ISSN 1472-4863

ARV4IDUs

ANTIRETROVIRAL TREATMENT FOR INJECTING DRUG USERS: A QUARTERLY BULLETIN

Volume 1 Number 4: English edition

December 2008

CONTENTS

Published by HIV i-Base

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Antiretroviral Tretment for Injecting Drug Users: A quarterly bulletin

ARV4IDUs is a quarterly bulletin published in electronic format by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered by fax or post using the form on the back page or directly from the i-Base website:

http://www.i-Base.info

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ARVs4IDUs is a not-for-profit community publication that aims to provide a review of the most important medical advances related to clinical management of HIV and its related conditions for injecting drug users, as well as access to treatments. Comments to articles are compiled from consultant, author and editorial responses.

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We thank those organisations for recognising the importance of providing widely distributed free access to information both to people living with HIV and to the healthcare professionals involved in their care.

HIV i-Base receives unconditional educational grants from Charitable Trusts, individual donors and pharmaceutical companies.All editorial policies are independent of funding sources.

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EDITORIAL

Welcome to the fourth issue of ARV4IDUs.

We are sorry that this is a little late - but hopefully the reviews - mainly from the World AIDS Conference held in Mexico City in the summer and journal reviews - will be interesting reading.

We are looking at a development grant for future issues, that will hopefully allow us to employ a new assistant editor who can steer the project, write original copy and work to commission articles.

Although we haven't got this funding confirmedy, we are interested to hear from people you may be interested in this post. If so, please send your CV to:

ARV4IDUs@i-Base.org.uk

We'd also like to encourage new writers who would like to contribute to future issues. This can include research reports and overview articles. If you would like to contribute to future issues or have news to include, please email:

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ARV4IDUs is produced in English and Russian and is distributed by email and published on the i-Base website.

ARV4IDUs is produced as a supplement to the i-Base HIV Treatment Bulletin (HTB) and has been supported by a grant from the International Harm Reduction Development Program of the Open Society Institute (www.soros.org).

CONFERENCE REPORTS

17th International AIDS Conference

3 - 8 August 2008, Mexico City

Introduction

The International AIDS Conferences are held every two years, and alternate between a developed and a developing country. Approximately 25,000 people attend and over 4,500 research studies are presented.

This year the conference had very few new scientific advances in terms of new drugs or treatment strategies, but it did have a few controversial studies. These large conferences focus more on epidemiology, prevention, policy, access to treatment and issues relating to social exclusion (drug users, sex workers, MSM, gay men, young people, sexual violence, women's rights, etc). These issues are covered in tracks C, D and E of the programme. Tracks A and B cover basic science and clinical science respectively.

Conference abstracts (reduced summaries of each study) are all available online, as are many of the powerpoint slides, web casts, transcriptions and daily 'rapporteur' summaries. Abstracts are accessed via the online conference programme. At the bottom of each daily programme (you need to scroll right down to find the abstract session) is a link to the searchable database.

As it is difficult to find, the direct URL for the posters is:

http://www.aids2008.org/Pag/PosterExhibition.aspx?presType=PE&D=04&S=621

The link for the programme is:

http://www.aids2008.org/Pag/PAG.aspx

This i-Base report includes references to a range of studies – from major presentations and large studies, to overview summaries and to examples of single posters. It is not meant to cover everything that happened, but to give an overview of some of the key themes.

Hyperlinks are either directly to the abstracts or to appropriate programme pages that include further links to abstracts, powerpoint slides or webcasts and abstracts.

Substance use and harm reduction

Adeeba Kamarulzaman

A powerful overview of all the issues associated with harm reduction was given by Dr Adeeba Kamarulzaman as a plenary lecture in a session that packed the vast main session hall.

This focused on the importance of IDU-related issues being seen as health-related rather than legal and law enforcement programmes – current spending give 2% to the former and 70% to the latter.

A summary of the transcription from the talk is included below – but better still, get to a broadband internet connection and watch it first-hand.

http://www.aids2008.org/Pag/PSession.aspx?s=32

I started life as an AIDS physician, and I still am, and every day I am confronted with patients such as this.

This is an x-ray of a 35-year old man with extensive TB who presented to me approximately three months ago, in severe respiratory failure and metabolic derangement. We were unable to do anything for him, and within two days of admission, he passed away.

This is just one example of a patient who died because of the failure of the Malaysian government to implement harm reduction measures 20 years ago.

Many of you see similar patients daily because at the recent estimation, there are approximately 11 million injecting drug users around the world, of whom more than 3.3 million are infected with HIV, and even more infected with hepatitis C virus. We know that outside the sub-Saharan Africa, 30% of HIV infections are due to injecting drug use and in Asia, the region I live, and in Central and in Eastern Europe, injecting drug use is the main drivers of the HIV epidemic.

The situation is even worse in prisons where the prevalence of HIV is more than 4 to 10 times the general community. And we know that prisons are an incubator that makes transmission of HIV and other infectious diseases, particularly tuberculosis, a lot worse. In the words of my colleague, Rick Altice, prison is like a semi-permeable membrane which with prisoners going in and out to the community, the HIV and other infections that occur within prison, then go out into the community and back into the prisons as the prisoners come back into the system.

Drug users do not live in isolation. This complex diagram from Bangladesh showing the social and sexual network of injecting drug users shows how injecting drug use can quickly fuel the HIV epidemic within the HIV community and eventually into the general community.

Now, we know that drug use is a chronic and relapsing disease for many years, the argument for or against harm reduction to prevent HIV transmission should be long over.

Extensive, scientific evidence for the effectiveness of opiate substitution therapy and needle exchange therapy have been done over the last 20 years. Review after review, including two by the Institute of Medicine in the U.S. have shown the effectiveness of harm reduction measures. Immediate action needs to be taken to slow the spread of HIV amongst injection drug users using multiple approaches, as was the conclusion of the review by the Institute of Medicine in 2006.

WHO and UNAIDS have also endorsed harm reduction in their policy briefs since 2005. Yet, out of the 158 countries that have injecting drug use, only 77 countries have implemented needle exchange. Even fewer countries have opiate substitution treatment with less than a million people globally receiving opiate substitution therapy.

So what is stopping us? Unfortunately, in the last few decades, criminalisation of drug use and law enforcement have taken over the health issues of drug use. Dominance of law enforcement over health takes over harm reduction, and moral and religious frameworks are linked to prohibition. Treatment, when it is available, is often geared towards abstinence and a drug-free environment.

Conflicting policies coming from the UN organisations often sends countries confused messages. The UNGASS on AIDS in 2005 emphasised the importance of “ensuring wide-range prevention programs and commodities, including condoms and sterile injecting equipment, and harm reduction, if it is related to drug use”. However, in Vienna, the UNGASS on drugs has said, since the Vienna Convention in 1988, to “establish stricter obligations to criminalise all aspects of cultivation and production, distribution and possession of illicit drugs”. No wonder many countries are confused.

A large percentage of countries report laws, regulations and policies that present obstacles to services for injecting. Recent reports for UNAIDS show that, especially in countries that need it most, there are many, many countries with laws that prohibit harm reduction.

The presence of laws that criminalise drug use, not only prevent access to much needed harm reduction measures, but most often, also leads to outright abuse of human rights. A recent raid in Cambodia led to many people, including non-drug users and children, being behind bars.

Funding for effective HIV prevention including harm reduction measures is abysmal, highlighted by a recent UNAIDS report from the recent Global AIDS update. Even in countries that have embraced harm reduction, the National Drug Policy funding goes mostly towards enforcement. In the Canadian Federal National Anti-drug strategy, funding for harm reduction is a mere 2% compared to 70% for enforcement.

I am moving on to treatment—opiate substitution treatment. The WHO says that medicines that satisfy the priority of healthcare needs of the population are criteria for medicines to be included into the essential medicines list. And they are selected with due regard to disease prevalence, evidence on efficacy and safety and comparative cost effectiveness. They are intended to be available at all times in adequate amounts.

Methadone and buprenorphine were listed in this list in 2005. However, in many countries, these two drugs, which are essential components of the harm reduction program, remain illegal, or unavailable. A report in the New York Times (on 22 July 2008) describes how Russia, up until now, does not make methadone available for its severe heroin problem.

In most instances, evidence-based treatment is put aside for treatment based on incarceration and punitive actions (which have no evidence base), as can be seen in pictures here from Malaysia, Russia, and Myanmar.

