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HIV and hepatitis B and C in a cohort of methadone maintenance clients in Geneva, 1988- 1995

Barbara Broers Kayser
Department of Epidemiology and Biostatistics
McGill University
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Abstract

This study evaluates the prevalence and incidence rates of infection with Human Immunodeficiency Virus (HIV), hepatitis B (HBV) and hepatitis C (HCV), in a cohort of drug users (DU) on methadone maintenance treatment in Geneva, Switzerland. Over 700 DU participated between 1988 and 1995; the follow-up rate was high. The prevalence rate at entry into treatment declined dramatically over time for all 3 viruses. Comparing DU born before 1961 to those born after 1970 the prevalence rate of HIV was 29.1% versus 2.0%, of HBV 71.3% versus 2.2%, and of HCV 83.6% versus 17.9%. The incidence rates for HIV and HBV were low (0.6 and 2.1 per 100 person years of follow up). For HCV the rate was high (4.2) with a slightly higher rate among women.

These data suggest that DU have changed HIV risk taking behaviour in response to HIV prevention campaigns. Current prevention efforts should focus on improvement of HCV prevention and maintaining safe behaviour.

Résumé

Dans cette étude les taux de prévalence et de l'incidence du virus d'immunodéficience humaine (VIH) et des hépatites virales B (VHB) et C (VHC) dans une cohorte de toxicomanes en traitement de maintenance par la méthadone à Genève, Suisse, sont évaluées. Plus de 700 toxicomanes ont participé entre 1988 et 1995; le taux de suivi fut élevé. Les taux de prévalence à l'entrée en traitement pour les 3 virus ont baissé considérablement. Si on compare les toxicomanes nés avant 1961 à ceux nés après 1970, le taux de prévalence pour le VIH fut 29.1% versus 2.0%, pour le VHB 71.3% versus 2.2%, et pour le VHC 83.6% versus 17.9%. Le taux d'incidence du VIH et VHB furent bas (0.6 et 2.1 par 100 personnes-années de suivi). Celui du VHC fut élevé (4.2), avec un taux légèrement plus élevé pour les femmes.

Ces données suggèrent un changement des comportements à risque pour le VIH parmi les toxicomanes suite aux campagnes de prévention. Les efforts de prévention actuels doivent se diriger vers l'amélioration de la prévention contre le VHC et la maintenance du comportement sûr.

Introduction

Soon after the first publications on the new disease now called the "Acquired Immune Deficiency Syndrome" (AIDS) in homosexual men in San Francisco in the early eighties (1) it became clear that other populations such as injecting drug users (IDU) were affected by this disease as well (2). It was only after 1985, when testing for Human Immunodeficiency Virus (HIV) became widely available, that the potential for a real epidemic of HIV infection among IDU was realised (3). Public health authorities in most industrialised countries responded in the years that followed by implementing different interventions aimed at containing the spread of HIV within this group, and from there to the general population.

The evaluation of these interventions has been hampered by the fact that drug users (DU) are a hidden population. As well, the introduction of many interventions, both general and specific, at the same time, has made it difficult to attribute change to any one intervention. Nevertheless, many studies evaluating HIV prevalence and incidence rates, as well as risk taking behaviour among DU, have been published. Most of them show a considerable reduction in risk behaviour after introduction of prevention activities, a decline in incidence, and a stabilisation or reduction of HIV prevalence (4-7).

This study evaluates the prevalence and incidence rates and trends in a cohort of DU on methadone maintenance treatment (MMT) in Geneva, Switzerland.

AIDS and HIV

General

Fifteen years ago the first reports of a new disease now called "Acquired Immune Deficiency Syndrome" (AIDS) appeared (1). Extensive attention was given in the lay and medical press to this disease, which is characterised by an important weakening of the immunological defenses of the patient, leading to opportunistic infections which are normally rarely seen.

The likely routes of transmission of the disease were identified before an etiologic agent was identified. The appearance of AIDS in disparate populations connected only by probable transmission suggested an infectious cause (8). First reports (June 1981) described AIDS among homosexual men, followed by AIDS among IDU and Haitians in 1982, as well as among recipients of blood and blood products, heterosexual partners of patients with AIDS, children born to mothers at risk, and Africans in 1983. At the time it appeared logical that the presence of AIDS was the result of an unknown infectious agent transmitted by transfusion or inoculation of blood, sexual contact or perinatal events (8).

