

aids treatment update

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in this issue

As we approach the final few months of 2007, it's clear that next year is going to be a busy one for *ATU*. We have *Atripla* on the way, bringing a new three-drugs-in-one pill combo, raltegravir will introduce another new class of therapy and the existing classes are expecting a fair few updates too.

It's this abundance of new drugs and improvements that help to reassure some of our concerns about managing HIV disease long term. But where one concern fades, others can take the spotlight. With articles on HIV in the brain, drugs and alcohol and cancer guidelines, this issue highlights some of the complex challenges we face as HIV interacts with our bodies and our lives.

It's important to remember that while these new challenges may be tough, they have arisen because the majority of us are living longer, healthier lives than we thought possible. While AIDS can still play a part of living with HIV, it's now more common to think in terms of the impact of advanced HIV disease and ways in which we can combat it.

It's with this in mind that *AIDS Treatment Update* could see a change in the coming months to become *HIV Treatment Update*. This isn't to draw from the impact that AIDS can have, but to better represent the full spectrum of those living with HIV, many of whom may never have an AIDS diagnosis.

page 3 HIV and cancer specialists have joined forces to bring us the latest British HIV Association (BHIVA) guidelines. With the risk of some cancers higher for those with HIV, *Upfront* takes a tour through the draft Guidelines for HIV Associated Malignancies and discovers the recommendations which could optimise our care.

page 4 We're often told the levels of HIV in our blood, but what about HIV in our brain? In *Brain drain*, we ask Professors Richard Price and Justin McArthur if the antiretrovirals we use today are protecting our brains from HIV-related damage.

page 8 While many of us are aware of the government warnings attached to drinking, drugs and cigarettes, when you combine them with HIV infection it can increase the dangers. *Sex, drugs and viral load* looks at some of the additional health concerns created by this precarious mix.

page 12 *News in Brief* reports on new European HIV treatment guidelines. We also look at some new FDA approvals and find out what factors have an impact on adherence.

page 14 The term 'advanced HIV disease' is slowly replacing the acronym AIDS as more people in the UK are living long lives with HIV. Should *AIDS Treatment Update* reflect this change with a new name? You decide.



aids treatment update

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new guidelines for hiv and cancer

by Edwin J Bernard and Rob Dawson

We've known for quite some time that an AIDS diagnosis brings with it a risk of many cancers linked to immune deficiency.¹ The majority of these AIDS-defining cancers, like Kaposi's sarcoma, have become increasingly rare as effective antiretrovirals offer protection against them. Recently though, our cancer radars have shifted focus to studies showing a heightened risk of some non-AIDS malignancies, despite antiretroviral therapy.²

While awareness of this increased risk does bring concerns, the future challenges that a combination of HIV and cancer could bring are by no means insurmountable. In order to ensure the best treatment and care, expert knowledge from a broad spectrum of therapeutic areas needs to be considered.

Consequently, the British HIV Association's (BHIVA) draft guidelines on the clinical care of HIV-positive individuals with cancer appear both necessary and timely. The guidelines draw from the latest research and clinical experience in the areas of oncology (cancer), haematology (blood) and HIV, and also include input from the community of people living with HIV in the UK.

"The clinical care of patients with these tumours requires a multidisciplinary approach drawing on the skills and experience of all healthcare professional groups," the guidelines note. "Moreover, optimal

care can only be achieved by the close co-operation of oncologists, haematologists and HIV physicians, and unless all these clinicians are intimately involved in the care of patients, it is likely that the outcome will be less favourable."

The draft guidelines cover detailed information on the diagnosis and treatment of the many variations of the three AIDS-defining cancers, as well as the following non-AIDS-defining cancers: AIN and anal cancer; Hodgkin's lymphoma; Castleman's disease; testicular cancer; lung cancer; and liver cancer. They also provide detailed guidance on the use of individual antiretrovirals and opportunistic infection prophylaxis in HIV-positive individuals being treated for cancer.

General recommendations

The guidelines' authors make some general recommendations on the management of cancer in people with HIV in the United Kingdom. These include:

- All patients with HIV and malignancy should be referred to centres that have developed expertise in the management of these diseases and serve an HIV cohort of >500.
- The multidisciplinary medical team managing these patients must include HIV physicians, oncologists, haematologists and palliative care physicians.

- In line with national cancer waiting times, all patients with suspected cancers must be referred urgently and seen within two weeks of referral.
- No patient should wait longer than one month from an urgent referral with suspected cancer, to the start of treatment.

