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editorial

Welcome to the second issue of AIDS Treatment Update to cover the 13th International AIDS Conference held in July. This month we review two issues which dominated proceedings at the Durban conference – the transmission of HIV from mother to baby, and the political machinations which surround moves to open up access to health care.

Durban examined the relationships between science, economics and politics in a way that most AIDS conferences fail to pull off, and was all the more refreshing for this change of focus. Working and living in London, it's easy to neglect these connections when reporting medical advances. Not so post-Durban. While the Mbeki government's HIV policy seems likely to be leading to an African Renaissance, it's perhaps not of the kind many would wish for. In a week of ghastly statistics and grislier estimates, the two which made most impact locally described a future South Africa where, if the epidemic continues unchecked, half of all 15 year olds will die because of AIDS, and the toll on the Black population will soon deliver a White majority.

Fitting then that we launch AIDS Treatment Update's new, twelve page format this month. You'll now find glossary terms explained alongside articles, better spacing of the text, and room enough to include graphics to help explain difficult concepts. These design features are all about making ATU an easier read. Please let us know what you think.

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treatment access

2 90% of people with HIV remain excluded from the achievements of modern HIV treatment by keith alcorn

Anti-HIV drugs remain out of reach of the vast majority of the population in many poor nations. In Uganda, the average cost of a triple regimen is equal to the salary of the highest paid government official. Initiatives from the United Nations Joint Programme on AIDS (UNAIDS) have failed to reduce drug costs; whilst prices have fallen in Cote d'Ivoire due to the government's introduction of tendering for the supply of antiretrovirals, they have remained stable or have risen in Uganda due to non-competition and a fluctuating exchange rate. For example, AZT costs \$2.43 a day in Cote d'Ivoire and \$4.34 in Uganda. This highlights the potential for drug prices to be reduced where the national government takes responsibility for procurement, rather than relying on drug donations from pharmaceutical companies.

On May 11 this year, five multinational pharmaceutical companies announced they would work with UNAIDS to look at improving access to treatments for HIV and AIDS in developing countries.

The announcement was widely interpreted as a promise to cut prices across the board, inspired by the fear that if the companies do not act, they will be undercut by generic drug manufacturers in Brazil and India who can make anti-HIV drugs much more cheaply. At the XIII International AIDS Conference in Durban in July, many delegates from developing countries were angered to learn that what they had read to be a promise to cut prices immediately was in fact a rather vague pledge to look at ways of improving access to treatments on condition that international

donors stump up the money, and intellectual property rights are respected.

The effect of TRIPS

The TRIPS (Trade-Related Aspects of Intellectual Property Rights) agreement, which applies to all 135 member nations of the World Trade Organisation, is intended to protect the intellectual property rights of patent holders. This allows for owners of intellectual property to control the exploitation of their inventions worldwide, determining the price at which they can be sold and the royalties they receive.

TRIPS is argued by its advocates to be essential for effective international trade. Companies need to know that their patents will be honoured worldwide, and that that they will have exclusive rights over a patent for the same period in every country. However, some countries do not presently observe the TRIPS agreement. For example, India only protects patent holders' rights for seven years, which has made it profitable for domestic drug manufacturers to produce their own versions for the mass market before the drug becomes old news. Adoption of the TRIPS agreement will extend patent rights to twenty years.

India is expected to begin to implement patent protections by 2005 under the TRIPS agreement. Whilst some domestic biotech businesses will benefit from the protection of their discoveries, India's generic drug industry will lose future opportunities to produce cheap versions of drugs like AZT, 3TC and nevirapine. A combination of these drugs costs less than \$100 a month from the Indian

manufacturer CIPLA; in comparison, the same combination supplied through a UNAIDS drug access initiative in Uganda costs \$750, roughly the same as it would in the UK.

Parallel imports

In India, Glaxo Wellcome has registered 3TC and sells it at a lower price than in the UK or Europe. However, the Indian version of 3TC is packaged in Hindi and two other Indian languages, which prevents its exportation to other countries, where the drug would likely be on sale at a higher price. These are called parallel imports.

