loss of CD4 cells, or whether falling CD4 cell numbers permit X4-tropic virus to start predominating.

Will CCR5 antagonists make us healthier or sicker?
All of the things that we don't yet know lead to the following question: if we give people a drug that blocks CCR5 and stops R5-tropic virus reproducing, will it make some people sicker quicker, by 'pushing' more of their virus population towards becoming CXCR4 virus? This question, and other concerns regarding the currently-recruiting CCR5 antagonist studies, will be explored in 'CCR5 antagonists on trial' on page 5.
There are many things that we don't yet know about CCR5 antagonists. As well as concerns about this class of drugs in general - will blocking CCR5 make some people sicker quicker, by 'pushing' more of their virus population towards becoming the more harmful CXCR4 virus? - currently-enrolling CCR5 antagonist trials are causing a great deal of controversy and dividing treatment advocates around the world. Is the three-horse race to produce the first CCR5 antagonist putting the health of HIV-positive people unnecessarily at risk?

Under starters orders…
Although there are several more candidates, there are currently three drugs that have similar properties and are at almost identical stages of development. They are:

- SCH-417690 (formerly SCH-D), from Schering-Plough;
- GW873140, from GlaxoSmithKline;
- UK-427857, now called maraviroc (a generic, not a trade name), from Pfizer.

All three drugs completed phase I safety and dosing studies in small numbers of people with HIV in 2003-4.

- SCH-417690 was given in three different doses to a total of 35 HIV-positive people in 2003 for 14 days. It produced a 1.5 log drop in viral load at the two highest doses.

Summary
- The EATG recommends that you should not join one of the CCR5 inhibitor trials for treatment-naive patients if you have a CD4 count under 150 cells/mm³ and/or a viral load over 100,000 copies/ml.
- If you are going to join one of these trials, it's very important to have a resistance test done beforehand. You should not join the trial if you have any resistance to other drug classes, as this will restrict your options if the experimental treatment fails.
- As part of the trial, your HIV will be tested for its 'tropism', but be aware that these tests cannot pick up minority populations of X4-tropic virus (under 5-10%).
- If you are considering joining one of the trials for treatment-experienced patients, remember that, like any other anti-HIV drug, CCR5 antagonists won't work on their own, so it's vital that your doctor selects the best 'optimised background' regimen for you, based on resistance tests.
GW873140 was given to a total of 40 people in four different doses for 10 days last year, again producing about a 1.5 log drop in viral load.

Maraviroc was given to a total of 63 people at eight different doses for 10 days last year, and produced a similar 1.5 log drop in viral load at the five highest doses.

Larger studies of all three drugs are now either underway or about to start:

- Two studies of SCH-417690 are already underway - ACTG5211 in the US, and P03802 in Canada and Europe, but not the UK. The first trial gives three different doses of the drug to volunteers, in addition to their regular antiretroviral therapy. The second one gives 14 days' worth of the drug alone and then adds in AZT/3TC (Combivir).

- Two studies of GW873140, both of which will be in individuals new to HIV treatment, are about to start worldwide, including various UK sites. One will give two different doses of the drug plus boosted lopinavir (Kaletra) to 175 people; the other will give 120 participants two different doses of the drug, plus Combivir.

- Three different studies of maraviroc have just begun worldwide, including several sites in the UK. One (A4001026) offers once- or twice-daily maraviroc plus Combivir to participants who have never taken HIV treatment. Another (A4001028) will give the drug, plus the best available HAART regimen (often called an 'optimised background regimen'), to people who have resistance to at least one drug in three of the four current anti-HIV drug classes. These studies are intended for people with R5-tropic virus alone, but a third, smaller study, A4001029, will give maraviroc plus 'optimised' HAART to people who have mixed-tropic virus, to see what happens.

Tropism problems so far

Nikos Dedes is Chair of the European Community Advisory Board, part of the European AIDS Treatment Group (EATG).

"The problem is this," he tells ATU. "The tests that determine viral tropism are new, and can't pick up on X4-tropic virus if it forms less than 5-10% of a person's virus.