The draft guidelines are currently being updated following a consultation period involving patients and professionals. The consultation period closed on the 19th October but with leading players in both diseases working closely together, the final document will no doubt be an important step in ensuring the combination of HIV and cancer gets the full force of available clinical care. The draft guidelines can be viewed on the BHIVA website: www.bhiva.org



brain drain

do we need brain-penetrating drugs to ward off neurological problems?
by Rob Dawson



While most scientists agree that today's antiretroviral therapy (ART) has reduced the severity of serious forms of HIV-related dementia, there is still much debate over its impact on less severe forms of neurocognitive impairment. Despite studies which show a decrease in incidence of HIV Associated Neurocognitive Disorders (HANDs)¹, they continue to cause significant concern for people living with HIV.

Soon after initial infection, our immune cells traffic HIV into the central nervous system. Immune cells within the brain are then targets for infection and become over-active in the presence of the virus, producing immune system messengers (called cytokines or chemokines) which damage neuronal cells. In addition, protein on HIV's outer coat can kill off cells in the brain by disrupting their internal chemistry and inhibit the ability of brain cells to regenerate.²

This assault on the brain can lead to a broad range of cognitive dysfunction such as memory loss, confusion, inability to concentrate and changes in personality. The extent to which ART protects from these neurological disturbances is not fully understood, but it's clear that it's having an effect.

New research has shown that current anti-HIV drugs appear to curb some HIV-associated brain damage. In one study, 21 out of 53 volunteers had high levels of a protein called neurofilament light protein, which is believed to indicate brain damage. Three months into ART, the high levels of the protein dropped to normal levels in almost half of the patients. After one year, just four patients still had high neurofilament light protein levels.³

An additional observational study showed that while the rate of neurological impairment in those with HIV was nearly twice that expected in a reference (HIV-uninfected) population, those who respond to antiretroviral therapy over prolonged periods show stable or improving cognitive function.⁴ The findings demonstrate an improved performance in neurological tests over a two-year period, three to five years after initiating potent HIV treatment. However, the mechanisms underlying the improvement are not clear since there was no association with CD4 counts, and the association with viral suppression was not unequivocal.

Commenting on the way antiretrovirals have changed neurological disease at

this year's International Conference of Evolving Mechanisms of HIV Neuropathogenesis in the HAART era, Dr Igor Grant of the University of California, San Diego, said: "There is certainly less of the severest form of dementia; certainly less of the apathetic withdrawn type of case that can't look after him or herself with severe motor [problems]. There is more of the milder type of disturbance; disturbances in learning new information, abstraction or executive functioning and then a mix of sensory and motor problems. These are people who are up and about in the community but they have problems with things like shopping, financial management, transportation, communication and so forth."

However, controversy remains over the role of antiretroviral therapy in central nervous system disorders partly because some drugs cannot reach therapeutic levels in the brain, which shelters the virus from the full force of treatment.

Penetrating the brain

According to the ongoing AIDS Clinical Trials Group (ACTG) ALLRT study, HIV treatment did not fully protect the brain or eliminate the risk of impaired brain functioning. Despite ongoing

treatment, while some participants with mild or mild-to-moderate cognitive impairment improved, more than half remained impaired during the follow-up period. What's more, 21% of participants with normal cognitive functioning became impaired during follow-up while on antiretroviral therapy.⁵ Researchers found that the risk for cognitive impairment was higher in people who started HIV treatment with low CD4 counts. Those older than 55 years also had a greater risk of neurological complaints but we would also expect this in the general population. The ACTG group suggested that the HIV drugs taken by participants may not easily cross the blood-brain barrier and therefore fail to completely suppress viral replication in the brain.

Previous studies have shown that ART which can penetrate to the central nervous system has greater effects upon viral load levels in the cerebrospinal fluid (CSF) around the brain. This was shown to lead to greater neurocognitive improvement in patients taking brain penetrating drugs, compared to those who did not.⁶

However, while such studies have tried to stress the importance of drugs that can penetrate into the central nervous system, there has been no widely accepted or clinically useful approach

to estimating the effectiveness of antiretrovirals in this capacity. Dr Scott Letendre and colleagues at the University of California have been addressing this important issue by creating an index of brain penetration.⁷ They hope this will allow doctors to make more informed decisions about the types of drugs used to treat HIV associated neurocognitive disorders.

The index gives individual antiretrovirals a penetration score of 0 (low), 0.5 (intermediate), or 1 (high) to rank drugs relative to one another. The rankings were based on publicly available information (i.e. package inserts, drug references, published manuscripts, and conference abstracts) on the drugs' chemical properties, concentrations measured in the cerebrospinal fluid, and effectiveness in the central nervous system in clinical studies.

Central nervous system penetration of antiretrovirals:

The Central Nervous System Penetration-Effectiveness (CPE) score of a regimen can be calculated by summing the individual penetration scores for each antiretroviral in the combination.⁷

As a step towards validating this method for clinical use, the group evaluated HIV viral load reductions in

the cerebrospinal fluid resulting from antiretroviral combinations which had varying CPE scores.