Pharmaceutical companies like Glaxo Wellcome will be better protected from parallel imports by the TRIPS agreement, but people with infections such as thrush in many developing countries won't be. *Diflucan*, a drug made by Pfizer used to treat oesophageal thrush, costs the South African government \$4/tablet. A Thai version of the same drug, fluconazole, costs 28 cents/tablet, but its import into South Africa will be illegal under the TRIPS agreement. Mark Heywood of South Africa's Treatment Action Campaign says that activists will travel to Thailand and bring the drug back in their luggage until the South African government grants a compulsory license to make a cheap version of fluconazole. Flights from Johannesburg to Bangkok are likely to be fully booked for some time: oesophageal thrush is the most common AIDS-defining illness in South Africa after TB.

French-speaking countries in Africa have been locked into an even tighter agreement which forbids parallel imports from outside the

Francophone bloc, thus preventing these nations from benefiting from generic production in South Africa, Brazil, Argentina, China, Russia, Thailand or India.

Examples of success

Whilst poor infrastructure is often cited as a barrier to the use of antiretroviral therapy in developing countries, research presented in Durban shows that therapy can be administered successfully in developing countries in urban settings.

In Senegal, a national scheme has been established, outside the UNAIDS programme, which makes antiretrovirals available at three clinics in the capital, Dakar. Patients with CD4 counts below 350 are eligible if they are symptomatic or if they are asymptomatic with a viral load above 100,000 copies. By June 2000, 75 individuals had been treated, and adherence was reported to be good, but due to the late stage at which therapy was initiated ten deaths have been reported. However, the mean CD4 count after six months had increased by around 80, and the mean viral load decrease at month 12 was 1.4 logs¹.

In Uganda, 900 patients had received antiretrovirals through the UNAIDS programme by March 2000. Drug prices are similar to those charged in the developed world, and everyone receiving drugs through the UNAIDS scheme has been required to pay, which necessarily limits access to certain sectors of the population. Seventy per cent of patients started therapy with CD4 counts below 200, and 74% were symptomatic at the time they began treatment. When patients lost

glossary antiretroviral

A substance that acts against retroviruses such as HIV.

CD4

A molecule on the surface of some cells onto which HIV can bind. The CD4 cell count roughly reflects the state of the immune system.

HAART

Highly Active Antiretroviral Therapy, a term used to describe anti-HIV combination therapy with three or more drugs.

oesophagus

The tube leading from the throat to the stomach.

viral load

Measurement of the amount of virus in a sample. HIV viral load indicates the extent to which HIV is reproducing in the body.

to follow-up were counted as clinical events, the event rate was 52% after one year. This conservative form of analysis is necessary because death reports are not mandatory in Uganda. However, only 58 deaths were actively reported, of which 50 were due to AIDS-related illnesses. Data on viral load and CD4 responses are much more limited².

Cheaper diagnostic tests needed

Evaluating the clinical success of these programmes has been difficult because of incomplete information on viral load and CD4 responses. Many patients cannot afford these tests, which may cost up to \$150 per test.

The UNAIDS Drug Access Initiative has reported that the annual cost of monitoring and follow-up in Cote d'Ivoire amounts to \$257 a year, using CD4 and viral load tests. In the UK, a single viral load test may cost up to £100 to perform, though bulk costs are lower. A single CD4 count costs around £20-£30, but a simplified version of the test developed by the Royal Free Hospital in London is reported to cost less than £3 per test.

A test that measures levels of HIV's p24 antigen has been shown to correlate well with HIV viral load (RNA) responses to treatment as measured by conventional viral load tests, and may detect virological failure earlier, at 25% of the cost of the viral load test³.