"If a drug-naïve person with a minority of CXCR4 virus strains takes part in one of these trials," he adds, "they are likely to experience drug resistance because they'll basically be on Combivir or Kaletra alone," depending on the study.

Studies of the three drugs so far have already included at least one individual who developed, or was discovered to have, X4-tropic virus during the trial. In the Schering and GSK trials, one participant in each trial turned out to have some X4-tropic virus that was not picked up in tests. However, despite the fact that the X4-tropic virus appeared after about 10 days, these individuals still experienced some reduction in viral load.

In the maraviroc study, one person was inadvertently enrolled who had X4-tropic virus that should have been detected, and did not respond to the drug. X4-tropic virus emerged near the end of the dosing period in another two individuals. X4-tropic virus 'went away' in one of these two participants after the drug was
stopped, but the other person still had mixed R5- and X4-tropic virus 40 days later.

However, with the exception of the participant with the undetected X4-tropic virus, all of the others did, in fact, respond to the drug. So all we can say is that at present we don't know what the impact of these drugs will be on people who have a mixture of X4- and R5-tropic and/or dual-tropic virus.

**Breakdown in communication**

*We first became aware of the design of these trials when Schering-Plough approached us last summer with the suggested protocol of their P03802 study,* says the EATG’s Dedes. "We were pleased they’d approached us but we didn't like what we read. The protocol said that anyone new to HIV treatment with a CD4 count over 50 cells/mm³ could join the trial. We felt this was unacceptable. Schering eventually agreed that no one with a CD4 count under 150 cells/mm³ should be recruited.*

*Pfizer approached us last August with their protocol. There was no lower CD4 limit at all for their naïve patients’ trial (we’re very happy with the trials for experienced patients). Pfizer said they’d informally recommend a limit of over 100 cells/mm³, but we want it stated in the protocol so that less-informed physicians don’t enrol vulnerable patients.*

*GSK approached us soon after Pfizer and agreed to a lower CD4 limit of 100 cells/mm³.*

Last month, after persuading state regulatory authorities in France, Germany and Spain not to allow the Pfizer study to recruit treatment-naïve individuals until the protocol was changed, the EATG issued a press release. In it they demanded that the "unethical" Pfizer study in treatment-naïve individuals “be changed” worldwide because, they say, it is unnecessarily putting people with HIV who have severe immune suppression at risk. They have since demanded that GlaxoSmithKline (GSK) change its protocol, too.

**Difference of opinion**

Individuals with low CD4 counts and/or high viral loads are at the highest risk of disease progression, and, argue the EATG, could benefit from currently available treatment options. It is often also the case that treatment-naïve individuals with advanced HIV disease have only recently been diagnosed with HIV and/or AIDS, and may not be in the best position to make informed treatment decisions.

"We don't see that there’s any medical rationale to put people with 80 CD4 cells on these regimens," says Dedes. "These days we have drugs that work for most people, so why be in such a hurry? Make it people who would not be endangered by one ineffective regimen, with, say, CD4 counts of 250-350.*

However, leading US activists are critical of the EATG’s position. Bob Huff, Editor of *GMHC Treatment Issues* says that "this is not an opinion shared by all HIV treatment activists. The opinions about whether this trial is ethical are based on individual beliefs about ethics, not on a careful consideration of the specifics of the drug and the science,* he says.

Mike Youle, Research Director at the Royal Free Hospital in London, one of the UK sites of the Pfizer and GSK trials, is confident that the studies are ethically sound. "The drug companies have listened to the EATG’s arguments and have made moves to modify the protocols,* he says.

He has other concerns, however. "I think the biggest problem will be managing disappointment if the first few patients have mixed-tropic virus and therefore fail to get a good drop in viral load."

"Until we get a CXCR4 inhibitor to go with these CCR5 antagonists, there remains a question about how best to use CCR5 antagonists,* he adds. "*CCR5 antagonists should work best in early infection, but at present the guidelines all suggest using them later.*"

**It’s your choice**

It is in the nature of clinical trials that some will fail. By participating in a CCR5 inhibitor trial you are consenting to a treatment whose efficacy is uncertain. On the other hand, there is a chance that the experimental drug could come to form an effective part of your HIV combination therapy - while preserving other more conventional classes of drugs for future treatment options.