All is not bad. There has been progress, including in my own country where the government allowed for the implementation of harm reduction programs, including opiate substitution therapy and needle exchange. Since 2005, we have more than 22,000 drug users on opiate substitution therapy, 11 needle exchange sites (including seven that are funded by the government) with more than a million needles and syringes distributed up to June 2008. More recently, we have also introduced pre-release prison methadone programmes in our prison system.

In China, the roll-out for harm reduction is very fast, as only the Chinese could do, with 88,000 people on methadone maintenance therapy, and 50,000 injecting drug users receiving needle syringe services, as of October 2007.

In the Islamic Republic of Iran, there are now 600 addiction clinics including 132 methadone clinics. Between 100,000 to 130,000 people are on methadone maintenance therapy, including a very large number of prisoners. More recently, they have even introduced automatic vending machines offering sterile syringes and condoms.

At this point I would like to take a minute of my presentation to appeal to the Government of the Islamic Republic of Iran to release Arash and Kamiar Alaei from custody and the charges that have been brought upon them.

I have met the brothers on many occasions and had the opportunity to visit your beautiful country as a Faculty member of the HIV/TB training course for the region that they organised. It was through the inspiration that was gained by the visit to your country that the Malaysian Prison Department has implemented opiate substitution therapy in the Malaysian prison system. As a fellow

Muslim, I appeal to the leaders of the Islamic Republic of Iran, in the name of Allah the Most Merciful and Compassionate, to release these brothers immediately.

If access to opiate substitution therapy and needle syringe programs is problematic, excess to antiretroviral therapy is equally abysmal. A review conducted by the WHO European region, showed, for example, that 83% of the HIV reported cases in Eastern Europe are injecting drug users, but only 24% of people on HAART are injecting drug users. These kinds of statistics are seen in many, many regions of the world, including Asia.

Why is this? Barriers to access can be sociopolitical, social marginalisation and the continued criminalisation and stigma and discrimination of drug users. Individual barriers including fear of side effects, psychiatric illness, homelessness, lack of trust, addiction and addiction related instability and ask the medical community equally at fault with our own perceptions and prejudice against drug users.

In an ideal world, we would like to see the integration of HIV treatment with opiate substitution therapy, tuberculosis, hepatitis C, and mental illness. Unfortunately, these kinds of services only occur in very, very select sites around the world.

If we continue to reject harm reduction it will be at a huge cost. For instance, in the US, where harm reduction is widely rejected at home, but also in countries where it financially supports health programmes.

In the US, 25-33% of injecting drug users are HIV-positive. In contrast, in Australia, where harm reduction was adopted in the early 80's, this figure is only 3-6%.

We need to stop arguing about the merits of harm reduction and just do it. We need to expand coverage in countries where this is currently not a priority. We need to raise funding for health measures at the same level as law enforcement. We need to harmonise public security and health policies, and lastly we need to integrate prevention and treatment services. We need to do all this based on science, public health and human rights.

Now ladies and gentlemen, while we sit here and argue, and while we sit here and collect statistics of drug users becoming infected with HIV and hepatitis C, I would like to share with you something that I think brings home to all of us that drug users are people like you and me. They are somebody's son, somebody's brother, somebody's daughter. This is a documentary that was done by the BBC more than 15 years ago, but the messages that it brings, I think is relevant until today.

The video shows the anguish of this mother over her son's drug addiction. Thank you.

Injection drug users and HIV: evidence-based review of clinical treatment considerations

Transcription: Simon Collins, HIV i-Base

Several oral presentations on IDU issues relating to treatment were included in a symposium on IDU and global responses.

Eric Goosby from University of California, San Francisco provided an evidence-based review of clinical treatment considerations for IDU, including ARVs as effective and life saving treatments, that recognised drug addiction as a chronic progressive relapsing condition and a treatable medical problem. [1]

Factors driving the importance of this emphasis on IDUs, include: drug use being globally the second most prevalent risk behavior associated with HIV transmission, later stage of presentation of IDUs to medical services, co-morbidities, and adherence difficulties associated with active psychoactive substance use and untreated co-morbid mental illness. He also stated that IDUs in western countries have high rates of HIV risk behaviors: 90% were sexually active in the previous year, 20% reported having sex with >5 partners and low rates of condom use (9% to 34%).

Unique aspects of management and care for IDUS include recognising existing prejudices from the medical system and social and legal differences. These factors are particularly prominent in prison populations.

Medical Schools do not always emphasise the complex medical and psychosocial aspects of the HIV-positive IDU, among whom rates of relapse to active drug use are high at >75-97%. Empathy, and a nonjudgmental approach are critical in obtaining a comprehensive and accurate personal and treatment history. Understanding that the addiction may involve multiple substances makes taking a medical history, but this is important, because the use of stimulants and alcohol are associated with increased sexual activity.

Specific history should include substances used, route of administration over time (IV, sc/IV, intranasal, inhaled, oral, anal, other), pattern of use (amount, frequency, most recent use, needle sharing), treatment history, both outpatient and inpatient.

Medical complications of substance use include needle-induced (viral, bacterial, fungal infections, peripheral vascular disease); drug-induced (overdose, withdrawal, organ-specific complications e.g. nephropathy due to heroin, cardiac ischemia due to cocaine, gastrointestinal, cardiac and neurologic disease due to alcohol); and major coinfections (TB, HBV, HCV and other STIs). Social complications include unemployment, family disruption, legal problems and homelessness.

Many effective risk reduction strategies already have a strong evidence base. These include: syringe exchange programs; opiate substitution therapy (OST) (methadone/buprenorphine maintenance, which all have better outcomes when combined with cognitive

behavioral therapy, motivational enhancement techniques or contingency management); peer-driven interventions; community outreach; risk reduction counseling; and diagnosis and treatment of mental illness. Methadone has been proven to reduce injecting drug use by 40% and use of shared equipment by 75%.

It is important to have a versatile and holistic approach which, for the most part, should come from the patients' preference and that 'one single approach does not always apply to the medical presentation'. Sometimes reducing drug use is more important that treating any psychiatric condition and sometimes vice versa, though both need to be addressed in order to optimise treatment of HIV or other illnesses.

The presentation then outlined management of a range of OIs and coinfections, all generally more prevalent in HIV-positive IDUs including bacterial infections (>4 times higher than HIV-negative IDUs), TB (IDU increased risk and HIV worsens outcome), hepatitis B and C, STIs, HTLV-1 and 2, cancer (more aggressive), before reviewing approaches to HIV treatment. The presentation also included an overview of interactions between methadone and ARVs and other medications that is summarised in Table 1.

Table 1: ARV interactions with methadone

ARV Affect on Methadone	
NNRTIs	Decrease methadone levels by 50% within 7 days after initiation of EFV/ NVP (85% will c/o withdrawal symptoms)
PI	NFV/RTV/LPV decrease methadone levels but variable in different patients
Methadone Affect on ARV	
AZT	AUC increased by 40% on methadone
DDI	AUC decreased by 60% on methadone
d4T	AUC decreased by 20% on methadone

The presentation concluded with three summary points relating to provider-patient interactions:

- The physician/providers attitude related to drug abuse is critical to the development of a trusting relationship.
- Providers who openly diminish the needs, complaints and requests of addicted patients are most often excluded from decisions that impact the patients ability to maintain adherence or enter care.
- Despite multiple and repeated documentation of the efficacy of drug treatment programmes, care givers and politicians often view treatment programmes as ineffective.

Principles to enhance physician-patient relationship include: mutual respect (educating the patient about HIV and addiction, recognising the effects of continued drug use, the impact on adherence, and transmission. Providers need to acknowledge that patients can benefit from drug treatment and HIV treatment.

References

This presentation was part of a symposium on issues important to a global response relating to injecting drug use: Injecting Drug Use and Infectious Diseases: Implications for the Global HIV/AIDS Response (An IAS/IDSA Partnership). Symposium TUSY06.

http://www.aids2008.org/Pag/PSession.aspx?s=18

1. Eric Goosby. Comprehensive care for injecting drug users: Syringe exchange, methadone and HIV care and treatment. Abstract TUSY0601.

Staphylococcal infections among injection drug users

Transcription: Simon Collins, HIV i-Base

Another talk in the IDU symposium was given by Frederick Altice from Yale University and looked at management of staphylococcal infections among IDUs. [1]

As an introduction, Professor Altice emphasised that skin and soft tissue infections are the leading cause for emergency room visits and hospitalisations for IDUs, with S aureus & S pyogenes the most common pathogens. [2] S aureus nasal carriage occurs in ~20% of people and is associated with development of community- and nosocomial-acquired S aureus infections. [3, 4] IDUs have a higher rate of S aureus colonisation than the general population and is associated with subsequent infections in IDUs, [3, 4, 5]

An overview of risk factors and the relationship to HIV was summarised from a published paper form 2002. [6]

Skin and soft tissue infections (SSTIs) among IDUs include local (cellulitis & abscesses) and necrotising (complicated abscesses, necrotising fasciitis, pyomyositis, myonecrosis) infections. They are related to local tissue trauma as a direct effect of injecting drugs, tissue ischemia and inoculation of bacteria.