Cheaper treatment options needed

In the developing world, dual therapy remains the predominant mode of treatment. Reports from Uganda, Cote d'Ivoire, Thailand, India and Senegal all reveal that where

antiretrovirals can be afforded, it is therapy with two nucleoside analogues that is most commonly purchased. This form of treatment is considered sub-optimal and can lead more quickly to the development of drug resistance that can compromise the effectiveness of future treatment options. Yet as Dr Pren Phanuphak of Bangkok argued in Durban, if a patient can afford two drugs now, he could be healthy and wealthy enough to afford HAART in the future, whereas untreated HIV disease will lead to loss of earnings and inability to afford any treatment in the long-term.

Adherence levels

Although it is suggested that poor adherence would impede the success of antiretroviral programmes in developing countries, a review of 99 patients in a Senegal antiretroviral access scheme found an average adherence level of 83% when patients were interviewed about their pill taking in the previous month⁴. Whilst this method of measuring adherence may be less than perfect, it seems to tally with results in the developed world, where – let's not forget – poor adherence is not uncommon.

Late presentation reduces benefit

In Uganda, late initiation of therapy, usually after the diagnosis of an AIDS-defining illness, and the high cost of drugs, has led to a situation where many patients choose to spend money on antiretrovirals without adding treatment for an opportunistic infection, or prophylaxis against other OIs. As a result, a substantial minority of those who started taking antiretrovirals have died before any significant and protective immune reconstitution could take place.

Plotting the way forward

How might wider access to treatments become reality?

Protecting pharmaceutical company profits is argued to be the key to maintaining innovation in drug development. Companies say they would have no incentive to invest in the development of new products if others are permitted to produce copy-cat versions, and given that anti-HIV drugs are far from perfect, it is widely agreed that a compromise must be reached which will allow profits to be maintained in the North whilst slashing prices in the South. A number of possible routes are open, none mutually exclusive:

- **Differential pricing:** Drug prices would be maintained in the North but cut in the South to a level where generic producers will not be able to compete.
- **Debt relief:** Countries could be excused from crippling debt repayments if the money is invested in health care infrastructure and HIV prevention rather than guns, for example. 'Structural adjustment' programmes designed to knock economies into good enough shape to pay their debts have cut investment in health care, and led to the introduction of charges for health care in many African countries.
- **UNAIDS-managed price competition:** UNAIDS could be mandated to institute a bidding process for the supply of essential drugs. If generic manufacturers could supply drugs more cheaply than patent holders, they would be permitted to do so. UNAIDS claims it cannot do this, but it could be mandated by the World Health Assembly, a UN body in which developing world countries form the majority.
- **An international purchase fund:** The French government launched a fund in 1996, but other governments in the Group of Eight (G8) leading economic powers have not pitched in yet. A fund would need to guarantee a market for drugs and find partners to support distribution. The International AIDS Vaccine Initiative is proposing a purchase fund for HIV vaccines.
- **Loans:** the US government has announced \$1 billion in loans for African countries to buy anti-AIDS drugs. The catch is that the drugs must be manufactured in the US, and the deal doesn't specify how much countries can be charged for the drugs.
- **Charitable and commercial partnerships:** The Gates Foundation has pledged \$50 million to support health care in Botswana, provided this is matched by another donor. Merck Sharp and Dohme is the partner, but hasn't yet said what quantity of drugs Botswana will get. Ironically, schemes of this sort are reliant on the continued financial success of Microsoft and other corporations that stand to benefit handsomely from the TRIPS agreement.

glossary

adherence

The act of taking a treatment exactly as prescribed.

antigen

Something the immune system can recognise as 'foreign' and attack.

nucleoside analogue

Chemical which resembles a nucleoside. Family of antiretrovirals which includes AZT, ddI, 3TC, d4T, ddC and abacavir.

prophylaxis

Taking a drug to prevent an illness.

resistance

A drug-resistant HIV strain is one which is less susceptible to the effects of one or more anti-HIV drugs.

RNA

The form in which HIV stores its genetic material.

