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COMMENTARY

Antiretroviral HIV treatment and care for injecting drug users: an evidence-based overview

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Abstract

AIDS-related mortality and the rate of progression to AIDS have dramatically decreased since the advent of highly-active antiretroviral treatment (HAART). The overall benefit from antiretroviral HIV treatment has, however, been lesser in HIV-infected IDUs than in other patient groups (e.g. men who have sex with men). Poorer outcomes in HIV-infected IDUs are related to a variety of factors, including increased rates of non-HIV related deaths, hepatitis C, delayed access to effective treatment, lower adherence to care and treatment regimens, continuation of illicit drug use, depression and negative life events. The available evidence strongly suggests the need for the large-scale implementation of comprehensive treatment and care strategies for IDUs that include both treatment of drug-dependence and HAART.

Keywords: HIV treatment, injecting drug use, review

The shared use of contaminated injecting equipment is a highly efficient mode of transmission of HIV and HIV has spread rapidly among injecting drug users (IDUs) in many parts of the world (Aceijas et al., 2004; Rhodes et al., 1999). One in ten of HIV infections worldwide are estimated to have occurred among IDUs (UNAIDS, 2006). However, at a time of increasing global commitment to scaling up access to care for HIV-infected patients, IDUs have disproportionately low access to antiretroviral treatment (ART) and accompanying care and support. In this commentary, we draw upon available data, especially from longitudinal studies, to review the efficacy of ART in IDUs and examine the social factors that may limit access to treatment and its effectiveness for this group.

HIV prevention and HIV treatment among IDUs

Cohort studies, ecological studies, observational data and epidemiological surveillance from many countries support the evidence that the HIV epidemic among IDUs can be successfully contained and reversed [Ball, 2005; Wodak and Cooney, 2005; Institute of Medicine of the National Sciences, 2006]. An impressive amount of research and observational data has shown this to be the case even among the most socially marginalized of IDUs, provided that a comprehensive package of interventions is offered [Ball, 2005]. The dramatic outbreak of HIV infection that occurred among IDUs in the early 1980s has led those earliest hit regions in Western countries to move from mostly law enforcement-oriented drug policy to public health-oriented policies. A public health strategy integrates harm reduction approaches, including a broadening of drug dependence treatment options such as opioid substitution therapy [Farrell et al., 2005]. Decreasing HIV transmission requires reducing the frequency of sharing of injection equipment and related injecting risk behaviour, especially in high risk IDU networks. This has been achieved through outreach work, increased access to drug treatment and low threshold provision of sterile injecting equipment (Institute of Medicine of the National Sciences, 2006; Wodak and Cooney, 2005; Farrell et al., 2005; Needle et al., 2005).

United Nation (UN) agencies have issued guidance and technical papers advocating for the urgent implementation of effective policies to prevent HIV infection among IDUs [WHO, 2005; UN Millennium Project, 2005]. Tensions within the UN appeared however, when the United States stated its unwillingness to fund programmes distributing sterile injection equipment. The Drugs Action Plan endorsed in 2005 by the European Union provides additional international support for a comprehensive harm reduction approach (EU Drugs Action Plan, 2005). Importantly, considerable funding and technical support for programmes targeting IDUs has become available in recent years through the Global Fund against AIDS, TB and Malaria.

Despite these recommendations, many governments remain reluctant to implement harm reduction interventions for IDUs because of prejudices against drug users, a lack of resources or political commitment, and difficulties in changing repressive drug policy towards an innovative public health approach. In several regions, particularly Eastern Europe and Central and South-East Asia, dramatic and large outbreaks of injecting drug use have led to the rapid spread of HIV (Rhodes et al., 1999, 2002; Kozlov, 2006, Wiessing 2006), in some cases threatening entire populations of IDUs and, possibly, the general population through sexual transmission outside IDU networks and sex work [UNAIDS, 2006]. It should be acknowledged however, that in Western countries, a shift towards public health-oriented drug policies was only achieved after acute public controversy and through strong advocacy. Some industrialised countries – such as USA, Sweden and Japan – remain reluctant to implement a comprehensive package of harm reduction activities.