A recent study identified several potentially modifiable risk factors for SSTIs in injection drug users. The practice of injection directly into skin or muscle when veins are no longer accessible ("skin-popping") is the strongest risk factor for abscess, followed by use of dirty needles and injection of a mixture of heroin and cocaine ("speedball"). The practice of drawing blood into the syringe before injection drug intravenously, known as "booting," seems to be a risk factor in those who do not engage in skin-popping. The only

protective factor identified was cleaning skin with alcohol before injection. Women may be at greater risk for SSTIs, presumably because they may have greater difficulty in accessing their veins.

The mechanism by which infection is established probably relates to tissue trauma, direct effect of drugs, tissue ischemia, and inoculation of bacteria. As a result of repeated injections into a single site, skin and surrounding tissue are damaged, develop local ischemia and necrosis, and become susceptible to infection. The drugs and diluents themselves may compound the tissue injury by causing vasospasm and thrombosis. Cocaine, in particular, has been associated with these complications.

Infecting organisms may come from the skin surface, contaminated needles, or saliva when the injection needle is licked or tablets are crushed between teeth before injection. Although one study suggested the drug itself might be the source of infecting bacteria, most other studies failed to establish this association. A recent outbreak of a clonal strain of group A streptococcus in Switzerland may have been caused by contaminated drug containers or by contaminated cocaine, but investigators were unable to prove that either was definitely the source.

Infection with HIV has been recognised as a risk factor by some but not all investigators. Immune disorders may contribute to injection drug users' predisposition to infection. Recent evidence for the expression of opiate receptors on immune cells, specifically receptors for morphine and the metabolites of heroin, support a connection between opiates and immune function. Opiates suppress several T-cell functions important for cell-mediated immunity and also inhibit phagocytosis, chemotaxis, and killing by polymorphonuclear neutrophil leukocytes (PMNs) and macrophages in humans. This impairment of phagocytosis and killing may be an important additional cause for the frequency with which injection drug users present with SSTIs caused by common bacterial pathogens.

Invasive infections among IDUs (most commonly S aureus > Strep > GNRs) usually include bacteremia from local source (lungs, SSTIs), endocarditis and osteomyelitis. Endocarditis is more likely to be right-sided among IDUs than among non-IDUs and duration of antibiotics is prolonged, though shorter duration may be possible for right-sided infections.

MRSA has increased significantly in North America, accounting for over 40% of ICU infection. When hospital-acquired (h-MRSA) it is plasmid-mediated, not associated with toxin production, associated with recent hospitalisation and use of antibiotics and highly resistant to most oral antibiotics, except linezolid. By contrast, when community-acquired (c-MRSA) it is chromosomally-mediated, associated with toxin production (Panton-Valentine leukocidin) and person-to-person transmission that is not associated with traditional risk factors (IDUs, sexual contact and crowding - ie athletes, prisoners, homeless shelters, day care centers). It also remains sensitive to many oral antibiotics (TMP/SMZ, tetracycline, etc).

Staphylococcal colonisation among IDUs is also increasing. A survey in 2000 to detect methicillin-resistant Staphylococcus aureus (MRSA) colonisation in Vancouver downtown east side injection drug users (IDUs) revealed an MRSA nasal colonisation incidence of 7.4%. This is a follow-up study to determine the current prevalence of MRSA colonisation and to further characterise the isolates and risk factors for colonisation. S. aureus was isolated from 119 of 301 (39.5%) samples; three (2.5%) participants had both methicillin-sensitive S. aureus (MSSA) and MRSA, resulting in 122 isolates. Of these, 54.1% were MSSA and 45.9% were MRSA, with an overall MRSA rate of 18.6%. USA-300 (CMRSA-10) accounted for 75% of all MRSA isolates; 25% were USA-500 (CMRSA-5). The antibiograms of USA-300 compared to USA-500 isolates showed 100% versus 7.1% susceptibility to tri- methoprim-sulfamethoxazole (TMP-SMX) and 54.8% versus 7.1% susceptibility to clindamycin. MRSA nasal colonisation in this population has increased significantly within the last 6 years, with USA-300 replacing the previous strain. Most of these strains are PVL positive, and all were susceptible to TMP-SMX.

In a 2001 analysis of a methadone (MM) and heroin (HM) maintenance programme in Basel, nasal carriage higher in MM (43%) than in HM (23%) patients. There was difference in recent or remote hospitalisation, MM subjects were more likely to have used antibiotics in previous month (12% vs 4%), to be HIV-positive (20% vs 6%) and have no IDU (34% vs 0%). In multivariate analysis, enrolled in MM was the only significant (AOR 2.27) correlate of S aureus colonization. No MRSA was isolated but subsequent studies have demonstrated MRSA transmission between drug users and introduction of new MRSA strains. [6]

A recent (2008) case-controlled study of 60 hospitalised opioid dependent (OD) and 60 non-drug users in Egypt, reported that colonization was higher in drug vs. non-drug users (30% vs 10%), an increased risk associated with duration of drug use and use of non-prescription antibiotics and that 58% of active MRSA infections associated with colonisation. [7]

MRSA colonisation persists for years, despite treatment of infection. Contact precautions and isolation of wounds are recommended but universal screening, isolation and eradication of the carrier state remain controversial.

In summary, the following five points were outlined.

- IDUs exist on all continents and are more likely to be colonised with S aureus.
- Morbidity and mortality related to S Aureus infections is greater among IDUs.
- Colonisation with S aureus, including MRSA, is associated with increased risk for infection.
- Infection can be reduced with skin cleaning and sterile syringes.
- MRSA prevalence is variable but growing in different regions of the world, thus requiring increased surveillance to guide clinical practice.

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This presentation was part of a symposium on issues important to a global response relating to injecting drug use: Injecting Drug Use and Infectious

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Abacavir and heart disease: SMART study supports an abacavir-associated increased risk of cardiovascular disease

Simon Collins, HIV i-Base

Jens Lundgren from the INSIGHT research group presented an analysis of nucleoside toxicity and cardiovascular disease from the SMART treatment interruption study. [1]

This issue was one of the most discussed clinical topics of the meeting as GSK also presented an analysis from their trial database. [3]

In February 2008, the D:A:D study showed an increased risk of cardiovascular risk from current or recent use of abacavir – a finding that was unexpected and challenging for people skeptical of a cohort study identifying a new effect with an as yet unexplained mechanism. [4]

Cautious reactions to the D:A:D results looked for validation from other studies which were not allayed by GSK's more limited data set, originally published as a letter to the Lancet. [5]

The SMART researchers analysed patients in the continuous treatment arm of SMART, by use of NRTIs relating to the previous D:A:D findings: using abacavir (but not ddI) n=1019, using ddI (but not abacavir) n=643, and other NRTI combinations with netheir abacavir nor ddI (n=2882). Baseline characteristics of these three groups were similar, including common cardiovascular risks (~4% prior CVD, 40% current smokers, 35% ischemic abnormalities and 7% diabetic). Lipid lowering drugs and blood pressure medications were each used by just under 20% of patients. 15% patients had ≥5 cardiovascular risk factors.

In multivariate analyses adjusting for CVD risk factors, all four categories of cardiovascular disease defined by the group showed increased hazard ratios (HR) for abacavir compared to other NRTIs (see Table 1).

Table 1: Adjusted HR of cardiovascular event with abacavir use vs. other NRTIs in SMART

CVD category	No. of events	Adj. HR (95% CI)
Clinical and silent MI, stroke, surgery for coronary artery disease (CAD), and CVD death	70	1.8 (~1.1-3.2)
Clinical MI as defined in D:A:D	19	4.3 (1.4-13.0)
CVD, major, expanded version (Major CVD plus peripheral vascular disease, Congestive heart failure (CHF), drug treatment for CAD, and unwitnessed deaths).	112	1.9 (1.0-3.1)
CVD, minor (CHF, peripheral vascular disease or CAD requiring drug treatment).	58	2.7 (1.3-2.9)

Importantly, the results were similar when patients receiving tenofovir were used as reference group and when the approximate 10% of patients with events in both D:A:D and SMART databases were excluded from the analysis.