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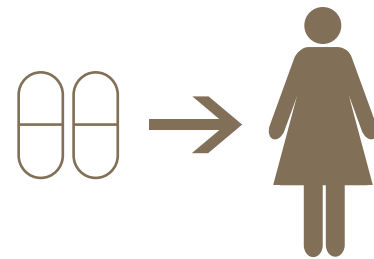
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mind the gap

6 news from Durban on global efforts to prevent HIV transmission from mother to baby by anna poppa

Of the many strands which make up the global HIV epidemic, none demonstrate the division between rich and poor better than mother to child transmission of HIV. In the developed world, the availability of HIV testing programmes, anti-HIV drug therapy, safe alternatives to breastfeeding, and good obstetrical care mean that nowadays fewer than one in fifty HIV-positive women give birth to HIV-infected children. In poorer nations, where few or all too often none of these facilities may be accessible to the majority, the rate is closer to one in five.

At this year's 13th International AIDS Conference in Durban, South Africa, where inequality eclipsed science, mother to child transmission (MTCT) was a natural focus. Whilst several excellent research presentations reported the positive effect of short anti-HIV regimens on MTCT rates, some policymakers in the developing world remain reluctant to



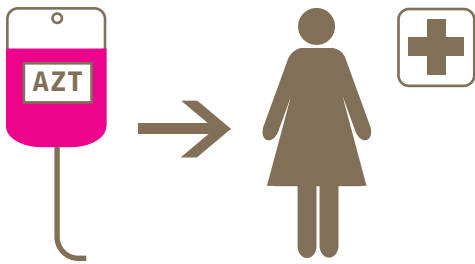
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implement transmission prevention programmes. As this issue of *AIDS Treatment Update* went to press, the South African government had once again voted against the approval of any treatment regimen for pregnant women, despite Boehringer Ingelheim's offer to provide free of charge their drug, nevirapine, considered one of the forerunners in this context. The need for intervention is astonishing – according to the government's own figures, more than one in five South African women attending antenatal clinics tested HIV-positive in 1999.

The success of MTCT interventions in the developed world presents different challenges. A large international study investigating the effects of a single dose of nevirapine in pregnant women taking other anti-HIV drugs was recently abandoned after it became clear that the low overall transmission rate would probably make any potential benefit derived from adding nevirapine impossible to detect. For women in richer nations, many important clinical questions remain unanswered, and whilst most new research presented in Durban concentrated on less well resourced settings, there was much of relevance to both contexts.

Which regimen is best?

Treatment guidelines in both the UK and US agree that being pregnant should not be a reason for HIV-positive women's health to be compromised through the use of treatments which would be regarded as sub-optimal for women who are not pregnant, (see diagram: 076 AZT regimen). Reducing viral load to very low levels reduces the risk of MTCT, and this is more likely to be achieved with HAART regimens than with AZT monotherapy, as well as being more



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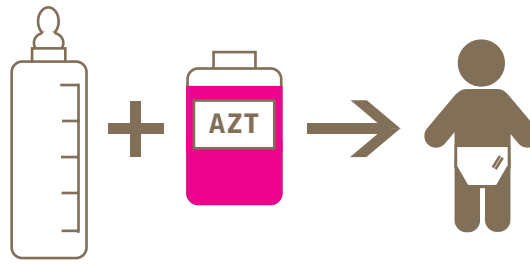
beneficial to the mother, and less likely to cause drug resistance.

In Durban, US researchers presented data from 1,492 pregnant women involved in the Women and Infant Transmission Study, which began in 1989¹. Transmission rates fell over the period studied as more complex drug regimens came into use. The rate amongst 391 untreated women was 20.5%; 19.4% in 206 women who received AZT monotherapy prior to 1994 (when the results of ACTG 076 were published, supporting use of AZT in pregnancy); 7.8% in 529 women receiving AZT monotherapy after 1994; 3.9% in 179 women taking two or more antiretrovirals excluding protease inhibitors; and 1.1% in 187 women taking three or more drugs including a protease inhibitor.

Given the relationship between reduced viral load and reduced transmission risk, these data are not surprising. However, even when women were grouped according to their viral load at delivery, transmission rates fell at all viral load levels with the use of more complex regimens.

Which regimen is safest?