They found that people who took antiretrovirals with lower penetration scores were more likely to have continued HIV replication in the central nervous system, as indicated by higher HIV viral loads in the cerebrospinal fluid.

Widespread control

However, while people with progressive neurological disease may benefit from ART with good central nervous system penetration, there is a growing body of evidence that ART with weaker penetration can be protective against some brain injury. This could be due to an indirect effect upon immune activation, rather than the capacity of particular drugs to suppress HIV replication in the brain.

Harvard's Dr Ken Williams turned to monkeys in a bid to explain how this works. He treated four macaques infected with SIV, a virus similar to HIV, with antiretrovirals and left four untreated monkeys to serve as controls. Drugs were specifically chosen which do not penetrate the central nervous system, though they could treat SIV in the rest of the body and have been shown to reduce the

Central nervous system penetration of antiretrovirals:

	Good (1)	Fair (0.5)	Poor (0)
NRTIs	Abacavir	Emtricitabine	Didanosine
	Zidovudine	Lamivudine	Tenofovir
		Stavudine	Zalcitabine
NNRTIs	Delavirdine	Efavirenz	
	Nevirapine		
PIs	Indinavir	Amprenavir-r	Amprenavir
	Indinavir-r	Atazanavir	Nelfinavir
	Lopinavir-r	Atazanavir-r	Ritonavir
		Darunavir-r	Saquinavir
			Saquinavir-r
		Tipranavir-r	
Fusion inhibitors			Enfuvirtide

-r : boosted with ritonavir

activation of monocyte and macrophage immune cells.

Twenty-eight days after untreated SIV infection, there was monocyte and macrophage activation (the cells were 'switched on') and significant decreases in a chemical called NAA (N-acetylaspartate) - an indication that the integrity of brain cells has been compromised in some way, either by damage, loss or dysfunction.

While treatment did not reduce viral load to undetectable levels, it did stop monocyte and macrophage activation. This correlated to significant and rapid neurological stabilisation of NAA levels, with three of the animals completely recovered.⁸

"Using this model, which I think is a reasonable model for HIV disease, it shows that you need active and continual monocyte/macrophage traffic into the brain [for ongoing disease], and lowering monocyte activation or infection seems to decrease disease," said Dr Williams.

Dr William's research suggests that the antiretrovirals may not need to get inside the central nervous system to stop ongoing active neuronal injury in the brain. This is in line with a 2006 Italian cross-sectional study showing no link between the use of antiretroviral drugs that are active in the brain and performance in a range of neurocognitive tests. When patients with and without neurocognitive impairment were compared, the investigators found no differences in the number of brain-penetrating drugs that the patients were taking as part of their anti-HIV combinations.⁹

"In the early stages, when immune function is quite preserved and cognitive functions are only moderately affected, the control of plasmatic HIV replication [replication in the blood] could be sufficient to control HIV replication in [the] central nervous system and the use of multiple central nervous system-penetrating drugs may not be absolutely required," the investigators said.

The evidence shows that brain penetration is not always vital, leading some scientists to propose that today's ART that reduces systemic activation of the immune system could often, though perhaps not always, effectively manage HIV in the central nervous system.¹⁰

Professional opinion

Understanding the effects of antiretrovirals in and outside the central nervous system is still a relatively new field and the need for further study into brain-penetrating combinations is clear. As the debate continues over the extent to which neurological damage is occurring during chronic HIV infection, ATU asked two leading neurologists for their views. Professor Richard Price (RP) is Professor of Neurology at the University of California, San Francisco and Professor Justin McArthur (JM) is Interim Chair of the Department of Neurology at the Johns Hopkins University.

ATU: Are the antiretrovirals used today protecting us from HIV-related damage to the central nervous system?

RP: There is no question that combination antiretroviral therapy has had a huge impact on major HIV-related neurological impairment, what we call ADC [AIDS Dementia Complex] or HIV dementia. What is controversial is whether there is still new, milder disease that develops before treatment initiation or despite it. Presentations often conflate [group together] increased prevalence [due to brain injury before effective antiretroviral treatment] and the continued increased incidence on ART. Major attention is now being directed at whether this milder disease occurs very early on before treatment, or continues despite treatment.