The SMART study also showed a strong association between elevated levels of some inflammation biomarkers with levels of viral load rebound and risk of serious event. In this analysis, patients using abacavir had D-dimer and IL-6 that were 27% and 16%

higher at study baseline than patients in the reference group using other NRTIs (both p=0.07).

These levels could have been higher for reasons unrelated to abacavir use and will need to be examined in a study looking prospectively at changes in these biomarkers in patients starting abacavir. Interestingly, the HEAT study from GSK reported reductions in hs-CRP and IL-6 in both the abacavir/3TC and tenofovir/FTC over 48 and 96 weeks with no differences seen between the two arms. [2]

Similar to D:A:D, the clinical significance in terms of increases in absolute risk from abacavir use was greatest in patients with the highest underlying cardiovascular risk factors. Those patients with five or greater cardiovascular risks or ischemic abnormalities on ECG showed three-fold increased risk from using abacavir compared to other NRTIs (both HR 3.1).

Earlier in the conference, GSK, reported that their retrospective meta analysis from 54 phase 2 and 3 abacavir registrational studies did not find an association between cardiovascular events and either abacavir or non-abacavir use. [3]

While this was important from a regulatory perspective – any safety signal requires a company to look at their own dataset – the limitations of both this database and the presented analysis were unlikely to resolve the concerns highlighted by D:A:D and SMART.

Of the 54 trials, only 13 were randomised for abacavir use, 33 included abacavir in background regimens and 8 did not include abacavir. Just over 14,000 adults and 500 children were included. Events were identified by a search for cardiovascular-related events and rates in naïve and experienced patients were calculated per 1000 person years.

No differences were seen in the relative rates by abacavir use for any cardiovascular event (RR=0.59; 0.35-1.01; p-value=0.055) or any MI (RR=0.863; 0.40-1.86; p=0.706).

Myocardial infarctions (MI) were only identified in 16 patients using abacavir (10 using non-PI and 6 on PI-containing regimens). Of the 11 MIs in the non-abacavir group, all used PI-based regimens except for one patient using an NNRTI-based combination.

Several limitations were raised concerning these data. Firstly, that there were too few events to have statistical power to detect an association either way. Many cardiovascular risks were not recorded at baseline, including smoking status, hypertension, HDL and LDL. Patient numbers were much lower (~7000 and 4500 PYFU in the abacavir and non-abacavir groups), and importantly median follow-up time was less than one year.

By comparison, D:A:D included 33,000 patients who needed to be followed for seven years (160,000 PYFU) until there was sufficient power to make associations to a single-drug effect.

Secondly, patients in clinical trials are and were generally younger, healthier, with lower cardiovascular risks. Interestingly, GSK did not present an analysis relating to the comparator regimens used in these studies, which were PI-based, and therefore already carried a higher risk of CVD.

C O M M E N T

The significance of these results from the SMART study, which are already published as a fast track paper in the 12 September edition of AIDS [6], is that they support the earlier D:A:D findings in two ways. They report a similar association between current or recent abacavir use and cardiovascular disease; and they found that the clinical impact was most significant in patients with highest underlying CVD risk.

BHIVA guidelines have, for several years, included the recommendation to routinely assess CVD risk using Framingham calculators on first diagnosis, prior to starting treatment and annually thereafter. Taken together, the D:A:D and SMART results suggest that for patients at the highest CVD risk (>20% 10-year Framingham), abacavir only be used when alternative options are not available.

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Selected other IDU-related studies

Simon Collins, HIV i-Base

The following summaries are a selection from the many posters presented at the conference. Impact of current, former or no injecting drug use on ARV access and response in Swiss patients

- Success in access to ART treatment for IDUs through PLHA network and community participation, Vietnam
- Model for scaling up access to HIV treatment for IDU in China
- Scale-up of ARV access in China
- User assessment of IDU services in Uzbekistan
- Drug treatment in Russia
- High mortality of HIV-positive IDU in Vietnam
- HIV doubles mortality rate of IDU in Chennai
- Causes of mortality in IDU in Vancouver

All references are to the Programme and Abstracts of the 17th International AIDS Conference, 3-8 August 2008, Mexico City.

Impact of current, former or no injecting drug use on ARV access and response in Swiss patients

An interesting poster of all patients in the Swiss cohort from 1997-2006 looked at the impact of IDU and access to drug treatment programmes (DTP) on access to ARV and treatment response.

They classified IDU into: (i) former; (ii) DTP (drug treatment program); (iii) DTP with ongoing IDU; or (iv) current drug use without DTP.

Of 8,660 patients, 6091 were never IDU, 1080 former, 741 DTP, 607 DTP with ongoing, and 141 current IDU without DTP.

The odds ratios of being on ART, interrupting ART, and having a viral load below limit of detection, detailed in Table 1 were adjusted for calendar year, sex, age, AIDS, and CD4 count.

Self reported adherence correlated with drug use behaviour, but not to the extent expected. Approximate adherence rates within the previous month were 79%, 70%, 70% 60% and 55% in non-IDU; former IDU; DTP; DTP with ongoing injection behaviour; and current IDU respectively.

Table 1: Odds ratios by IDU definitions compared to non-IDU patients

	Being on ART	Suppressed viral replication on ART	Interrupted ART
Non-IDU	1	1	1
Former	1.19 (1.06-1.32)	0.96 (0.87-1.07)	1.00 (0.88-1.14)
DTP only	1.08 (0.95-1.22)	0.94 (0.84-1.06)	0.98 (0.85-1.14)
DTP with IDU	0.53 (0.47-0.61)	0.79 (0.67-0.92)	1.85 (1.58-2.17)
Current IDU	0.44 (0.34-0.57)	0.67 (0.52-0.87)	2.01 (1.49-2.73)

Importantly, the likelihood of being on ART and virological outcome were comparable between never- and former-IDU. In contrast, the results differed between the different IDU categories. Former IDU and persons in a DTP were more likely on ART and had an improved virological outcome compared with people currently injecting drugs with or without DTP.

Ref: Huber M et al. Adherence to antiretroviral treatment (ART) of HIV-infected persons with or without injection drug use (IDU) or in a drug addiction treatment program: the Swiss HIV cohort study. Abstract TUPE0206
http://www.aids2008.org/Pag/Abstracts.aspx?AID=5706

Success in access to ART treatment for IDUs through PLHA network and community participation, Vietnam

A poster from Hang and colleagues reported on the successful involvement of People Living with HIV in Vietnam, where 70% of HIV-positive people are from the drug using community. The challenges in successful ARV care include adherence, lost to follow up and drug resistance.

The poster explained how the clinic in Thuy Nguyen established a comprehensive network model supporting PLHA and other marginalized communities including IDUs. The network gets involvement of self-help groups of PLHA, community health care workers, empathy clubs, local and INGO who are implementing projects in the area. Many of the patients accessing treatment services at the clinic are IDUs. Services include home visits, treatment adherence, ARV information, HIV/AIDS education, drug use. They also create community awareness on HIV/AIDS/Drugs use to reduce stigma and discrimination and provide peer support. The supporting network receives feedbacks from patients about the services of the clinic. Within a span of 10 months the network referred 100 patients and supported both ART and OI treatment.

This model helps reduce rate of lost to follow up and ART treatment failure and the network is planned to expand to involve groups such as Women's Union, Youth Union and family members to provide this key factor for treatment success, especially IDUs.

Ref: Hang NT, Thangsing C. Success in access to ART treatment for IDUs through PLHA network and community participation, Vietnam. Abstract MOPE0160.
http://www.aids2008.org/Pag/Abstracts.aspx?AID=10514

Model for scaling up access to HIV treatment for IDU in China

Wang and colleagues presented a poster outlining an ARV roll out programme in Yunnan Province, which has the largest number of HIV cases in China with local IDU-driven epidemics.

Provincial and local authorities with support from the Clinton Foundation have implemented HIV treatment in 11 sites since July 2005. Cumulatively 2315 patients were on ARVs with 4335 additional people followed in care by November 2007.

An integrated services approach links hospital-based clinics with community outreach/peer support centres that follow patients in clinic and out in their communities. Linkages with methadone maintenance, needle exchanges, and TB control programs extend the net of services to enter and retain IDUs in care. Extension of HIV treatment into enclosed settings has begun to ensure continuity of ARVs and re-entry into community-based medical care upon release. A model decentralising care from hospital clinics to township and village levels has been piloted with lines for consultation, referral and oversight by HIV-trained clinicians. Retention in care, and treatment benefit documented by CD4 and viral load, show good results.