As a result of harm reduction and HIV prevention strategies, the proportion of IDUs among newly diagnosed HIV infections has decreased dramatically in a number of regions. Yet in 2005, increasing HIV prevalence rates among IDUs have been observed in some EU countries at a national (UK) or regional level (Italy) [Wiessing, 2006; Health Protection Agency, 2006]. Outside of Sub-Saharan Africa, injecting drug use accounts for around one third of new infections (UNAIDS, 2006), with HIV prevalence rates among

IDUs of 20% or more in around one third of countries where data on HIV is available (Aceijas et al., 2004). Despite high mortality rates before the advent of HAART, the high incidence of infection in the 1980s means that many of those acquiring HIV through injecting drug use have been infected for a long time.

Both HIV infection and drug dependence are chronic conditions. Treatment for HIV-infected IDUs should include both treatment for HIV infection and drug dependence. We know that the progression of HIV infection can be effectively controlled in patients receiving ARTs (ART Cohort Collaboration, 2006). Outcomes of ART are better when these drugs are initiated before severe immune deficiency occurs (Egger, 2002, Sabin, 2006).

Given the chronic nature of both HIV infection and drug dependence, we examine below available data from longitudinal studies to assess the impact of HAART in IDUs, focusing on mortality and the occurrence of AIDS and opportunistic infections as outcomes of ART.

Mortality and progression of HIV disease in IDUs

Questions about whether there is a specific pattern of HIV progression and mortality among HIV-infected IDUs as compared with other patient subgroups, and the impact of continuing drug use on disease progression, have been raised since the early years of the AIDS epidemic [Hendriks, 1998; Prins & Veugelers, 1997].

Prior to HAART, mortality among HIV-positive drug users was known to be higher than in other groups of HIV-infected patients, mainly due to mortality from overdose, non-HIV related bacterial infections and suicide [Prins, 1998]. Opiate users remain at high risk of death compared with the age and gender-matched general population, including in countries adopting harm reduction policies [Hickman, 2003, OFDT, 2004, Rehm, 2005]. For example, in the Amsterdam Cohort Study which has recruited HIV-negative and HIV-positive IDUs born in the Netherlands from 1985, as many as 27 % of those who

were alive in 1989 (n=1237) had died by 2002 [Termorshuisen, 2005]. Half of the deaths were related to AIDS (94 out of 183).

Life expectancy was calculated for the period 1996-2003 in two British Columbia cohorts of HIV-positive individuals [Lloyd-Smith, 2006]: the HOMER study (HAART Observational Medical Evaluation and Research) is a cohort of patients who began HAART between 1996 and 2003. HCV infection was used as a marker for injecting drug use (1573 out of a total 2217). The BART study (Barriers of Antiretroviral Therapy) is an HIV positive sub group of an open prospective cohort of IDUs in which 291 of 430 patients received HAART.. Life expectancy at 20 was found to vary from 38.9 years among HCV-negative ART-treated individuals to 19.1 for untreated IDUs. The variation across subgroups indicated both the negative impact of drug use and of its correlate HCV infection, while life expectancy decreased two fold in individuals not receiving HAART.

The changing pattern of mortality associated with the introduction of HAART has been widely documented. In the Swiss cohort [Keiser, 2004], the mortality of HIV-infected patients was studied over the period 1990 to 2001 and compared to the general population for different subgroups of patients, including IDUs (n=3853 of 10977 HIV positive patients followed through that period). The overall yearly death rate decreased from a maximum of 13% in 1995 to 3% after 1998, while the proportion of patients on HAART increased (5393 of 7037 alive had begun HAART). Compared with the general population, the standard mortality ratio (SMR) decreased from 79.3 (95%CI 77,2-81,5) prior to HAART to 15.3 (95%CI 14,2-16,4) after the introduction of HAART. Such a decrease was observed both in IDUs (from 98.2; 95%CI, 94,9-103.5 to 40.9; 95% CI 37,0-44,8) and non-IDU HIV-infected patients (69,2; 95%CI 66.9-71.6 to 9.4 95%CI 8.5-10.4). SMR were lower in patients who initiated HAART during the study period. However, since the advent of HAART, the gap in mortality between IDUs and non-IDUs had increased. The causes of death were not considered in the study.

Among the patients enrolled in the CASCADE collaborative study of seroconvertors where data were pooled from 22 cohorts originating from Europe, Australia and Canada,

2427 out of 7740 subjects had been infected through injecting drug use [CASCADE Collaboration, 2003]. The adjusted hazard ratio of progression to AIDS did not differ between exposure categories in the pre- and early-HAART periods, while in 1999-2001, when HAART was widely used, both men and women IDUs were at higher risk of AIDS than men having sex with men (MSM) and individuals infected heterosexually. All causes of death hazard rates were higher in 1997-98 and 1999-2001 whereas they did not differ in the pre-HAART era. Both results show a lower benefit from HAART among IDUs.