JM: The data suggest that the incidence of HAND [HIV Associated Neurocognitive Disorders] has diminished since the introduction of HAART, but that the prevalence has risen and remains about 30%, even in HAART-treated populations. There is evidence too that the phenotype [i.e.

physical manifestation] of the impairment has changed with less severe deficits, less progression, and partial reversals of impairment. The definitional criteria were recently changed to include an 'asymptomatic neurocognitive impairment' category, i.e. measurable impairment that is not symptomatic for patients. This corresponds to the practice in other types of dementia such as Alzheimer's disease where we are trying to identify 'presymptomatic' or early stage of disease. So, one could argue that current ARTs are at least partially protective, but that there is a treatment gap between the effect of ART and the irreversible nature of some cases of HAND. I would argue that in some individuals reversal of dementia with ART does not occur, either because there has been sufficient/critical neuronal loss, or because other pathogenic mechanisms [factors leading to cognitive impairment] have become activated, such as oxidative stress or apoptosis [cell death], and which do not shut down even when there is virological suppression.

ATU: Current research opposes the view that drugs that penetrate the central nervous system are needed to treat patients with HIV-associated neurological disturbances. If antiretrovirals don't get to the brain, how can they be protective?

RP: This is an area of dogma based on presumption rather than fact. As you say, how can the brain be protected if drugs don't get in? But HIV is a systemic disease [throughout the body] with secondary involvement of the brain. Treating systemic disease may therefore be paramount - reducing entry of new virus and maintaining host defenses that can control it somewhat in the brain. But all this is largely theoretical and we need better information. Another issue is that many of the drugs do penetrate, but don't maintain as high concentrations in the brain as systemically.

JM: Prevention or protection from HIV-associated neurocognitive disorders appears to rely more on reducing the numbers of activated/infected monocytes

[immune cells] in general circulation rather than an effect in the brain compartment. Obviously once viral replication is occurring in the functioning cells of the brain, there needs to be sufficient brain penetration of an ART regimen to achieve suppression, but in terms of prevention of neurological disease I believe that the critical factor is the successful and durable suppression of systemic infection. In treatment of established dementia, the ART regimen probably makes a bigger difference.

ATU: There is research which argues that problems in the central nervous system are getting worse for some patients, despite suppressive antiretroviral therapy. Are people living with HIV always going to have an increased risk of these disorders, no matter what medications we take?

RP: This is the big question. I think it is wrong to think in terms of getting worse, but we should ask whether they

are getting 'better enough'. Also, keep in mind that there is a great bias for investigators to declare that things are worse; they are concerned for their patients with cognitive complaints. I don't mean this as real criticism, but it is human nature.

JM: The concern for the long run - greater than ten years [of HIV infection] - is that the brain may be a sanctuary for HIV, especially in long-lived cells, and that virological suppression is more challenging in the brain because of the penetration issues. It is also very clear that vascular disease [narrowing of blood vessels in the brain due to the same factors that cause heart disease] and other comorbidities, including age, drug abuse and coinfections may add to the neurological burden in chronically HIV-infected individuals. The worst case scenario is a population of HIV-positive people with good systemic control [of the virus] but mild to moderate neurological impairment which actually

progresses over time because of these comorbidities and might, in a sense, accelerate the aging process.

The impact of antiretrovirals

We may not know exactly how likely we are to develop neurological impairment but it seems clear that most antiretrovirals are protecting us to some degree. Other factors come into play too and where other conditions co-exist, such as alcoholism and substance abuse, we may have to work harder to keep our brains in shape. Differences in the genetic make-up of HIV could also affect the risk of developing HIV-related neurological disease as can differences between individuals' immune responses to HIV. In general though, promising steps have been taken in protecting our brains from serious neurological damage. Where serious, symptomatic infection of the central nervous system occurs, we have penetrating drugs to minimise damage. For the rest of us, general systemic therapy could be helping to keep it at bay.

glossary

AIDS Dementia Complex (ADC) A brain disorder caused by HIV which has nervous system and mental symptoms that affect a person's ability to think clearly and can impact on daily activities.

Blood-brain barrier A protective membrane that controls the entry of substances from the blood into the brain.

Brain penetrating (or central nervous system penetration) A substance which is able to pass through the protective barrier surrounding the brain (the blood-brain barrier).

Cognitive Relating to intellectual activity (e.g. thinking, reasoning, remembering, imagining, or learning words).

Central nervous system (CNS) The largest part of the human nervous system, including the brain and the spinal cord.

Cerebrospinal fluid (CSF) A watery, colourless, clear fluid that bathes and

protects the brain and spinal cord and fills the gaps between nerve cells.

Dementia A group of symptoms that lead to a decline in intellectual functioning that is severe enough to interfere with the ability to perform routine activities

HANDS (HIV Associated Neurological Disorders) The range of disorders that can be caused when HIV infection damages the human nervous system (including the brain and spinal cord). These can be mild or severe and can affect the ability to think clearly.

Immune activation The widespread activation or 'switching on' of our immune systems as a result of HIV infection.

Monocyte A white blood cell that ingests foreign substances in the blood and forms part of the human body's immune system.