These hypotheses were confirmed after the discovery of the infectious agent in 1983 (9). The etiologic agent of AIDS was a virus now called Human Immunodeficiency Virus (HIV). In 1985 commercial tests became available to detect antibodies to HIV. Antibodies were found in almost all patients with AIDS and also in populations considered to be at risk for AIDS (10). It became evident that a person could have antibodies to HIV without having AIDS nor a decrease in immunological functioning, as measured by T4 (CD4) lymphocyte count. Subsequent studies have shown that a large majority of the patients infected with HIV eventually develop AIDS or AIDS-related diseases. Once immune deficiency is established, morbidity and mortality are high (11).

The main transmission routes of HIV are (8) inoculation of blood, sexual contact and perinatal events. Inoculation or infusion of blood can occur through transfusion of blood or blood products, needle sharing among IDU, injection with non-sterilised needles, or needle-stick accidents in health care workers. Sexual transmission can occur through homosexual and heterosexual contact, with a more efficient transmission from men to women than from women to men. Perinatal transmission of HIV virus can occur either intrauterine, peripartum or through breast feeding.
There has been a lot of fear concerning other potential routes of transmission such as mosquito bites, tears, saliva, sweat, and close (professional or household) contacts, but none of these has been shown to be involved in transmission (8), with the exception of very isolated and unexplained cases (12,13).

Currently there is no curative treatment for HIV infection. Several anti-retroviral medicines can (temporarily) improve immunological functioning. Anti-mycotic, antibacterial and anti-viral treatments can be given to treat or prevent opportunistic infections. A vaccine to prevent HIV infection is not yet available (11).

Prevention of HIV infection is feasible in theory through testing of all blood and blood products for HIV before donation, use of sterile needles and syringes for any injection, and use of condoms with any sexual intercourse. There is no safe alternative to completely prevent perinatal transmission from HIV infected mothers other than avoidance of pregnancy, although anti-viral treatment during pregnancy, delivery and the newborn period lowers the risk by two-thirds (14).
It is clear that prevention of HIV in the population is possible theoretically, under certain conditions that include: knowledge of risk behaviours, change in behaviour and maintenance of protective behaviour, availability of condoms and sterile injection material, and screening of all blood donations. However, prevention efforts have been hampered by practical and socio-cultural barriers.

Epidemiology of HIV and AIDS

Although the first reports about AIDS came from the USA, it soon became clear that the epidemic affected all continents. In industrialised countries the first populations to be affected were homosexual men, followed by IDU. Studies using stored sera show that HIV was introduced among IDU in the mid-seventies in the USA and a few years later in Europe (15). Recipients of contaminated blood or blood products were infected between 1982 and 1985, when screening of blood donations became feasible. Secondary transmission led to cases in the heterosexual population (16). In Africa and Asia the epidemic appeared to start later, although probably in Africa it started before, and has been characterised by a predominantly heterosexual transmission (17).
The HIV epidemic is composed of distinct epidemics each with their own features and force, affecting disproportionately the developing world. From the beginning of the pandemic until mid-1996, an estimated 27.9 million people world-wide were infected

with HIV. Ninety-three percent of infections are estimated to have occurred in the developing world, mainly in sub-Saharan Africa (68% of total) and in South and Southeast Asia (18%) (17).

Epidemiology of HIV and AIDS among drug users

General

The most important mode of transmission of HIV among DU is sharing of HIV infected injecting equipment, mainly recently used needles and syringes (18). In theory other injection paraphernalia such as cookers, spoons and glasses can be sources of HIV transmission, but the risk seems low (19). The indirect sharing technique of front loading or back loading (the preparation of a solution for 2 or more users in 1 syringe with injection of part of the solution into the front or back of the other syringes) was also identified as a risk factor for HIV. Transmission of the more virulent hepatitis C virus (HCV) is even more frequent this way (20,21).

Sharing of injection equipment, be it borrowing or lending, seems to be determined mainly by scarcity of new injection equipment, ignorance, social circumstances, life-style factors, and less by cultural and social barriers than was originally thought (19,22,23). Risk factors for sharing needles and syringes include homelessness, poly-drug use, cocaine use and psychopathology (24,25)

DU are sexually active, and prostitution is frequent, with the result that sexual transmission is a significant (though less frequent) source of HIV (23,26). However, heterosexual contact between DU and non DU is clearly a source of HIV infection for the non DU population (27).