In the EuroSIDA cohort, ARV-naïve individuals were followed until 2003 to assess factors associated with progression to AIDS, and with HIV-related and non HIV-related death [Mocroft, 2004]. Homosexual males were the predominant transmission group (1767/3872) in the cohort and IDUs accounted for 21.2 % of the study population (n= 819). Seventy one percent of patients started HAART during follow-up, most of whom began treatment in 1997 and at a median CD4 cell count of 220/mL. Patients were followed to the first event defined as progression to AIDS or death, either HIV- or not HIV-related. Two-thirds of the 499 recorded events in the study were not related to HIV. An increased risk of non-HIV-related death was observed among IDUs (IRR: 1.36 IC95% 1.02-1.82). The proportion of deaths related to liver disease was also higher among IDUs as compared to the other groups of patients. The excess in non-HIV-related death rate among IDUs was seen after a long follow-up period and was not observed in the early period of HAART. The authors concluded that the higher death rate among IDUs in this study was not attributable to a poorer response to HAART.

In a more recent analysis of the Swiss cohort, focusing on the period 1996 to September 2003, a delay in the initiation of HAART was documented among IDUs [Sterne, 2005]. In addition, the benefit of treatment appeared lower in IDUs compared to other groups of treated patients. Thus, compared to no treatment, the hazards ratio of progression to AIDS or death among HAART-treated patients was 0.27 (0.12-0.61) among IDUs and 0.08 (0.03-0.19) among the other groups. Drug dependence treatment, persistence of drug use and injection, HCV co-infection were not considered in these analyses.

Findings on the impact of HCV co-infection on mortality are inconsistent across longitudinal studies and vary according to whether mortality is considered as a whole or by cause. An association of co-infection and mortality/progression to AIDS is found in studies with longer follow-up periods, while in studies with shorter follow-up, HCV co-infection does not have an impact upon the response to HAART or HIV progression [Sullivan, 2006; Sulkowski, 2002]. Hepatitis-related death has become almost as frequent as HIV-related death [Bonacini, 2005, Salmon-Ceron, 2005] among patients co-infected with HIV and HCV. The proportion of liver disease-related deaths is even higher among patients co-infected with both HCV and HBV [Salmon-Ceron, 2005]. However, in this study, up to 50% of hepatitis-related deaths among co-infected patients had more than 200CD4/mm³ at death.

In the GEMES Spanish cohort of 1129 seroconvertors, IDUs accounted for 70% of the sample [Perez Hoyos, 2006]. The median age at seroconversion was 25.9 years. Progression to AIDS and HIV-related death were studied for each calendar period between 1996 and 2004 – at introduction of HAART, in the early HAART period, and “post HAART”. The hazard ratios decreased over time. IDUs exhibited a two-fold higher rate of progression to AIDS than MSM (HR 2.28 ; 95%CI 1.47-3.54) as well as a faster progression to death (HR 2.17; 95%CI 1.22-3.87). The results were compiled without individual information on HAART uptake, immunological status, adherence to treatment, current substance use or drug dependence treatment.

Similar findings were also reported in a cohort from the United States of 827 HIV positive individuals followed up between 1995 and 2002 [Moore, 2004]. Progression to AIDS was compared among patients infected through injecting drug use and other patients (1314 non-IDU). All patients had access to HAART. CD4 cell counts and plasma levels of HIV1-RNA did not differ between IDUs and non-IDUs at baseline. However, IDUs exhibited an overall shorter duration of HAART. No difference in the occurrence of AIDS-defining illness was found before 1998, but from 1999, IDUs were shown to be at greater risk of AIDS-defining illnesses (IDU adjusted incidence ratio compared to non

IDU 1.45, 95%IC 1.21-1.7). Half of the IDUs in the cohort continued to inject drugs during treatment, but neither drug using behavior nor drug treatment were considered in the statistical analysis.

Factors associated with a poor impact of HAART in IDUs

The evidence summarised above indicates that IDUs benefit significantly from antiretroviral treatment but that mortality remains higher in HIV-positive ART-treated IDUs as compared with non-drug user HAART-treated HIV-positive patients. Several factors contribute to the overall lower impact of HAART on mortality in HIV-positive IDUs, including delayed initiation to treatment, poor adherence to treatment regimen, interruptions in medical care and continuing drug use.