Next steps are to expand capacities for patient follow-up at village level and access to care in enclosed settings.

Ref: Wang Y et al. Scaling up comprehensive HIV treatment for injection drug using populations in Yunnan Province. Abstract CDB0248.
http://www.aids2008.org/Pag/Abstracts.aspx?AID=14468

Scale-up of ARV access in China

A second poster from China analysed the impact of Global Fund programmes in seven provinces in China form 2005-2007.

The number of patients on ART in 76 program counties in the 7 program provinces increased from 89 at baseline to 12,495, with a higher than the national average growth rate. The highest growth rate was witnessed in Yunnan where the number of patients on ART increased from 6 at baseline to 5616, with an average quarterly growth rate of 0.6. Since the launch of the program, the ART service network has expanded considerably, covering PLWHA in both program and non-program counties.

PLWHA were mainly infected through injecting drug use.

Ref: Zheng H. Analysis of progress in antiretroviral therapy (ART) in seven program provinces of China Global Fund Round 4/China-UK AIDS program. Abstract CDB0311.
http://www.aids2008.org/Pag/Abstracts.aspx?AID=10360

User assessment of IDU services in Uzbekistan

In Uzbekistan, HIV incidence is increasing, with 2205 newly reported HIV infections in 2006 and 30% of IDUs testing HIV-positive in Tashkent between 2003 and 2004.

Three initial Trust Points (TPs) during 2000-2003 providing harm reduction services (mostly needle exchange) were scaled up to 10 TPS in 2004 to provide more comprehensive HIV prevention and Harm Reduction services.

To evaluate the programme, 100 IDUs were interviewed about accessability, availability, variety and quality of services provided; the effectiveness of those services and the satisfaction of the survey participants.

70% were satisfied with services, especially needle and syringes exchange, psychological support and referral to HIV testing. 30% of survey participants did not find Voluntary Counseling and Testing (VCT) available in TP and 20% were not satisfied by the fact of being referred to AIDS centre for testing part of the VCT, anticipating its availability in TP. 50% got information about substitution treatment from TPs and 30 were referred to substitution treatment.

The study concluded that while many IDUs are satisfied with services rendered in TPs, further improvement for provision of more comprehensive services including the complete VCT available in TPs is essential.

Ref: Makhkamov M. Trust points as an effective approach to scale up HIV prevention among injecting drug users. Abstract CDB0334.
http://www.aids2008.org/Pag/Abstracts.aspx?AID=4470

Drug treatment in Russia

Approximately 80% of HIV-positive people in Russia acquired HIV from IDU-related activities and a high proportion are likely to need ARVs.

A poster reported on two research projects on accessibility of ARV treatment for drug users.

One research project from 2007 focused on low quality of drug dependence treatment as an impediment to users' access to ART. Documentation was carried out in four Russian cities and included interviews with 60 IDUs, over a dozen of whom were living with HIV and AIDS. The other study is an ongoing monitoring of access to hepatitis C, HIV and tuberculosis treatment in 20 Russian regions.

The research revealed: problems with procurement and distribution of ART in Russia; a lack of important diagnostic tests; lack of treatment for opportunistic infections; and discriminatory attitudes by health care providers that have in effect denied treatment to drug users in need. They reported lack of clear government support for harm reduction programmes proven to reduce HIV infections among IDUs, insufficient engagement of harm reduction programs in ART provision, inadequate information about HIV at government health care facilities; and lack of coordination between HIV, drug dependence, and tuberculosis clinics.

They also reported that after the findings of the research report were publicised, a new activist group emerged in St. Petersburg that will advocate for improving access to ARV therapy and high-quality medical care for drug users living with HIV.

Ref: Ovchinnikova M and Lohman D. Drug treatment in the age of HIV/AIDS in Russia. Abstract WEPE0094.
http://www.aids2008.org/Pag/Abstracts.aspx?AID=10929

High mortality of HIV-positive IDU in Vietnam

A poster from Vietnam that showed approximate 20% mortality over one year for HIV-positive people vs 2-3% for HIV-negative.

This prospective cohort study (from August 2005 to July 2007) of 856 male IDUs in Thai Nguyen province, all of whom injected heroin, and 23% were HIV-positive. Median age was 32 (range 18-59).

During 689 person-years of follow up, 43 injectors died (26% were drug overdose deaths). The overall mortality rate was 6% per year, and was significantly higher ($p<0.001$) among HIV-positive IDUs (14%/year) than among HIV-negatives (4%/year). In multivariate analyses, injecting benzodiazepines in addition to heroin during the 3-month period prior to enrollment increased the hazard of overdose deaths by 4.9 times (95% CI = 1.3-17.9) compared to heroin injection alone.

For non-overdose deaths, IDUs who were HIV-positive at enrollment had a 20% increase in the hazard of deaths (HR = 1.2, 95% CI = 1.1-1.4) compared to HIV-negative IDUs, and a history of tuberculosis increased the hazard by 2.2 times (95% CI = 1.4-3.5).

The study concluded that the observed death rate was high and that IDUs should be informed of the risk of fatal overdose associated with injecting benzodiazepines. Increased access to effective tuberculosis treatment and antiretroviral therapy may help reduce premature deaths among the drug users.

Ref: Quan VM et al. Premature deaths among Vietnamese injection drug users: predictors and prevention. Abstract MOPO0247.
http://www.aids2008.org/Pag/Abstracts.aspx?AID=9931

HIV doubles mortality rate of IDU in Chennai

A poster from India characterised the higher rates of mortality related to HIV and IDU in Chennai.

Of 1158 IDUs recruited between April 2005 and May 2006, 293 (25%) were HIV-positive. 70 deaths were observed over 2168 person-years (PY) of follow-up (Incidence Rate [IR]: 3.2; 95%CI: 2.5 - 4.1). The risk of mortality among HIV positive IDUs (IR: 5.7 per 100 PY) was more than twice that of negative IDUs (IR: 2.3 per 100 PY).

This association persisted after adjustment for age, hepatitis C virus status, injection frequency, types of drugs injected, alcohol use, and incarceration. The leading causes of mortality in both HIV negative and positive IDUs were overdose (n=19), tuberculosis (n=12) and accident/trauma-related (n=9). Death rates from overdose and tuberculosis were higher in HIV positive than negative IDUs, though not statistically significant. Only 4 deaths in HIV positive IDUs were identified as being AIDS-related (IR: 0.7 per 100 PY).

Ref: Solomon SS et al. High incidence of mortality in a cohort of HIV positive and negative injection drug users in Chennai, India. Abstract MOPO0244.
http://www.aids2008.org/Pag/Abstracts.aspx?AID=8338

Causes of mortality in IDU in Vancouver

A poster from Sadr and colleagues examined the rates and causes of mortality in a cohort of 204 IDUs taking HAART between January 1998 and June 2007 (1,032 person years).

Mean age at enrolment was 40.8 years, 150 (74%) were males, 107 (52%) were Aboriginal, and all were current or previous injection drug users.

There were 65 deaths for a cumulative mortality of 34.6% (annual mortality rate of 5.3%). Mean age at time of death was 42.5 years (44.1 yrs for males, 37.9 yrs for females). The cause of death was HIV-related in 36 (55%) cases, including AIDS without a specific pathological diagnosis (17); community-acquired pneumonia (5), tuberculosis (3), cryptococcal meningitis (2), mycobacterium avium-complex (2), lymphoma (2), PCP pneumonia (2), PML (2), and Kaposi's Sarcoma (1). The 29 (45%) deaths not directly HIV-related included end-stage liver disease (9), drug overdose (6), cardiovascular disease (6), stroke (2), suicide (2), chronic lung disease (1), endocarditis (1), cancer (1), and undetermined (1). At the time of death, the mean CD4 count was 198 cells/mm3 and 23% had a plasma viral load less than 50 copies/ml.

The researchers concluded that despite HAART, mortality rates remained extremely high. In addition to a wide range of HIV related opportunistic infections, non-HIV related events accounted for nearly half of the deaths. Renewed efforts are needed to engage

drug users in HIV care and address the social, environmental and addiction-related factors that contribute to these preventable and pre-mature deaths.