Prevalence

HIV among DU (especially IDU) is a multinational problem. Des Jarlais et al summarize this in a review, showing that in both developed and developing countries HIV is a problem in this group (4). However, there is a great variation in HIV sero-prevalence rates among DU in different studies (cf Table 1).

Table 1. Variation in HIV sero-prevalence among drug users in selected regions (adapted from (4), published in 1992, otherwise references indicated)

low (0-10%)	**moderate (11-40%)**	**high (>40%)**
Antwerp, Belgium	Copenhagen, Denmark (29)	Paris, France
The Hague, Netherlands (19)	Berlin, Germany	Milan, Italy (33)
Glasgow, Scotland	London, England (30)	Rome, Italy
Lund, Sweden	Amsterdam, Netherlands (19)	Madrid, Spain
Oslo, Norway	Innsbruck, Austria	Valencia, Spain (34)
Moscow, Rusland	Verona , Italy	Edinburgh, Scotland
Zagreb, Yugoslavia	Geneva, Switzerland	Belgrade, Yugoslavia
Los Angeles, USA	Warsaw, Poland	San Juan, Puerto Rico
Hong Kong	Buenos Aires, Argentina	Buenos Aires,
Hiroshima, Japan (28)	Montreal, Canada (31)	Argentina (28)
Kathmandu, Nepal (28)	Vancouver, Canada (32)	Bangkok, Thailand
	Sydney, Australia	Manipur, India
	Rio de Janeiro, Brazil	Yunan Province, China
	Baltimore, USA	Rangoon, Burma (28)
	Chicago, USA	New York City, USA
	Miami, USA	(35)
	Detroit, USA	Johannesburg, South
		Africa (28)

In Europe, a North-South gradient is present, with the highest HIV prevalence found in the South. An exception is Edinburgh, Scotland, where HIV prevalence was documented at 50%. Prevalence can vary even within nearby cities (e.g. Amsterdam versus The Hague, Edinburgh versus Glasgow).
In the USA the sero-prevalence among DU in drug treatment programmes was highest in the Northeast (10-65%) and Puerto Rico (45-59%), lower in the South Atlantic (7-29%), and lowest in non-metropolitan areas in the West, Midwest and South (5% and less) (3). Prevalence rates among Hispanics and blacks were usually higher than among whites (4,23).

These variations could be due to a real difference in sero-prevalence, related to the dynamics of the local epidemic and year of study, or to the inclusion of only IDU versus all DU including those who do not inject, or to differences in sampling methods. Important differences in prevalence rates by site of recruitment can occur. For example Stark (36) found an HIV prevalence rate of 6% in treatment centres, of 20% in storefront units, and of 56% in an infectious disease clinic among DU in Berlin.
Many studies have, for reasons of convenience, recruited DU from treatment programmes, but even among them there can be substantial differences in prevalence rates. Different programmes may attract DU at different levels of risk. Sometimes all individuals receiving treatment are included, sometimes only new entrants. Some studies (e.g. New York City, Bangkok) showed a higher HIV prevalence rate among subjects in treatment, while other studies (Miami, San Francisco) showed higher prevalence rates among subjects from non-treatment settings (4).

The prevalence rate of HIV infection among DU depends on several factors (37): the rate of new infections among existing DU; the loss of HIV infected individuals from the active DU pool due to AIDS-related fatal illnesses; and the addition of new uninfected individuals into the pool of DU. The rate of new infections will depend on the pre-existing prevalence of HIV in the population of DU and on the prevalence of risk taking behaviour.
Many studies suggest a rapid increase in prevalence rates (more than 20% within 1 year) followed by a stabilisation afterwards, even in the absence of effective prevention

campaigns. Two factors that greatly facilitate the rapid transmission of HIV among DU are: a lack of awareness of local AIDS threat (especially in the early years in the USA and Europe and more recently in Thailand, China and India) as well as efficient mixing of the population, meaning that injection equipment is shared in a random manner (4). Stabilisation or even declines in HIV sero-prevalence rates have been observed in many cities: Amsterdam (38), New York City (4), Milan (33), Rome (39), Bangkok (4), Copenhagen (29) and London (30).