So if HAART seems likely to be more effective in reducing MTCT than taking simpler regimens, and is more suitable treatment for the mother, then why not treat all pregnant women this way? Certainly, this is the ethos behind antenatal care in a number of HIV clinics in the developed world, and has been for some time. The concern for others, however, is that the safety of most antiretrovirals, when taken during pregnancy, has not been established, and must continue to be studied. Enshrining HAART in treatment guidelines now would not preclude doctors from



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continuing to report safety information to medical authorities – this happens already anyway. But it may remove the incentive to study HAART regimens in well-constructed, controlled clinical trials, which would seem to be the best way to resolve the remaining clinical questions.

One unresolved issue is the possibility that multi-drug therapy, in particular with protease inhibitors, may be associated with a greater risk of premature birth. New data from The European Collaborative Study presented in Durban found that women who received protease inhibitor-based combination therapy in pregnancy were two and a half times more likely to deliver prematurely than untreated women². Receipt of dual therapy or NNRTI-containing regimens was associated with a doubling of the prematurity rate.

These new findings emerged from a Europe-wide observational study involving 2,728 HIV-positive pregnant women and 2,923 newborns. Evidence of a possible association between use of HAART during pregnancy and prematurity was first reported by a Swiss team at the Geneva World AIDS Conference two years ago. Subsequent analysis from an American study group of 462 pregnant women who gave birth between 1998 and 1999 did not support the association, however, and so it must be considered unproven.

Whilst the data are relatively scarce, aside from a French report suggesting a cluster of eight abnormal births may have been the result of damage to cellular components known as mitochondria caused by exposure to nucleoside analogues, there have been few other compelling reports of birth defects which can be clearly

076 AZT regimen

ACTG 076 is the name of the trial which established that AZT could reduce mother to child transmission. This regimen has since been recommended to pregnant women. It involves:

- 1 taking AZT from the beginning of the second trimester (14 weeks)
- 2 giving AZT intravenously during delivery
- 3 giving AZT syrup to the infant for the first six weeks of life.

However, taking drugs alone (monotherapy) risks the development of drug resistance. Women who have previously used AZT may gain less benefit from taking it again when pregnant.

infant prophylaxis

Doctors remain undecided over the most appropriate treatment for infants born to HIV-positive mothers taking HAART. The safety of multi-drug prophylaxis for infants whose HIV status is unconfirmed, hasn't been fully tested.

breastfeeding

New information on the HIV transmission risks associated with breastfeeding, and its negative impact on maternal health, was reported in Durban. Space prevents coverage in this issue, but a full review is available on NAM's website aidsmap.com. Follow the *Options during pregnancy* link in *Anti-HIV therapy*.

mind the gap continued

associated with anti-HIV therapy. This French connection has not been supported by case reviews conducted in both the US and UK.

Compared to the risks attendant in being born with HIV infection, it would seem at the moment that the risk of early, serious complications as a result of exposure to HAART, is relatively small. Whether other risks may present themselves over the longer-term cannot be known at present.

How late can treatment begin?

One of the ways of reducing the potential harm which may be caused by drug therapy is to delay starting treatment until late in pregnancy. Though this may not be the best option for women who are already on treatment when they become pregnant, (because stopping and restarting may produce an increase in viral load which may itself raise the risk of antenatal transmission), pursuing interventions which are effective even when started late in pregnancy is an important goal for several reasons aside from needing to limit potential toxicity. In the developed world, a significant number of women are not diagnosed until this point, and in countries where resources are very limited, only very short courses of anti-HIV therapy are considered affordable and practical.

Following the success of an earlier Thai study which established that taking AZT during the last four weeks of pregnancy and during labour reduced MTCT by 50%, researchers recruited 1,437 Thai women to a double-blind study designed to evaluate four different AZT regimens³. These were:

- a long maternal course begun at 28 weeks of pregnancy, plus 6 weeks treatment for the infant (Long-Long)
- a similarly long maternal course plus a short course for the child of 3 days treatment (Long-Short)

- a short maternal course begun at 35 weeks, plus the long infant course (Short-Long)
- or a short maternal course plus a short infant course (Short-Short).