Ref: Sadr A et al. Causes of mortality among injection drug users enrolled in an antiretroviral program in Vancouver, Canada. MOPO0253.
http://www.aids2008.org/Pag/Abstracts.aspx?AID=7351

ANTIRETROVIRALS

Antiretrovirals calculated to extend life expectancy by 35 years but still a 10 year difference for IDU

Simon Collins, HIV i-Base

An analysis from a large international cohort study from the Antiretroviral Therapy Cohort Collaboration (ART-CC) has calculated that antiretroviral treatment currently extends life expectancy for HIV-positive people to an average of 65 years. The study model used patients from high-income countries who start treatment when either 20 or 35 years old.

Using data from 43,000 patients from 14 cohorts from Canada, Europe and the US, the researchers estimated the life expectancy since 1996 on the basis of reported deaths within the cohorts. They compared rates in treatment-naïve patients starting treatment in the 1996–99 period to patients starting treatment from 2003–05.

Compared to the earlier treatment group, life expectancy for patients starting treatment in 2003-05 increased by 13 years.

Although life expectancy increased similarly in all groups there were significant absolute differences between different groups of patients,

Women had higher life expectancies than men (overall mortality rates/1000 patient years [95%CI]: 9.1 [8.2-10.1] vs 12.9 [12.3-13.6].

Patients with presumed transmission via injecting drug use had lower life expectancies than did those from other transmission groups (32·6 [1·1] years vs 44·7 [0·3], based on starting treatment aged 10).

Life expectancy was lower in patients with lower baseline CD4 cell counts than in those with higher baseline counts (32·4 [1·1] years for CD4 cell counts below 100 cells/mm3 vs 50·4 [0·4] years for counts of 200 cells/mm3 or more).

COMMENT

One of the most common responses to an HIV-diagnosis, and one of the key unanswered questions even for long-term survivors relate to life expectancy. It is therefore important to draw on the most recent studies to inform these discussions.

Antiretroviral therapy since 1996 has dramatically reduced mortality and extended life in all countries where there is access treatment, and as experience with treatment and availability of new and better drugs improves, projected life expectancy has similarly increased.

Every few years a new study produce more optimistic figures – 12 years, 25 years and now 35 years in the latest studies. [1, 2] However, these reports underscore higher mortality among HIV-positive IDU compared to HIV-negative IDU and HIV-positive people who are not drug injectors. The focus of HIV care and treatment should be broadened to address prominent causes of non-AIDS related death among IDU, such as overdose, and suicide.

Although it is likely that future studies will further close the gap between HIV-positive and HIV-negative populations, we are not there yet. The paper from ATCC still shows 10-20 year differences due to HIV status. Patients starting at lowest CD4 levels have 10–20 years lower life expectancy and injecting drug use also impacts by 10 years.

ARV treatment, if used carefully, does not appear to have a built-in shelf life. Once virus is suppressed to below 50 copies/mL, ongoing viral evolution is stopped, rather than slowed, and resistance is related to poor adherence, or more rarely, re-infection with a resistant strain.

Experience with HAART over ten years suggests that initial concerns about compartmental sites, especially in relation to drug penetration and compartmental resistance has not led to systemic virological failure on a significant or measurable level. There are little data to predict whether this will become an important concern with longer use of treatment.

However, real concerns related to HIV-positive patients and aging include the greater risks for neurological complications, brain disorders (including Alzheimer's and Parkinson's), reduced bone mineral density, bone disease and fractures, virally-mediated cancers, diabetes, and heart disease.

The extent to which an extended period of uncontrolled viraemia prior to starting treatment may explain some of these increased risks is one of the questions addressed by several research groups, including the START study, due to enrol later this year. [3]

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http://www.annals.org/cgi/content/abstract/146/2/87
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JOURNAL REVIEWS

An estimated 3 million injecting drug users worldwide could be HIV-positive

Polly Clayden, HIV i-Base

A report in the 24 September 2008 online edition of the Lancet estimated that about 3 million injecting drug users worldwide could be HIV-positive. [1]

Bradley Mathers and co-authors, on behalf of the 2007 Reference Group to the UN on HIV and Injecting Drug Use, performed a literature search of peer reviewed and non-peer reviewed "grey" literature databases. Requests were also made to UN agencies and other international experts.

The authors considered 200 countries and the review revealed documented drug use in 148 of these. They reviewed 11,022 documents and noted that reports were only available for a small number of countries in the Caribbean (6/15) and sub-Saharan Africa (13/47).

They found that prevalence estimates of injecting drug use could be made for 61 countries representing 77% of the total population worldwide aged 15-64 years. Extrapolated estimates from this review suggested that 15.9 million (range 11.0-21.2 million) people worldwide could be injecting drug users. They found the largest numbers of injecting drug users in China, the USA and Russia with midpoint prevalence estimates of 12%, 16% and 37% respectively.

HIV prevalence among injecting drug users was 20–40% in five countries and was greater than 40% in another nine (they noted that areas of particular concern are countries in southeast Asia, eastern Europe, and Latin America). China, Russia, and the USA all had midpoint estimates of HIV prevalence in these populations of over 10%.

The authors estimated that worldwide about 3 million (range 0.8-6.6 million) people might be HIV positive. They explain that the study has many limitations, not least that data from which to extrapolate prevalence estimates are inconsistent and populations typically hard to access.

They write: "People who inject drugs have the right to enjoy the highest standard of health attainable. There is a clear mandate to invest in HIV prevention activities such as needle and syringe programmes and opioid substitution treatment and to provide treatment and care for those who are living with HIV/AIDS."

In a separate editorial comment, Kamvar Arasteh and Don Des Jarlais from the Beth Israel Medical Center, New York, highlights the importance of the disturbing trends observed in the article for Asia and eastern Europe. [2]

In China, with the largest estimated population of injecting drug users and an HIV prevalence of 12% in users, HIV infections have been rising. In Vietnam, the prevalence of injecting drug use is estimated at 0·25% with an HIV prevalence of 34%. In Malaysia, the prevalence of injecting drug use is 1·3% with an HIV prevalence of more than 10%.

These estimates reveal large gaps between the numbers of IDUs who access prevention services and HIV testing. In 2007, less than half of IDUs in China had received an HIV test in the previous 12 months and knew their status, only a third reported using a condom during their last sexual intercourse, and only 40% reported using sterile injection equipment the last time they injected.

They concluded "if HIV-prevention efforts are implemented on a large scale when prevalence is low in injecting drug users, it is possible to avert larger HIV epidemics. Thus it should be an imperative—for both resource-constrained countries and international donors—to implement large-scale evidence-based programmes for HIV prevention wherever there is an indication of a problem with the development of injecting drug use."

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Depression improves to a similar extent when using substitution therapy with either methadone or buprenorphine

Simon Collins, HIV i-Base

A study by Angela Dean from the University of Queensland and colleagues in the journal European Psychiatry has reported similar improvements in depression in patients using either methadone (MM) and buprenorphine (BM) as opiod substitution therapy (OST). [1]

This is important because this benefit of OST is not widely understood, or reported for methadone, and because early studies of buprenorphine emphasised it's antidepressant effect as a potential advantage.

This was a sub-study of a much larger trial. [2] The authors studied the antidepressant affects in 54 patients who were part of a randomised controlled trial (with additional matched placebo) of daily 30mg MM syrup vs 4mg BM sublingual tablets in 405 heroin-dependent patients seeking opioid maintenance treatment. Doses were individually titrated based on patient assessment to optimise response.

Daily dosing occurred for 6 weeks, after which alternate day dosing began. Those on buprenorphine received double their previous daily dose (or increased to the maximum permitted dose of 32 mg) on alternate days and placebo on interposed days. Methadone patients received a corresponding increase in their placebo buprenorphine tablets to maintain the blinding.

Baseline demographics included approximately 60% men, 40% women; age 30; 6-7 years heroin use (with a wide range); and 70-80% prior treatment for opiate dependence.

Depression was measured using the self-report Beck Depression Inventory (BDI) at baseline and after 3 months. Symptoms of depression significantly improved in both treatment groups over the study period ($p<0.001$) with no differences between groups ($p=0.83$). Neither previous duration of heroin use, nor dose levels of either drug were related to results on the depression score. These results are detailed in Table 1.

Table 1: Depression score results

	Methadone	Buprenorphine
N	(n = 79)	(n = 68)
Days in trial (SD)	74 (30)	71 (32)
BDI baseline (SD)	22.3 (10.2)	24.9 (11.0)
BDI 3 months (SD)	11.5 (9.7)	13.5 (8.9)
Mean daily dose (mg) at 3 mo (over past 30 days)	50.1 (24.3)	8.6 (4.1)
Dose range (mg/day)	20-150	2-32
Adherence at 3 mo (% dose taken in last 30 days)	88%	87%

With patients in the methadone group, a higher baseline depressive symptoms predicted higher symptoms at 3 months ($p<0.01$) and there was a significant relationship between adherence (as % of doses taken in last 30 days) and BDI at 3 months ($p<0.05$). Neither factor was significant for the buprenorphine group ($p=0.38$ and $p=0.58$ respectively).