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**further information**

NAM produces a Patient Information Booklet called ’Clinical Trials’ which can help you decide whether or not entering a study is right for you. ’Clinical Trials’ can be downloaded from [www.aidsmap.com](http://www.aidsmap.com) and it is also available for free by calling us on 020 7840 0050 or by emailing: info@aidsmap.org.uk

Check [www.aidsmap.com](http://www.aidsmap.com) for the latest clinical trials in your area, or ask at your HIV treatment centre.

See the April 2005 news feature, ‘European activists claim Pfizer’s CCR5 antagonist trial unnecessarily putting most vulnerable at risk; US activists disagree’ on [www.aidsmap.com](http://www.aidsmap.com) for more on the CCR5 antagonist controversy.

**references**

1. See Kuritzkes D. 12th CROI, Boston, oral presentation 57, 2005.
Whilst controversy over CCR5 antagonists has focused on their effects on HIV in individuals with more advanced disease, there has been little discussion of their potential for long-term toxicity. Indeed, the companies spearheading the development of this new drug class have been remarkably upbeat about the long-term safety of their experimental products.

Haven’t we been here before? Back in 1995 protease inhibitors were on the horizon, and were considered to have little potential for long-term harm.

Within three years, lipodystrophy had been recognised as a side-effect of protease inhibitor treatment and the first reports of heart disease associated with the drug class had surfaced.

Summary

- CCR5 antagonists will do artificially what 1-in-50 Caucasians already have naturally; stop HIV from using the CCR5 co-receptor to attach to CD4 cells.

- Studies of people with this natural genetic mutation have found that they mostly come to little or no long-term harm. In fact, they had a reduced risk of heart attack, decreased severity of multiple sclerosis and rheumatoid arthritis and improved survival after kidney transplant.

- However, other studies have found that people who lack the CCR5 co-receptor are also more prone to hepatitis C infection, have more severe cases of lupus, and that women with certain kinds of breast cancer have a shorter disease-free survival time.

- CCR5 antagonists might offer fewer short-term side-effects than other classes of antiretrovirals, but until people have been on them for several years we won’t known the mid- and long-term side-effects.

The good - and the bad - news

This time around, beliefs regarding the long-term safety of the CCR5 antagonists appear to be derived from studies that looked at the effects of the CCR5 delta 32 polymorphism in HIV-positive and HIV-negative people.

These studies show little or no long-term harm to individuals who lack one or both of the gene sequences that determine the presence or absence of CCR5 on immune cells.

Indeed, CCR5 polymorphisms have been associated with a reduced risk of heart attack, decreased severity of multiple sclerosis and rheumatoid arthritis and improved survival after kidney transplant.

However, a number of worrying findings did emerge from these studies:

- Individuals with the CCR5 delta 32 polymorphism experience more severe cases of lupus (a very serious, chronic, autoimmune disorder), and other serious inflammatory diseases¹.

- In women with breast cancer that is not associated with the more aggressive p53 mutation, disease-free survival after initial intervention was shorter in those with the CCR5 delta 32 polymorphism². Normally, women with the p53 mutation have a poorer prognosis than those without. On the other hand, the development of the p53 mutation has been found to be less common in women with the CCR5 delta32 polymorphism. Given the role of the p53 gene as a tumour suppressor in other human cancers, further research is needed in this area. Spanish researchers reporting the finding stated:
"These results indicate that the role of chemokines in tumour progression is complex and poorly understood." Pfizer plans to look at the effects of maraviroc on tumour development in a test-tube model. Dr Steve Felstead, development leader for maraviroc, told ATU that it is important to bear in mind that the Spanish findings on breast tumours need to be confirmed by other groups.

The CCR5 delta 32 polymorphism was more frequently found in patients with chronic hepatitis C infection, and these patients had higher HCV viral load.