The maternal AZT dose was 300mg twice daily, and then 300mg given orally, every three hours, during labour. The infant dose was 2mg/kg every 6 hours. All infants were formula fed.

When an interim analysis found an increased risk of transmission in the Short-Short group (10.6%) compared with the Long-Long group (4.1%), the Short-Short arm was closed. After 180 days of life, transmission rates were very similar in the Long-Long group (6.7%) and the Long-Short (5.7%), and slightly higher in the Short-Long group (8.4%).

When data were pooled for a secondary analysis, short maternal treatment was associated with a higher infection rate at birth (5.0%) than long maternal treatment (1.8%). Therefore, while the six week infant course may add no benefit to a three day course where mothers begin treatment at 28 weeks, it may be useful where women begin treatment later.

The study group also noted that transmission rates in the Long-Long and Long-Short groups appear similar to that observed in the original ACTG 076 study, where AZT treatment was begun at 14 weeks gestation plus six weeks therapy for the infant was associated with a transmission rate of 8.3%. They suggest, therefore, that maternal treatment with AZT monotherapy begun before 28 weeks may not provide additional benefit. This supports current UK advice that AZT monotherapy (an option for women with less advanced disease, see sidebar page 9: caesarean section) should be deferred until the third trimester (28 weeks) to limit the risk of drug resistance. Though these data do not describe the best time to begin a HAART regimen, they appear to support the principle that drug interventions taken later in pregnancy can be effective.

Use of nevirapine prophylaxis

Data from two studies, HIVNET 012 and SAINT, further strengthened the case for

employing nevirapine in the prevention of MTCT in the developing world. A regimen of just two doses had a significant impact on transmission even after accounting for the impact of ongoing exposure via breastmilk⁴. Whilst longer courses are undoubtedly more effective, the nevirapine regimen is very simple to administer, and it's cheap – about £2.50 to those who can afford to pay for it, and free to those that can't, thanks to Boehringer's offer.

The hope has been slightly tempered by the finding that a proportion of women involved in these studies have developed nevirapine resistance as a result, despite having taken only one tablet. Four of seven women with mutations six weeks after delivery were genotyped again at 14 to 18 months after delivery. All four women had reverted to a wild-type genotype; as would be expected given the long period off treatment, and the resultant lack of selective drug pressure. Whilst it is highly likely that resistant mutants remain 'archived' in these women as minority sub-species too small to be picked up by resistance testing, the wild-type majority population would be expected to remain sensitive to the effects of nevirapine, and this may allow the drug to be re-used in future pregnancies.

Only time will tell if this is the case, but in the meantime, researchers propose that the emergence of resistance mutations is not sufficient reason to delay implementation of this effective intervention in resource-poor settings⁵.

In the developed world, where the NNRTI class is a vital component of current treatment options, employing nevirapine in this way does not appear to fit with the recommendation that a woman's use of treatment during pregnancy should not compromise her own health. A preliminary report from the recently terminated PACTG 316 study, where nevirapine prophylaxis was added to a background of anti-HIV therapy, also found nevirapine mutations in 4 of 32 women who took one dose of the drug at delivery, and had viral load above 3,000 copies at this point⁶. Developing resistance to nevirapine renders the whole NNRTI class ineffective.

Of course pregnant women will not always be fit and healthy, new to anti-HIV therapy, able to tolerate the side-effects and the adherence demands of treatment, or respond well virologically. The need to individualise treatment choices, rather than adopt dogmatic positions, remains important.

key conclusions

- Transmission of HIV from mother to child is less likely where women have very low viral load. Because taking three drugs is more likely to reduce viral load than taking one or two, HAART may be more effective in preventing transmission than single or dual therapy.
- However, the safety of HAART in pregnancy is not known. To limit the risks, some women choose to take HAART later in pregnancy, to take fewer drugs, and/or deliver their baby by planned caesarean section. This form of delivery reduces the risk of transmission in women who take no treatment or take AZT alone. It may or may not be helpful with multi-drug combinations.
- There is some evidence that HAART may raise the risk of premature birth, but this relationship is unproven.
- There is little evidence that anti-HIV therapy causes serious birth defects, but the longer-term risks are unknown.
- Treatment choices in pregnancy must be individualised, considering treatment history, the mother's health, tolerability, safety risks for both mother and infant, and likely impact on the mother's viral load.