Macrophage A white blood cell that ingests foreign substances and which migrates from the bloodstream to other tissues to form part of the human immune system.

Nervous system A vast network of cells specialised to carry information (in the form of nerve impulses) to and from all parts of the body in response to stimulation and in order to stimulate action.

Neurocognitive Cognitive functions closely linked to the function of particular areas in the brain.

Neurological: Conditions occurring in the nervous system, including the brain and spine.

Neurons Nerve cells.

Neurotoxins: Substances which are toxic to nerve cells.



sex, drugs & viral load

By Rob Dawson

Research on smoking by Tim Molloy

It is perhaps testament to some of the strains and pressures of living with HIV that we are more likely to smoke, drink and take drugs than those who are HIV-negative. Yet these behaviours can have a profound effect on our health and well-being, and instead of providing the relief that some may hope to find, chronic use is all too often far more destructive. While some researchers argue that data around substance use include high numbers of gay men who are already more prone to these behaviours than other groups, even when looking solely at gay men, those with HIV smoke more and take more drugs.¹

There are many other factors contributing to higher levels of substance use in the HIV-infected population. Drinking, taking drugs or smoking may increase the risk of HIV infection. There is a growing recognition that smoking can weaken our defences against HIV and it is thought that this is due to immunological changes, including depression of antibody responses.² This heightened risk of infection could also be explained by a link between drug or alcohol use and unsafe sex, in both gay and African populations.^{3,4}

Whether this is through disinhibition or dispositional factors such as excitement seeking and impulsiveness, remains to be seen.

Whatever the reason for greater use, HIV-positive people are also disproportionately affected by the health concerns associated with this intoxicating mix. While most of us will have read the health warnings on cigarette boxes and alcohol ads, there are further complications associated with HIV disease that aren't as widely publicised.

alcohol

Alcohol dependency is common amongst those with HIV⁵, and chronic drinking mixed with infections can spell trouble. When we drink heavily, our immune system could be at risk. High alcohol consumption has been linked with increased illness and even death related to infectious diseases. Studies conducted in both animals and in cultured cells suggest that alcohol can interfere with the normal functions of various components of our immune system (e.g. natural killer cells and T-cells), impairing our body's immune response to infection.⁶ To highlight this effect, one test tube study looked at immune cells - including CD4 cells - that were isolated from healthy, non-HIV-infected people, both before and after they consumed up to nine alcoholic drinks over two days. The results suggested that alcohol consumption damaged the immune system, because when the isolated cells were infected with HIV in a test tube, the virus multiplied faster in the cells harvested after alcohol consumption. Furthermore, cells isolated after drinking exhibited reduced CD4 functions compared with cells isolated before alcohol consumption.⁷

Outside of the test tube, similar results on the detrimental effects of heavy drinking have been seen. A recent study carried out in monkeys found that long-term alcohol consumption can affect the turnover of immune system cells in the intestine, and the depletion of these cells by the simian immunodeficiency virus (SIV).⁸ Although similar effects of alcohol and HIV on immune cells in humans were not studied, the researchers argued that alcohol has the potential to affect the activity of the immune system during early HIV infection and that this, in turn, may cause higher viral loads by increasing HIV replication.

Studies that look at humans have found that heavy alcohol use is harmful for HIV-positive people who are not on antiretrovirals. HIV-positive heavy drinkers not taking antiretroviral treatment tended to have lower CD4 counts than moderate drinkers or those who never drink.⁹ Interestingly, alcohol consumption didn't appear to affect viral load, but the difference of around 50 CD4 cells/mm³ does imply that someone who consistently drinks heavily would be quicker to reach the point at

which treatment is recommended than someone who is teetotal. While the same difference in CD4 count isn't true for heavy drinkers who were taking antiretrovirals, they were more likely to be non-adherent to their treatment than those who didn't drink.

"Heavy alcohol consumption has a negative impact on the CD4 cell count in HIV-infected persons not receiving ART," the authors concluded. "In addition to the known deleterious effects of alcohol on ART adherence, these findings suggest that avoiding heavy alcohol consumption in patients not on ART may have a beneficial effect on HIV disease progression."

With the party season on its way, some people may find themselves drinking a little more than usual. It's worth keeping moderation in mind. A New Year's resolution to cut down drinking could help. Previous studies on alcoholic HIV-infected patient's undergoing detox have found that the patients' levels of CD4 cells improve when they stop drinking.¹⁰

where to get help

If you're worried about your drug or alcohol use, there are national helplines that can locate appropriate services for you.