Although financial barriers limiting access to treatment have been removed in most Western countries, delay in treatment initiation among IDUs is still observed: in a national random sample of HIV-positive patients in France, CD4 counts at the time of initiation of HAART were lower in IDUs than in non-IDUs, except for migrants who remain most often diagnosed at advanced stages of HIV infection [Dray-Spira, 2007]. In Spain, in a multicenter hospital-based cohort, among naive patient followed from 1997 to 2003, IDUs were found less likely to start HAART compared with male homosexuals (HR 0.67 95%IC: 0.57-0.79) (Rodriguez-Arenas, 2006). Comparing HAART initiation among IDUs with known dates of HIV-seronversion, accross European sites, Van Asten (2005) found variations in CD4 counts at initiation: in Amsterdam, Innsbruck and Edimburg, HAART started with lower CD4 counts than in Paris, geneva and Glasgow. Late access to treatment may be dependent on patients or on physicians' attitudes and stereotypes (Ding, 2005). However poor knowledge of HIV positive IDU regarding HIV treatment was not found associated with their acceptance of HAART (Clarke, 2003). In the early period of HAART in France, patients with ongoing heroin use were three times less likely to be prescribed ART than former IDUs [Carrieri, 1999]. Substitution therapy may however decrease or avoid these delays. Thus, among ART-naïve HIV-positive IDUs recruited in the BART cohort in Vancouver (n=234), the uptake of HAART

occurred earlier among patients who were on methadone substitution, both at baseline and during follow-up (69.7 % vs. 44.4 % at 24 months) [Wood, 2005]. In a Cox model adjusting for time since receiving results of the HIV test being on methadone significantly increased the chance of initiating ARV treatment (relative hazard 2.10 95%CI 1.28-3.46). The study concluded that social stabilisation obtained via substitution treatment favours the initiation of HAART.

Adherence is a key issue to prevent failure of HAART, particularly in the early months following initiation of therapy. Evidence from several studies, and reviewed in this volume by Carrieri and Spire (2007), indicate that ongoing injecting drug use, alcohol consumption and cocaine use are associated with non-adherence and adherence failure. In former IDUs who are not on substitution treatment, social vulnerability is the only factor associated with non-adherence. In IDUs on substitution treatment, adherence was found to be significantly higher than in active IDUs and higher (although statistical significance was not reached) to that of former IDUs. Substitution therapy with methadone or buprenorphine often allows the patient to be followed at regular intervals in an integrated network of care involving physicians, pharmacists, and other health care and social workers.

In the MANIF 2000 cohort of HIV infected drug users, poor adherence to ART was positively associated with younger age, alcohol use, negative life events in the last six months and current drug use [Moatti 2000]. IDUs often exhibit a high prevalence of psychiatric co-morbidities. Among patients with CD4 cell counts above 200/mL at initiation of ART, progression, as defined by the occurrence of AIDS-related death or CD4 counts <200/mL, was found to be correlated with depressive symptoms, independently of adherence. Factors in addition to adherence may contribute to a poorer impact of HAART in IDUs [Bouhnik, 2005]. In the cross-sectional VESPA survey in France, among a representative sample of 2932 persons living with HIV, almost one in three patients with an history of injecting drug use reported interruptions in medical care for six months or more, whereas this proportion was below 10 % in other groups of ART-treated HIV-positive patients [Dray-Spira, 2007].

Evidence on the relationship between continuing drug use, drug treatment and progression of HIV disease are inconsistent, due to the diversity of populations studied and study designs. As mentioned above however, continuing drug use tends to be associated with poorer outcomes.

Among women (n=1148), included in a cohort study during pregnancy and followed up from 1989-1995 to 2001, hard drug use (defined as injecting, cocaine or heroin) at any time (at baseline or during follow-up) was not found to be associated with changes in CD4 cells count, nor in HIV RNA level, nor with an increased mortality from all causes [Thorpe, 2004]. Women who used drugs were however more likely to develop non-fatal infections and to reach stage C of HIV disease (1.65 95%IC 1.00-2.72).