glossary

More terms are explained on pages 3 and 5.

antenatal

Before birth.

genotype

The genetic make-up of an organism.

mutation

A single change in gene sequence.

regimen

A drug or treatment combination and the way it is taken.

toxicity

The extent or ways in which a drug is poisonous to the body.

wild-type virus

Virus that has not been exposed to anti-HIV drugs before.

caesarean section

Women who wish to take AZT monotherapy may choose to deliver by a planned caesarean section. Employing these two interventions together is also associated with very low rates of transmission. It is unclear whether this form of delivery will also benefit women who take more complex regimens.

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Abacavir warning

Glaxo Wellcome has issued a warning about the potential for severe hypersensitivity reactions after the reintroduction of their HIV drug abacavir, in people who have no identified history or diagnosed symptoms of hypersensitivity to the drug. Hypersensitivity is a type of allergic reaction.

The warning follows a number of reports where the company believes that hypersensitivity was not spotted prior to an interruption in abacavir therapy. For example, hypersensitivity may have been mistaken for an acute respiratory illness, a gastrointestinal infection or a reaction to other medicines.

However, some individuals discontinued abacavir due to interruptions in drug supply or the need to treat other illnesses, and suffered severe hypersensitivity reactions when abacavir treatment was resumed. This may have occurred because abacavir hypersensitivity reactions can take a number of weeks to emerge, and if treatment stops in the early weeks, the clock isn't re-set; a severe reaction can resume within hours if the drug is begun again.

Although the symptoms vary, they tend to involve fever, rash, nausea, vomiting, diarrhoea, abdominal pain, lethargy and malaise. Less common symptoms include shortness of breath or difficulty breathing, cough, sore throat,

muscle or joint pain, headache, numbness on the skin, puffiness of the throat, face and neck, swollen glands, conjunctivitis, mouth ulcers and low blood pressure. People taking abacavir should routinely be provided with a patient information leaflet detailing these symptoms, and advising them to contact their doctor immediately should any occur.

Typically, a pattern of symptoms build up over a period of days, often worsening as successive doses of the drug are taken. Death has occurred when respiratory symptoms due to a hypersensitivity reaction were mistaken for a respiratory infection. In this new series of cases, where hypersensitivity had not been diagnosed, patients typically had only one of these key symptoms.

The abacavir hypersensitivity reaction is most commonly seen in the first six weeks of taking the drug, often in the initial fortnight. Though the risk should be taken seriously, it's important to remember that hypersensitivity is rare, occurring in approximately 4% of people who take the drug.

The European Agency for the Evaluation of Medicinal Products, the EMEA, issued a public statement on the matter on August 14th, which can be viewed on the web at <http://www.eudra.org/humandocs/Humans/PS.htm>. They advise that wherever abacavir is discontinued and hypersensitivity cannot be

ruled out, the drug should only be re-started in hospital. If abacavir is stopped for any other reason, re-starting must be done in a setting where medical assistance is readily available. This latter recommendation effectively rules out using abacavir in a structured treatment interruption strategy.

The UK's Medicines Control Agency have responded by issuing an urgent safety restriction which can be read at <http://www.open.gov.uk/mca>

Clarification on ddI

At the time of going to press, we learned that Bristol-Myers Squibb (BMS) were due to write a letter of clarification to UK HIV healthcare workers regarding dosing of their nucleoside analogue ddI.