- The **FRANK National Drugs Helpline** can be reached on: 0800 77 66 00
- **The DrinkLine National Alcohol Helpline** can be reached on: 0800 917 82 82
- The NHS site www.gosmokefree.co.uk offers advice on stopping smoking
- Information and support around drugs and alcohol, specifically designed for gay men, can be found at www.gmfa.org.uk/drugsandalcohol. GMFA also run smoking cessation courses for gay men.

drugs

The combined effects of drug use and HIV infection are less clear. It's harder to carry out studies when illegal substances are involved, as much of the data is from animal studies, rather than controlled trials. However, some studies do show greater problems associated with non-injected recreational drugs for those with HIV.

Effects on the immune system were seen in a 2006 study into methamphetamine (crystal) use. It found that the drug could increase production of a docking protein that promotes the spread of the HIV-1 virus in infected users, allowing more of the virus to invade the immune system.¹¹

Some research has shown that poppers (amyl nitrite) also weaken parts of the immune system, but many of these results are controversial since studies only tested mice or cells outside the body. In addition, they often administered poppers at higher doses and for longer periods than typical human use. In the late 90s, Professor Soderbergh of the University of Arkansas injected tumour cells into mice and then exposed them either to a form of poppers or to air for 45 minutes a day. While he did find that poppers increased tumour growth in this study¹², it's unlikely that we would be exposed to the drug in quite the same quantities.

Cocaine and ecstasy have also been the subjects of debate. A study of specially

bred mice, transplanted with human immune cells, found that cocaine increases the production and spread of HIV. Mice given cocaine by injection had much greater losses of immune cells and increases in viral load than the mice used as controls (who were given salt water).¹³ Again, the effects on humans are unclear. With ecstasy, there have been some human studies but only short-term effects have been recorded. Researchers enrolled 17 healthy male subjects and gave them 100mg ecstasy once or twice over a period of 24 hours. Blood samples were collected before, during and after the study. The researchers found that a single dose of ecstasy taken by mouth caused a dramatic fall in CD4 cells (a decrease of about 30%) within hours after taking it.¹⁴ The effects were short-lived and levels returned to normal within a day. At higher doses (those receiving two doses of the drug, four hours apart) the decline in CD4 cells was even more dramatic, reaching a level 40% below normal. A day later the levels did rise but did not return to normal. Unfortunately, the effects beyond a day were not measured. However, considering the relatively high use of the drug amongst gay men, it is likely that any profound effect would have been noted in clinical practice in the time since the study was reported.

But it's not just the effects on our immune system that can cause concern.

Some case reports have identified rare life-threatening interactions between some protease inhibitors and recreational drugs like GHB, ecstasy and methamphetamine.¹⁵ Case reports look at an event that has happened and then try to determine a reason; for example a death from ecstasy use in the context of antiretroviral therapy. While cause and effect can often be difficult to prove in these circumstances, especially where no formal interaction studies take place, in most of the case reports adverse reactions to recreational drugs were not experienced prior to protease inhibitor treatment. In the case of ecstasy, knowledge of the metabolism of the drugs made it likely that ritonavir could boost ecstasy levels two to three-fold. However, it still remains that most of the guidelines on possible interactions are 'informed guesswork' based on the way the drugs in question are metabolised by liver enzymes.

There are many other serious effects of drug use which can be harder to determine in clinical trials, such as an increased risk of acquiring sexually transmitted infections for drug users.¹⁶ Drug and alcohol use can also affect your daily life, making work, relationships and taking your antiretrovirals more difficult. There are also links with drugs use and problems in later life, such as serious mental health concerns.¹⁷



smoking

Smoking has probably the largest set of new data when it comes to the effects of drugs on people with HIV, and it suggests that smoking can be even worse for your health if your immune system has been weakened. Quitting smoking could therefore improve HIV-related health. According to a study published in the September 2007 edition of the journal, *AIDS Patient Care and STDs*, quitting smoking can help to reduced HIV-related symptom burden, after an average of three weeks.¹⁸

“Along with the decreased risk of numerous adverse health outcomes associated with smoking, cessation may represent an effective way to reduce the daily impact of HIV disease and treatment side-effects,” the authors said.

As well as affecting daily life, smoking has many long-term effects related to HIV. Cigarette smokers are more likely to be diagnosed with an AIDS-defining condition or to die, according to a large observational study of HIV-positive women from the United States.¹⁹ Smokers had a 36% increased risk of developing an AIDS-defining illness which could negate some of the benefits of potent antiretroviral

therapy. However, the risk of AIDS-related deaths did not differ between smokers and non-smokers in this study. This increased risk of AIDS-defining conditions has also been backed by other studies showing that HIV-positive women who smoke are twice as likely to acquire bacterial pneumonia²⁰, and three times more likely to acquire human papilloma virus (HPV), which can lead to cervical cancer.²¹

It's well known that smoking increases the risk of heart disease, high blood pressure, and stroke. This could be particularly concerning if you have HIV, because you might be increasing the risk even further.