The 9% of the study group using antidepressants had a smaller improvement in BDI scores but a modest but significant relationship between BDI scores and heroin use over the previous month.

This study therefore found no differential benefits of buprenorphine vs methadone on depressive symptoms. The high levels of depressive symptoms at treatment entry and subsequent improvement over time in both groups are consistent with other research. [3, 4]

However the authors also noted that given the small sample size, the power to detect group differences is low, and that larger samples would be required in future studies. Other factors that could have impacted on the results, included differences in dosing and under-reporting of antidepressant use.

C O M M E N T

Double blind studies with methadone and buprenorphine are very difficult to do.

Certainly the antidepressant effect of methadone and buprenorphine are well recognised clinically, but few studies are designed to

document the effect. This study was designed to show that the antidepressant impact of buprenorphine may have an advantage over methadone, but by comparing both drugs in a randomised placebo-controlled study, the methadone effect was also clearly identified.

The cause-effect relationship is complicated. Clearly OST has an antidepressant effect, but is it the medication, or is it the cessation of all those psychosocial negative impacts of chaotic heroin use, and the benefits of achieving some control over your life, which is the antidepressant effect?

Alternatively, it may just be the cessation of the rapid up-and-down cycles associated with regular heroin use. Maybe repeated low-grade withdrawal is a depressant, and preventing it, a powerful antidepressant?

Many questions, few answers.

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Lower rates of spontaneous HCV clearance in HIV-positive IDUs

Simon Collins, HIV i-Base

Vincent Soriano and colleagues from the EuroSIDA cohort published an analysis in the November edition of JID of HCV genotype, viraemia and rates of spontaneous HCV clearance in HIV-positive patient in Europe and Argentina. [1]

All HCV antibody-positive (Ab+) patients the cohort with stored samples were tested for serum HCV RNA and viraemic patients were genotyped.

Of 1940 HCV Ab+ patients, 1496 (77%) were serum HCV RNA positive. Injection drug users (IDUs) were less likely to have spontaneously cleared HCV than were homosexual men (20% vs. 39%; adjusted odds ratio [OR], 0.36 [95% confidence interval {CI}, 0.24–0.53]), whereas patients positive for hepatitis B surface antigen (HBsAg) were more likely to have spontaneously cleared HCV than were those negative for HBsAg (43% vs. 21%; OR, 2.91 [95% CI, 1.94–4.38]).

Of patients with HCV viraemia, 786 (53%) carried HCV genotype 1, and 53 (4%), 440 (29%), and 217 (15%) carried HCV genotype 2, 3, and 4, respectively. Higher HCV RNA levels were associated with a greater chance of being infected with HCV genotype 1 (OR, 1.60 per 1 log higher [95% CI, 1.36–1.88]).

The authors concluded that “more than three-quarters of the HCV Ab+ HIV-positive patients in EuroSIDA showed active HCV replication. Viraemia was more frequent in IDUs and, conversely, was less common in HBsAg-positive patients. Of the patients with HCV viremia analyzed, 53% were found to carry HCV genotype 1, and this genotype was associated with greater serum HCV RNA levels.

An editorial comment by Raffaele Bruno and Paolo Sacchi pointed out that the high (25%) clearance rate should to be done by repeatedly using a more-sensitive test, such as a transcription-mediated amplification, rather than using single time point RNA. [2]

They explained that “In the absence of HIV infection, spontaneous HCV clearance occurs in 20% of patients. Spontaneous HCV clearance, which seldom occurs >12 months after primary infection, is less likely in men, people of black race, chronic carriers of HBV, and probably those who become infected after early childhood. Clearance of HCV does not convey immunity, because new exposure can result in reinfection. The rate of spontaneous clearance may be 2-fold higher (40%) in IDUs who clear their primary infection in the absence of HIV coinfection. Nonetheless, the majority of HCV reinfections become chronic, as seen in people with hemophilia who used contaminated plasma derivatives before 1983. Mehta et al noted that, compared with primary infection, clearance of HCV reinfection increased among HIV-negative but not HIV-positive IDUs. [3]

“Given their low rate of spontaneous clearance and poor response rates, preservation of immune function with early antiretroviral treatment may be the best way to avoid a poor outcome of liver disease in HIV-positive patients. Further study of this strategy is warranted.”

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DRUG INTERACTIONS

Key papers on methadone and ritonavir

Two papers will come to be recognised as pivotal contributions to our understanding of the mechanism of ritonavir changes in drug disposition.

Paper 1 provides clear evidence (data in healthy volunteers) that the effect of ritonavir on methadone clearance results from increased renal clearance and induced hepatic metabolism. It is important to note that the induction of methadone metabolism occurred despite profound CYP inhibition in both intestine and liver (the expected effect). So these data clearly suggest that there is no role for CYP3A4 in methadone metabolism.

Paper 2 describes short term (2 day) and steady-state (2 week) ritonavir effects on intestinal and hepatic CYP3A4/5 (probed with iv and oral alfentanyl) and P-gp (probed with fexofenadine), and on methadone pharmacokinetics in healthy volunteers. The authors conclude that acute ritonavir inhibits hepatic CYP3A (>70%) and first pass CYP3A (>90%). The fexofenadine data suggested P-gp inhibition. While mild induction of P-gp and hepatic CYP3A by steady state ritonavir was apparent, the overall net effect was still marked inhibition.

References

1. Mechanism of ritonavir changes in methadone pharmacokinetics and pharmacodynamics: I. Evidence against CYP3A mediation of methadone clearance. _Kharasch E, Bedynek P, Park S, et al. Clin Pharmacol Ther, 2008, 84(4): 497-505.

http://www.ncbi.nlm.nih.gov/pubmed/18615008

2. Mechanism of ritonavir changes in methadone pharmacokinetics and pharmacodynamics: II. Ritonavir effects on CYP3A and P-glycoprotein activities._Kharasch E, Bedynek P, Walker A, et al. Clin Pharmacol Ther, 2008, 84(4): 506-512.

http://www.ncbi.nlm.nih.gov/pubmed/18615009

Source: www.hiv-druginteractions.org (3 October 2008).

http://www.hiv-druginteractions.org/frames.asp?new/Content.asp?ID=398

Buprenorphine/naloxone interactions with tipranavir/ritonavir

A poster at the 48th ICAAC conference held in Washington in October reported an interaction between buprenorphine/naloxone and the protease inhibitor tipranavir that was not overcome by ritonavir boosting.

This was a multiple dose, open-label, sequential, non-randomised study in HIV negative subjects stabilised on at least 3 weeks of BUP/NAL therapy.

At day 7 of concomitant administration, buprenorphine AUC and C24h were not affected by co-administered TPV/r (<6% change relative to BUP/NAL alone) while Cmax decreased approximately 14%. However, although AUC, Cmax and C24h of norbuprenorphine, the major BUP metabolite, were decreased almost 80% and naloxone AUC and Cmax were decreased approximately 44% and 36%, respectively, when coadministered with TPV/r, there was no clinical evidence of opioid withdrawal and no need to modify buprenorphine dose.

Compared to historical controls AUC and C12h tipranavir levels decreased by 26% and 39%, respectively and Cmax was unchanged. Ritonavir C12h was similar, but Cmax and AUC were lower in by 40-50% and 35%, respectively.

The authors concluded that no modification of BUP/NAL is required but that caution should be used when combining BUP/NAL with tipranavir/r due to sgnificantly decreased tipranavir plasma concentrations.

Ref: Bruce R et al. Pharmacokinetic Interactions between Buprenorphine/Naloxone & Tipranavir/Ritonavir in HIV-Negative Subjects Chronically Receiving Buprenorphine/Naloxone. 48th ICAAC. Poster abstract A-967a.

ON THE WEB

Web resources

The following organisations all include web resources about ARV4IDUs:

http://www.drugtext.org/library/legal/eu/default.htm	http://who.org
http://www.harmreduction.org	http://unodc.org
http://www.erowid.org	http://www.soros.org/initiatives/issues/health
http://www.union.ic.ac.uk (see health and well-being section)	http://www.ihra.org
http://www.dancesafe.org	http://www.hit.org.uk
http://unaids.org	http://www.opiateaddictionrx.info

FUTURE MEETINGS

IHRA Harm Reduction Conference 2009

19 - 23 April 2009, Bangkok

IHRA's harm reduction conferences have been held around the world each year since 1990, and the next event in this highly successful series takes place in Bangkok, Thailand. The theme for this event will be Harm Reduction and Human Rights.