In the ALIVE cohort (AIDS Linked to Intravenous Experience), drug use and drug treatment were not identified as independent prognostic factors of survival between 1988 and 2000 [Galai, 2005]. HIV-related and non-HIV-related deaths from infectious conditions were studied among HIV-positive patients with CD4 cell counts below 500/mL at entry. They were investigated in both the pre-HAART and HAART periods, taking into account treatment with methadone, ongoing use of heroin, cocaine and crack, and heavy alcohol intake. The overall survival of patients improved in the HAART era, but risk factors for progression did not differ between the pre-HAART and HAART periods. Drug use was not found to be a prognostic factor of progression, except for the use of crack, which appeared as “protective” across all CD4 strata. This counter-intuitive finding is interpreted by the authors as dependent on a selection bias: individuals able to use crack might have been less debilitated than others.

The association between methadone maintenance treatment and outcome of HAART has recently been investigated by matching the data of the VIDUS cohort (Vancouver Injection Drug User Study) for the period 1996-2003 with those of the British Columbia treatment monitoring system [Palepu, 2006]. Among 278 participants on HAART, methadone maintenance treatment was found to be independently associated with

enhanced viral suppression (aOR 1.34; 95%CI 1.00-1.79) and greater increases in CD4 cell counts (aOR 1.58; 95%IC 1.26-1.99).

A more recent analysis assessed the impact of active drug use on the course of HIV disease in Baltimore (USA) [Lucas, 2006]. In this study, HIV positive subjects (1851) were defined as persistent heroin and/or cocaine user, intermittent user, or non-user. For each six month period before intake and during follow-up, active substance use was assessed. Over 36 months, the risk of opportunistic infection was observed to be lower in non-users than in intermittent users, and lower in intermittent users than in persistent users. In intermittent users compared to non-users, the risk of opportunistic infection during six month abstinence periods was similar, while it was higher during active substance use periods (OR 2.2; 95%IC 1.4-2.9) as it was for persistent user (OR 1.9; 95%IC 1.2-2.8). The authors suggested several interpretations for the association of active drug use with HIV progression. The hypothesis of a direct impact of drug use on progression of HIV infection is not consistent across studies. A second hypothesis was the decreased access to effective HIV treatment either from the physicians who could be uncomfortable treating drug users or from the patient's behavior through poor adherence to treatment, unstable living conditions, poor social support or irregular attendance at medical appointments during periods of active drug use. However, taking account of heavy alcohol use and adherence to treatment did not alter the effect of active drug use on HIV progression. The mechanisms linking current active drug use to lesser benefit from HAART remain unexplained.

Pharmacokinetic interactions between opioid substitution drugs and antiretroviral drugs have been suspected of leading to possible complications in the treatment of opioid-maintained patients [McCance-Katz, 2005, Bruce, 2006] . Studies of interactions between methadone and ARV have shown both withdrawal and excess opioid syndromes, depending upon the ARV medication. Despite the increasing use of buprenorphine in drug dependence treatment, studies on its interactions with ARV remain limited. Available data, from in vitro and pharmacological studies and from case reports, require that HIV specialists manage carefully patients with both treatments. However to date,

specific guidelines for HAART in opioid-maintained HIV-infected patients have not been considered necessary.

Conclusions

In Western countries, despite good and mostly free access to medical care, social factors such as poverty, discrimination, risky behavior and social exclusion, in combination with discriminatory attitudes from physicians, often lead to delays in initiating treatment. Cohort studies have shown that, despite these difficulties, HAART was clearly beneficial in HIV-positive patients infected through drug use, resulting in a decrease in AIDS-related deaths. Other causes of death and co-morbidity have not however been strongly affected by the availability of ART. Substitution treatment can facilitate social stabilisation and patients' demand for ART and for support for adherence to treatment.

In countries with a history of drug dependence treatment, treatment of addiction and HIV are often structured vertically in separate systems and a comprehensive provision of care for HIV-positive IDUs in one site remains the exception. The chronic-relapsing nature of opioid dependence, alternating between heavy and controlled drug use and abstinence or drug dependence treatment, makes it difficult to capture the possible associations between unstable drug use, drug dependence treatment and outcomes of HAART over time.

In regions with emerging epidemics of injection drug use, drug treatment has not been seen as a public health priority. In Eastern Europe and Central Asia, IDU account for more than 80% of persons living with HIV but only 14 % of people on HAART; in South and South-East Asia, these figures are respectively 1.8 % and more than 20% [Aceijas et al., 2006]. The availability of ART emphasises the urgent need for implementing comprehensive care programmes targeting HIV-infected IDUs, including the integration of treatments for HIV infection, drug dependence and hepatitis. There is a need for innovative approaches with flexible regimens in countries with emerging epidemics

among IDUs to make ART available for all who are in need and to achieve an objective of universal access to effective HIV care.

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