It is usually suggested that that the stabilisation of prevalence rates is due to observed changes in injecting/sexual behaviour of DU. Blower (40) suggests an alternative hypothesis not requiring any behaviour changes. Stabilisation of sero-prevalence rates could be the result of behavioural heterogeneity within various subgroups of DU, and a loose connection between low and high risk groups. A high degree of behavioural heterogeneity has been described in DU communities, so that any community can be considered to be composed of a number of behavioural risk subgroups. These subgroups have two characteristics: a sub-group level of particular sexual and/or injecting behaviour and a subgroup-specific probability function for selecting sexual and/or injecting partners from another subgroup (mixing matrix). The probability that an individual becomes infected with HIV depends upon his or her risk taking behaviour, the transmission efficiency of this behaviour and the probability that the partner is HIV infected (and his/her infectivity related to stage of disease). If there is very little mixing between the subgroups, the sero-prevalence levels can be very high in some subgroups and very low in others, even if both maintain a certain risk behaviour. This will lead to a stabilisation of sero-prevalence rates that can last for years, but in the absence of any behaviour change this will only be temporary. Blower uses a mathematical model to explain why sero-prevalence levels have stabilised at different levels in various parts of the world (40).

Incidence

The direct calculation of incidence rates of HIV infection in DU requires a retrospective or prospective cohort study design. These studies are both expensive and time consuming. DU usually form an unstable study population, so that data on HIV

incidence are often scarce or of mediocre quality, in large part due to important dropout rates.

The HIV incidence rate is usually expressed as the number of seroconversions per person-time of follow-up, although some studies express the results as a "seroconversion proportion" (number of seroconversions divided by study population) (41).

Table 2 gives a summary of the main cohort studies done in DU. Most studies are done in IDU and in treatment settings, some studies consider a mixed in- and out of treatment or a mixed IDU and non-IDU population (42-44). The initial HIV sero-prevalence among study participants varies between 11 and 52%. The numbers of HIV negative individuals entering the study range from to 89 to 20,361, follow-up rates vary between 26.5% and 91%. In two studies (27,42) HIV negative individuals were selected for the calculation of the HIV incidence rate only if follow-up was available. The total time of follow-up (denominator for the incidence rate) range from less than 100 to more than 12,000 person-years.

It is impossible to give an overall conclusion on a normal seroconversion rate since the studies differ so much in design, sampling method, year of study and quality of follow-up. The incidence rates range from 2.4 to 12 per 100 person-years of follow up. Holmberg (45) used a components model from a review of different published and unpublished documents, data sets and information obtained from public health personnel to estimate the HIV incidence for high-risk populations in 96 large US metropolitan areas. He estimates the actual HIV incidence rate among IDU at 1.5 per 100 person years. In general a declining incidence over time is found, as well as a lower incidence among DU in treatment settings.

Two studies found a higher incidence rate among women (49,50), one a higher incidence among men (31), while others found no differences by gender (29,34). As expected the studies that compare IDU with non-IDU find a higher incidence among IDU (44).

Almost all the studies assume that the date of seroconversion is the mid-point between the last HIV-negative and first HIV-positive test. Only in the studies in Bangkok (44) and in Montreal (31), was it assumed that subsequent seroconversions have occurred with uniform probability throughout the interval between last HIV-negative and first

Table 2. Overview of main cohort studies for HIV infection in drug users.

Study site /design	Period studied	Study population	% HIV+ follow-up	Seroconversions / total PY	Incidence/ 100 PY	Trends in incidence rate
Stockholm (S) prospective cohort (41)	1984-90	4 treatment sites n=300	HIV+ 11% HIV- n=267 FU 37%	12/ 99 persons (PY ?) =12.1%	?	proportion 1985: 32% 1989-90: 0%
Copenhagen (DK) historic cohort (29)	1985-90	STD clinic n=1,029 volunteers IDU	HIV+ 12% HIV- n=901 FU 40%	20/ 837 PY	2.4	1984-87: 2.8 1988-90: 2.4 men: 2.9 women: 1.7
Amsterdam (NL) prospective cohort (42)	1986-89	volunteers (OT/IT) n total=? selected n=346	HIV+ 36% HIV- n=209 selected if FU available	16/ 326 PY	4.9	1986: 11.7 1987: 4.1 1988: 4.6 1989: 1.8
Milan/N-Italy prospective cohort (33)	1987-90	treatment sites: detox, MMT n total=3192	HIV+ 52% HIV- n=1532 FU 56%	42/ 1194 PY	3.5	1987: 61 1988: 4.2 1989: 2.1 1990: 1.6
Rome (I) prospective cohort (46)	1985-89	treatment sites: detox, naltrexone MMT n=1180	HIV+ 38% HIV- n=734 FU 41%	37/ 553 PY	6.9	'85-'86: 8.9 '87-'88: 5.3 men: 4.9 women: 15.4