Atherosclerotic vascular disease (hardening of the arteries) has been observed more frequently in HIV-positive individuals taking a number of antiretroviral drugs. Atherosclerosis is the build-up of fatty deposits in the walls of the arteries. Over time, these deposits of cholesterol, fat and the smooth muscle cells that line the arteries are transformed into a thickened mass (atheroma). This can reduce blood flow through the vessels making heart disease and stroke more likely.

minimising risks

While some studies have shown that drug use and smoking have no effect on actual HIV progression or increase the risk of AIDS-death,²⁷ if you smoke, drink or take drugs, there are definite increased health risks. Many of us hear the warnings but find hee ding the advice more difficult. It was Dr Brian Gazzard who really made me think with a point he made at the recent International AIDS Society conference. For many people, both doctors and patients, if we saw any health benefit from switching a drug in an antiretroviral regimen, the decision to change would be at the forefront of our minds. However, these benefits are often small compared to the larger health benefits that we could experience by reducing the amount of drugs, cigarettes and alcohol we consume. If we let changes in these behaviours take equal precedent, we could see a real difference in our future health. If you drink, smoke or take drugs to relieve some of the strains of living with HIV, it is important to remember the support services, such as counselling and groupwork, which are available to you, so that you can get some help without the harm.

treatment policy

European treatment guidelines: start treatment at 350

All HIV-positive people in Europe should be encouraged to start antiretroviral therapy if they have a CD4 cell count below 350, say new European HIV treatment guidelines published in October by the European AIDS Clinical Society.

The guidelines also state that the aim of any new therapeutic regimen should be to achieve a viral load below 50 copies/ml for the patient within six months - even for patients with extensive drug experience.

"The minimum goal of what needs to be achievable with salvage therapy is now an undetectable viral load," said EACS President, Dr José Gatell.

The new European recommendations follow the arrival of two new classes of antiretroviral drugs, CCR5 inhibitors and integrase inhibitors, and evidence from clinical trials that undetectable viral load is now a realistic goal for the majority of highly treatment-experienced who include one of these drug classes in their new treatment regimen.

The revised guidance on when to start treatment follows a host of studies suggesting that earlier HIV treatment may be beneficial. At present guidance in the United Kingdom and some other European countries recommends that treatment should start before the CD4 cell count falls below 200. However a recent UK audit by the British HIV Association showed that 60% of patients had started treatment when their CD4 cell count was below 200, and one-third of these had been in care for more than six months.

new drugs

Integrase inhibitor steps closer

The US Food and Drug Administration (FDA) has granted accelerated approval to Merck's integrase inhibitor, raltegravir (*Isentress*).

Raltegravir is the first integrase inhibitor to be approved and provides a new approach to treating the HIV in the US. The drug inhibits HIV's integrase enzyme, which acts to integrate HIV's genetic material into human immune cells.

Raltegravir is an important treatment option for patients with extensive experience of antiretroviral therapy, and who have resistance to drugs from the main three classes. Data presented at International AIDS Society Conference this year, suggested that raltegravir may also be a safe and effective treatment for those new to therapy.

The approved dose of raltegravir is 400mg twice daily in combination with other antiretroviral drugs. The side-effects most commonly associated with raltegravir are diarrhoea, nausea, and headache. Approval for raltegravir in Europe is expected in the first quarter of 2008.

new drugs

Once-daily *Telzir*?



A new once-daily dose of the protease inhibitor fosamprenavir (marketed in the United States as *Lexiva* and in Europe as *Telzir*) has been approved by the US Food and Drug Administration.

The approval gives US patients new to HIV treatment the option of taking fosamprenavir as a once-daily dose of two 700mg tablets with a single booster dose of 100mg of ritonavir. This halves the current dose of the ritonavir booster.

A study in healthy volunteers showed that the lower levels of ritonavir did not result in significantly lower fosamprenavir levels, but volunteers receiving the 100mg ritonavir dose experienced fewer side-effects.

In Europe, fosamprenavir is currently licensed for use in both treatment-naïve and treatment-experienced patients at a dose of 700mg twice daily plus 100mg of ritonavir twice daily.

adherence

Barriers to adherence



Financial worries are strongly linked to poor adherence to antiretroviral therapy, according to a US report in the online edition of the *Journal of Acquired Immunodeficiency Syndromes*. Participants who used drugs and alcohol were also found to have poorer adherence.

Poor adherence is a common reason for anti-HIV drugs failing and so research that identifies factors that predict low adherence is vital. While some studies have looked at the relationships between certain behaviours (like drug and alcohol use) and adherence, few have examined any affect from differences in HIV-related quality of life.