In addition, studies in mice genetically engineered to lack the CCR5 receptor show that antibody responses to certain infections are also poorer. These infections include cryptococcus and listeria.

**CCR5 and hepatitis C**

The effect of CCR5 antagonists on hepatitis C has been the subject of controversy, but after initially excluding people with HIV and hepatitis C virus (HCV) coinflection from their studies, drug companies are becoming more confident that CCR5 antagonists will not have a negative effect in people coinfected with HIV and HCV.

CCR5-associated immune responses appear to be important for clearance of primary HCV infection and for the success of interferon monotherapy, so the absence of CCR5 might be expected to result in higher rates of HCV infection and studies do indeed show that people with the CCR5 delta 32 polymorphism are more likely to be infected with HCV (although less likely to be infected with HIV, since the polymorphism is protective against HIV) and less likely to clear HCV after interferon monotherapy.

Whether these findings have any relevance for people with HCV is questionable, since they are already infected, and interferon monotherapy is now considered sub-standard treatment. In fact, several studies have now shown that people without CCR5 receptors are significantly less likely to have liver inflammation and also have milder fibrosis, implying that CCR5 antagonists might benefit people with HCV.

Drug companies developing CCR5 antagonists now appear to be comfortable enough with these findings to recruit coinfected people with liver enzymes within the normal range to clinical trials, but longer-term studies following large numbers of people with HIV and HCV will be needed in order to review the effect of this new drug class on liver disease in coinfected people.

**Potential positive impact of CCR5 antagonists on long-term toxicity**

CCR5 antagonists could help reduce long-term toxicity if they turn out to have no substantial side-effects of their own. CCR5 antagonists might permit a shift away from the use of nucleoside reverse transcriptase inhibitors, like AZT (zidovudine, Retrovir, also found in Combivir and Trizivir) and d4T (stavudine, Zerit), that are associated with mitochondrial toxicity and which can lead to fat loss and nerve damage.

Lipid elevations have not been reported in the limited populations studied so far, so CCR5 antagonists might also permit more lipid-friendly drug combinations to be prescribed and might reduce the risk of cardiovascular disease in people with elevated lipids, especially those with multiple risk factors for heart disease. However, if CCR5 antagonists prove to be more successful when levels are boosted by ritonavir, lipid benefits might be lessened.

What is the CCR5 delta 32 polymorphism?

This is a genetic mutation (also known as a polymorphism) that occurs naturally in just under two percent of Caucasians, but is found less commonly in people of African heritage. Since studies have suggested that plague and smallpox use the same CCR5 receptor as HIV to infect cells, this genetic mutation may have become more common in Caucasians due to the widespread smallpox and bubonic plague epidemics in Europe during the Middle Ages. People with two copies of this mutation are almost completely protected against HIV. Those with one mutated and one normal copy can be infected, but they tend to have lower viral loads, and natural disease progression is slower. People with two normal copies of the CCR5 gene are most susceptible to HIV infection.

**Further information**

For more details on hepatitis C and CCR5 antagonists see the March 2005 news story, CCR5 antagonists unlikely to aggravate hepatitis C infection, French study reports on www.aidsmap.com

**References**

UK sexual health services improving, but could do much better

A survey conducted by the Terrence Higgins Trust (THT), the British HIV Association (BHIVA) and the Providers of AIDS Care and Treatment (PACT) has found that sexual health services improved slightly in the UK last year, but many clinics are still finding it hard to provide appointments and are turning away patients. Only a quarter of doctors reported being able to provide an appointment for a sexual health screening within a week, and over a third said that waiting times for an HIV test were over two weeks. A third of doctors also said that they often had to turn away patients without providing treatment and 66% said that they expected to overspend their drugs' budget.

Terrence Higgins Trust, PACT, BHIVA. Clinical Trials? The third annual survey of how English HIV and sexual health clinicians and Primary Care Trusts view their services. January 2005.