This 5-day conference will be the main meeting point for all those interested in harm reduction, and an invaluable platform for advocacy, debate, and discussion. For nearly two decades, these events have been the key forum for the dissemination of harm reduction ideas and practice, and have helped to put harm reduction on the map.

The programme will aim to cover a wide range of topics from around the world and is dependent on the submission of quality abstracts.

http://www.ihra.net/Thailand

Conference listing

The following meetings are taking place during 2009.

A detailed listing of international meetings compiled by the European Opiate Addiction Treatment Association in available on their website:

http://www.europad.org/events.asp

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

The fully searchable website is designed to be fast to access, easy to use, and simple to navigate.

http://www.i-Base.info

All i-Base publications are available online, including editions of the treatment guides.

It can be used to order publications and regular subscriptions to be delivered by post or email (as PDF files).

The site also includes a web-based Q&A section for people to ask questions about their own treatment:

http://www.i-base.info/questions/index.html

Non-technical guides to treatment

i-Base produce five non-technical guides to treatment. All guides are available in print, PDF and online formats:

http://www.i-Base.info/guides

- **Introduction to combination therapy**
- **Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support**

- **Guide to changing treatment: what to do when your treatment fails**
- **Guide to HIV, pregnancy & women's health**
- **Guide to avoiding & managing side effects**

Translations of i-Base guides

Original material published by i-Base can be translated and reprinted, and has so far been produced in over 30 languages, including: Bosnian, Bulgarian, Chinese, Czech/Slovak, Croatian, French, Greek, Hindi, Indonesian, Italian, Kosovo, Macedonian, Nepali, Polish, Portuguese, Romanian, Russian, Serbian and Spanish.

More information about this process is available on the i-Base website.In addition, PDF files of some of the translated publications are available on the site.

Some of these translations are from earlier editions of the treatment guides, so check the publication date before relying on all information.

http://www.i-base.info/about/downloads.html

Treatment 'Passports'

These popular booklets are for HIV-positive people - whether newly diagnosed or positive for a long time - to keep a record of health and treatment history. Like all i-Base publications, they are available free as single copies, or in bulk.

HIV Treatment Bulletin (HTB)

A review of the latest research and other news in the field. HTB is published six times a year in a printed version, in a pdf file that we can email to you, and on our website.

The printed version is available at most HIV clinics in the UK and is available free by post.

Treatment information request service - 0808 800 6013

i-Base offers specialised treatment information for individuals, based on the latest research.

We can provide information and advice over the phone, and we can mail or email copies of the latest research studies relevant to the caller.

For details, call the i-Base treatment information free phone line on 0808 800 6013. The line is usually staffed by positive people and is open Mondays, Tuesdays and Wednesdays from 12 noon to 4pm. All calls are in confidence and are free from the UK.

Online Q&A service

A new 'question and answer' service has been added to the i-Base website. Questions can either be answered privately, or if you give permission, we will post the answers online (omitting any personally identifying information).

http://www.i-base.info/questions/index.html

Recent questions include:

- Is treatment different for older people?
- Are the medications in Erithrea the same in the UK?
- Is impetigo a reason to start treatment?
- Do HIV-positive people get free dental treatment?
- Am I infective if I am passive and undetectable?
- What does a CD4 count of 0 mean?
- Can I use PEP if I am HIV-positive?
- Will I use the same meds for my treatment that I used in pregnancy?
- Will my baby have HIV if we do not go for spermwashing?
- What do you know about raltegravir (Isentress)?

- How detrimental it is to stop treatment while on NNRTI?
- Is the reinfection something that is true or another myth?
- What are the risks of non-HIV cancers?
- How do I handle adherence times in a different time zone?
- What do you know about raltegravir (Isentress)?
- Does PEP extend the window period?
- What is the possibility someone re-infected with HIV to go on new medication that will work for them again?
- Is oral candida an early symptom of HIV-infection after 50 days?
- Are the women at the same risk?
- Is this a significant drop in my CD4 count?
- Options if I am getting efavirenz side effects?
- Am I doing OK after TB and HIV treatment?
- Can I use the same medications in Thailand as in the UK?
- Can you test for the CCR-5 delta 32 deletion that reduces the risk of infection?
- How much does the treatment cost?
- Is creatine safe with HIV drugs?

Assessing the treatment information needs African people in the UK living with HIV

This report by Winnie Sseruma and i-Base includes an analysis from workshops held last year and details African use and experience of current treatment information resources.

http://www.i-base.info/pdf/africantreatmentneeds.pdf

Training manual – revised, updated and now fully online

This training resource has been revised and updated and is now online in new format.

http://www.i-base.info/education/index.html

The Training Manual for Advocates provides entry-level curriculum relating to HIV and treatment.

It is made up of 8 modules for learning about aspects of HIV care has been updated and published online as an interactive resource. It provides entry-level curriculum relating to HIV and treatment.

http://www.i-base.info/manual/en/index.html

Sections include:

1. Immune system and CD4 count
2. Virology, HIV and viral load
3. Introduction to antiretrovirals (ARVs)
4. Side effects of ARVs
5. Opportunistic infections and coinfections
6. HIV and pregnancy
7. Drug users and HIV
8. Clinical trial design and the role of advocates
9. How to read science

Each module includes learning objectives, non-technical review material, test questions, an evaluation and a glossary.

We hope this will be useful for training advocates and other related healthcare workers as well as for HIV-positive people who want to know more about aspects of their healthcare.

The training manual was previously only available online as a PDF document and has been widely translated. Earlier editions are

available in Russian, Portuguese, Hindi and Nepalese as are available as PDF files.

i-Base Book: "Why we must provide HIV treatment information"

Photography by Wolfgang Tillmans

i-Base has worked as a treatment literacy project for over six years. Over this time we have always produced copyright-free material and encouraged other organisations to use, translate and adapt our material. Through this work, we have been very lucky to develop links to many other advocacy projects outside the UK.

A recent meeting, held in Cape Town earlier this year, focused on how to raise the profile of treatment literacy. One result from the meeting is a publication "Why we must provide HIV treatment information".

With text provided by activists from 25 countries and 50 full colour photographs by Wolfgang Tillmans, this limited edition 100-page publication is being sold by i-Base to raise funds to help support our international treatment literacy projects.

UK CAB: reports and presentations

The UK Community Advisory Board (UK CAB) is a network for community treatment workers across the UK that has been meeting for three years. Each meeting includes two training lectures and a meeting with a pharmaceutical company or specialist researcher.

The CAB has a separate website, where reading material, reports and presentations from these meetings are posted.

http://www.ukcab.net

World CAB - reports on international drug pricing

Two reports from meetings between community advocates and pharmaceutical companies, that focused on pricing issues and global access to treatment, and that are now available online. Both are available to download as a PDF file from the i-Base website.

http://www.i-base.info/wcab/index.html

Find HTB on AEGiS

AEGiS.org - the longest established and largest global resource of online HIV information - includes HTB in the regular journals that it puts online. You can find us at:

http://www.aegis.org/pubs/i-base/2007

Order i-Base publications via the internet, post or fax

People with internet access can use our website to order and receive publications. You can access our publications online or subscribe to receive them by email or by post; and you can order single copies or bulk deliveries by using the forms at:

http//www.i-base.info/forms/index.htm

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HIV Treatment 'Passports' - Booklets for patients to record their own medical history

1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____ _____ _____

Guide To HIV, Pregnancy and Women's Health *(July 2007)*

1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____ _____ _____

Introduction to Combination Therapy *(June 2006)*

1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____ _____ _____

Changing Treatment - Guide to Second-line and Salvage Therapy *(April 2007)*

1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____ _____ _____

Guide To Avoiding and Managing Side Effects *(February 2005)*

1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____ _____ _____

Guide to HIV and Hepatitis C coinfection *(May 2007)*

1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____ _____ _____

Earlier versions of many treatment guides are available in other languages as PDF files on the website

Adherence planners and side effect diary sheets - In pads of 50 sheets for adherence support

1 Sheet ☐ **1 pad** ☐ **5 pads** ☐ **10 pads** ☐ **Other** ☐ _____ _____

Please fax this form back, post to the above address, or email a request to HIV i-Base:

020 7407 8489 (fax) subscriptions@i-Base.org.uk