In this study, volunteers answered questions about their HIV-related quality of life before adherence was assessed using medication bottles which contained electronic counters. The questionnaire enquired about overall functioning, sexual

function, health worries, medication worries, disclosure worries, financial concerns, 'HIV mastery', life satisfaction, and trust in their HIV care provider.

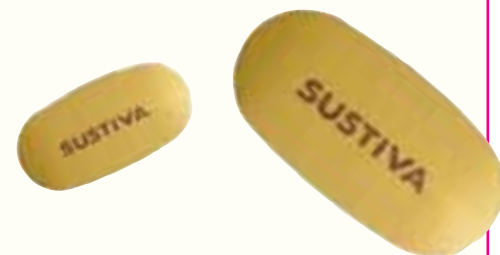
If participants took 95% or more of their medications, they were assessed as good adherers; those who took less were poor adherers.

While both alcohol and drug use in the previous year were significantly associated with poor adherence, the only HIV-related quality of life measures associated with below 95% adherence to antiretroviral therapy were financial worries. These measures included "having to live on a fixed income", concerns about "how to pay the bills", and having too little money "to take care of myself the way I think I should."

"Financial worries should be assessed in behavioural interventions designed to improve adherence", concluded the investigators.

side-effects

Efavirenz risk from rare gene



A twelve-year-old girl was found with seven-to-eight times the normal blood concentration of efavirenz (*Sustiva*) because she carried a rare genetic mutation. The rare gene (called CYP2B6-516) left her incapable of effectively clearing efavirenz from her system.

Efavirenz is known to cause side-effects which affect the mind and brain and such high levels of the drug can cause severe psychosis. Psychotic behaviours had been developing for over a year before the girl was hospitalised and included withdrawal, decreased concentration and social skills, delusions, and suicidal and homicidal thoughts. The onset of these symptoms coincided with an increase in the patient's daily efavirenz dose.

All tests on the girl were normal with the exception of a drug level monitoring test that showed the level of efavirenz was much higher than expected. Her doctors concluded that her psychosis was related to the excess levels of efavirenz in her blood and symptoms gradually improved after treatment with efavirenz was stopped.

The reporting investigators suggest that patients who develop "prolonged psychiatric symptoms" after starting efavirenz should have tests to determine concentrations of the drug in their blood, and possibly for the genetic mutation underlying the excess levels of efavirenz observed in their patient.

atu to become htu?

by Caspar Thomson

Time flies! Remarkably it has already been two years since we re-launched *AIDS Treatment Update (ATU)* with the design you see today (if you've only recently started reading the newsletter, you can see how *ATU* looked before October 2005, below).



The new design has attracted a great deal of positive response. Our 2006 readers' survey revealed that 99% of respondents found the new

look newsletter easier to navigate, 96% found it more appealing to read and, interestingly, 94% found it more trustworthy since the redesign!

Perhaps it's not surprising that the new design received such high approval ratings. We took a lot of time, in the run up to the re-launch, sounding out readers' views and testing ideas within focus groups.

We had originally intended to change the title at the same time as the design. We had received feedback that the use of the acronym AIDS was off-putting for some potential readers - and that it didn't accurately reflect the newsletter's content. After all, thanks to the amazing advances in treatment over the last decade the overwhelming majority of people in the UK are living with, and being treated for, HIV not AIDS.

However, at the time, many readers felt that a new title created too much change. *AIDS Treatment Update* is, after all, a trusted title and people were concerned that changing its name,

as well as its look, was a step too far. Something might be lost. With such a level of disquiet at the proposal to change the name, the idea was shelved and *ATU* kept its original title.

But now, two years on, the new look has established itself and, I hope, you as a reader feel reassured that the newsletter continues to provide the same level of high quality information to enable you to keep up to speed with the rapidly evolving world of HIV treatment.

At NAM, we like to take a Ronseal approach to our titles! In other words, we strive to ensure that our titles say exactly what's "in the tin" (i.e. accurately describes the contents of the publication).

We therefore feel that it is an appropriate time to change the newsletter's name to *HIV Treatment Update*, starting with the

Yes, I'd be happy with *HIV Treatment Update*

No, I'd be unhappy if *ATU* became *HIV Treatment Update*. I'd be unhappy because:

.....

.....

.....

I don't mind either way.

Thanks for your views. As part of our mission we aim to ensure all our resources are rooted in the experience of people most affected by the epidemic. We therefore truly value your opinion.

January/February edition. You can see how this would look, had we applied this title to last month's edition, below.



We want to check that you think we are taking the right decision on this and would welcome your views. With this in mind there is a cut-off reply form on the next page, which we'd be delighted if you would complete, pop in an envelope and return to us at:
NAM, Freepost LON 17995, London SW9 6BR.

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