Two UK studies find that many are being diagnosed with HIV later than necessary

Between 1993 and 2002, one in four of the gay and bisexual men in England and Wales diagnosed with HIV were diagnosed after their CD4 cell count had fallen below 200 cells/mm³. This put them at greater risk of illness, and gave them a ten times higher risk of death within one year, than people who had higher CD4 counts at diagnosis. One study has found that late diagnosis was associated with living outside London, non-white ethnicity and older age.

Another study, from south London, has found that Africans have their HIV diagnosed at a later stage than white or Caribbean individuals. The investigators also found that, compared to both white and Caribbean individuals newly diagnosed with HIV, Africans were more likely to be diagnosed while they were hospital in-patients and were less likely to perceive themselves as being at risk of HIV.


Diagnosing and treating depression can help with pill adherence

A study has found that adherence to antiretroviral therapy is improved by antidepressant treatment in depressed HIV-positive people. Depression is more common in HIV-positive people than in the general population: studies have found that HIV-positive people have a 22-45% chance of being diagnosed with depression during their lifetime, compared with a 15% chance for the general population. Untreated depression has been associated with reduced adherence to
antiretroviral medication. In this study, 65% of depressed people on antidepressants and antiretroviral therapy took their medicines on time compared with 35% of depressed people on antiretroviral therapy but not on antidepressants. The study suggests that diagnosing and treating depression - whether it is treated with antidepressants or therapy, or both - might help those of us who are struggling with taking antiretrovirals on time but might not be aware that we are depressed.


Don't take efavirenz during pregnancy

The US arm of Bristol-Myers Squibb (BMS), the drug company that makes efavirenz (Sustiva), has sent a letter to healthcare providers strengthening their previous warning about the use of efavirenz during pregnancy from "risk of foetal harm cannot be ruled out" to "positive evidence of foetal risk". This is a reaction to four reports of serious birth defects occurring in the brain or spinal cord of infants born to women who took efavirenz during the first three months of pregnancy. BMS advise women who are capable of becoming pregnant to have a pregnancy test before starting treatment with efavirenz and suggest that women who take efavirenz use barrier contraception (e.g. the male and/or female condom or diaphragm) in combination with other contraceptive methods.

Don't combine tenofovir and ddI

The European Medicines Agency (EMEA) and its Scientific Committee for Human Medicines (CHMP) have issued a clear warning about combining tenofovir (Viread) and ddI (Videx/Videx EC). This follows previous reports of this combination leading to treatment failure in people taking anti-HIV therapy for the first time, and CD4 declines in treatment-experienced people. They say that use of tenofovir and ddI together is not recommended in any antiretroviral combination, and particularly not for individuals starting treatment with high viral loads and low CD4 cell counts. If a combination that includes both tenofovir and ddI is considered absolutely necessary, doctors should be monitoring their patients very closely to ensure that the regimen is working and that they are not developing side-effects.

Soft gel saquinavir and ddC to disappear in 2006

Drug company Roche has announced that it will discontinue production of two of its antiretrovirals, Hivid (zalcitabine, ddC) and Fortovase (soft gel saquinavir) in 2006 or shortly after. The protease inhibitor Fortovase has been superseded by the development of a 500mg Invirase (hard gel saquinavir) tablet that is better tolerated when boosted with ritonavir. The nucleoside analogue (NRTI) ddC, the third anti-HIV drug to be licensed (after AZT and ddI), was never very popular due to its association with peripheral neuropathy. It is no longer recommended as a preferred component of combination therapy in the UK and US, and is not recommended as a component of regimens for resource-limited settings by the World Health Organisation. Roche says that it is giving plenty of advance warning so that both doctors and patients have time to consider alternative options and move onto them.

UK guidelines for liver transplants in HIV-positive patients published

The first-ever UK guidelines for liver transplants in HIV-positive individuals have been published after consultation between the British HIV Association (BHIVA), the UK and Ireland Liver Transplantation Centres and the British Transplantation Society Standard Committee. They can be downloaded from the BHIVA website: www.bhiva.org.

Next month’s ATU

In June, we will be re-examining the legal aspects of HIV transmission in the light of recent court rulings, as well as helping women choose the best contraception method to complement their antiretroviral therapy, and vice versa.
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