Last month, the publication of 48 week results from a study comparing once daily ddI with d4T and nelfinavir, against AZT/3TC/nelfinavir, in people new to treatment, showed a superior response amongst AZT recipients. Though this study was not designed to compare once daily ddI with twice daily ddI, the results prompted the US drug approval body, the FDA, to recommend that the preferred dosing of ddI should be twice daily, because there are more data to support that regimen, but that once daily ddI can be considered for patients whose management requires once daily dosing.

Back in the UK and European Union, where a licence variation allows once daily dosing of ddI, BMS have confirmed that at present there is no need to switch from once daily tablets to twice daily, and that once daily dosing is "perfectly acceptable" according to the European licence.

BMS expect that their new capsule formulation of ddI, *Videx-EC*, will not be affected by this matter. This drug will be fully approved for prescription in the European Union within weeks, and in the meantime is currently available on named patient basis.

This scheme provides *Videx-EC* to any doctor who applies on behalf of a named patient who is unable to tolerate, or has experienced treatment failure on, the once daily tablet regimen. Details of how to obtain *Videx-EC* are available to healthcare professionals only (and cannot be provided to patients for legal reasons), by contacting BMS.

At present, *Videx-EC* is available only as a 400mg capsule, limiting its use to people who weigh over 60kg. A lower dose is recommended for lighter people.

Metformin on trial

Researchers from Boston have reported results from a small, randomised, controlled study of metformin in 26 people taking anti-HIV therapy, who had signs of fat redistribution, high insulin levels and/or abnormal glucose tolerance, commonly termed lipodystrophy. After three months, insulin levels, weight and blood pressure fell significantly in those treated with metformin compared to controls. The treated group also experienced a non-significant reduction in waist size and reduced visceral abdominal fat.

Metformin is an anti-diabetes drug used to treat insulin resistance, whereby the body does not process insulin, a hormone which regulates blood sugar levels, normally. French doctors have previously reported that metformin reduced insulin resistance, reduced triglyceride levels and improved abdominal fat distribution in a randomised study of 27 people receiving protease inhibitors. HIV wasting expert, Dr Carl Grunfeld, has also reported that metformin has shown positive results in the treatment of HAART-associated insulin resistance and diabetes, producing an associated decrease in body fat.

The report from the Boston research group can be read in full in the *Journal of the American Medical Association* on July 26th; Hadigan C et al. Metformin in the treatment of HIV lipodystrophy syndrome. *JAMA* 284:472-477, 2000.

editor's note: lopinavir

Last month we were a little confused over the name of Abbott's new protease inhibitor. Lopinavir is the generic name for the ABT-378 component only, which makes the co-formulation lopinavir/ritonavir.

nam forum

This month's forum is on *New anti-HIV drugs* and takes place at the University of London Union, Malet Street, London WC1 on September 25th, 7-9pm. Entrance is free.

AIDS treatment phonenumber

Despite the closure of AIDS Treatment Project, the treatments phonenumber remains open. Call 0845 9470 047 Mon and Wed 3-9pm, Tue 3-6pm.

health advisors

In our recent *Factsheet* for recently diagnosed people we neglected to mention the valuable role which health advisors play in supporting people who test HIV-positive. We'd like to rectify that by reminding readers that health advisors are available at HIV treatment centres and GUM clinics, and can provide ongoing support to anyone with HIV. Ask at your clinic for details.



credits

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any questions

For an introduction to HIV treatment issues
The booklets in NAM's Information Series for Positive People are free to people with HIV. This easy-to-read series covers six key topics: Viral Load, Clinical Trials, Nutrition, Anti-HIV Drugs, Resistance, and a Glossary.

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NAM's resources are also available online at aidsmap.com. These include our extensive and searchable treatments database, the latest news on treatment developments, our online directory of AIDS organisations, hundreds of links to recommended HIV-related sites, and free downloadable resources.

Monthly NAM information forums in London
Each month an expert speaker discusses a treatment-related topic. Entry is free. Future forums are advertised inside this newsletter.

AIDS Treatment Phonenumber 0845 9470 047
From AIDS Treatment Project: Mon & Wed 3-9pm, Tue 3-6pm.

NAM recommends that you discuss all your treatment decisions with your doctor.



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