(continued)

Table 2 (continued)

Study site /design	Period studied	Study population	% HIV+ follow-up	Seroconversions / total PY	Incidence/ 100 PY	Trends in incidence rate
Valencia (E) prospective cohort (34)	1988-92	AIDS info /test center, volunteers n=4131	HIV+ 48.4% HIV- n=2130 FU 28.4%	97/ 807 PY	12.0	1988: 9.8 1990: 13.9 1992: 10.2 men: 13.0 women: 11.7
Philadelphia (USA) prospective cohort (43)	July 1989-90	IT n=152 OT n=103 all volunteers	HIV+ 12% HIV- IT n=37 FU 91% OT n=87 FU 85%	IT 6/ 200 PY OT 13/ 121 PY	IT: 3.0 OT: 10.7	n.a.
New York (USA) prospective cohort (37)	1990-91	MMT n>2000 volunteers for INH prophylaxis	HIV+: 40% HIV- n=235 (selected) FU: 75%	2/ 155 PY	1.3	n.a.
New York (USA) retrospective cohort (27)	1990-92	IDU >1984, 1st entry in detox center n=132	HIV+ 23% HIV- n=132 selection if FU available	30/ 457 PY (Δ date start IT-1st injection)	6.6	
New Haven (USA) (47) prospective "needles" cohort	Nov '90-May '92	needle/syringe exchange n=132 syringes: 1920	HIV+: 42% HIV-: 1115 needles	0/ 96 PY (modeling)	MLE: 0 95% CI: 0-10.2	n.a.

(continued)

table 2 (continued)

Study site /design	Period studied	Study population	% HIV+ follow-up	Seroconversions/ total PY	Incidence/ 100 PY	Trends in incidence rate
New Haven (USA) prospective cohort (48)	1982-??	MMT n=146	HIV+=? HIV- n=89 FU ?	IT: 1/135 PY partial OT: 8/185 PY (Δ ns)	IT 0.7 partial OT 4.3	n.a.
Baltimore (USA) prospective cohort(49)	1988-'92	volunteers (IT/OT) n=2960	HIV+: 24% HIV- n=2247 FU: 68%	188/ 4951 PY	3.8	incidence ↓ over time, highest in young women/ active DU
Montreal (CDN) prospective cohort (31)	1990-'95	needle exchange attendees n=2066	HIV+: 15.0% HIV- n=1756 FU random: 26.5%	45/ 564.7 PY	8.0	1990 12.8 1992: 8.1 1994 6.9 1995: 10 higher for men, lower for regular attenders
Bangkok (TH) historic cohort (44)	1987-'92	IT sites (IDU/non-IDU) n=26,392 tested n=25,676	HIV+ 21% HIV- n=20,361 FU: 38.3%	2,311/ 12,704 PY	18.2 IDU 11-57 non-IDU 0.2-5	IDU: 1987: 20 1988: 57 1991: 11 1992: 11

Legend: IT = in-treatment, OT = out-of-treatment, MMT = methadone maintenance treatment, detox = detoxification (drug free) center, FU = follow-up (for HIV- DU), IDU = injecting drug user(s), non-IDU = non injecting drug user(s), n.a. = not available, MLE = Maximum Likelihood Estimate, Δ= difference, PY=person-years.

HIV-positive tests. The contribution of seroconverters to the denominator (time) declines as the first positive result approaches (see Methods section). This method has been shown to give a generally similar but smoother and more realistic estimate than the mid-point assumption (31,44,51).

Hepatitis B and C

General

Hepatitis B virus (HBV) is one of the "oldest" viral infections known to be related to injecting drug use. Transmission can occur parenterally, sexually or vertically, and is much more efficient than transmission of HIV. After infection, up to 10% of individuals will become chronic carriers of the virus, and those patients usually develop chronic hepatitis (52). There is no cure, but vaccination has been available for over 10 years. Presence of HB antigen and/or antibodies in blood indicate infection with HBV.

Hepatitis C virus (HCV) was discovered in 1989 and is the most frequent cause of non-A-non-B hepatitis. Its transmission route is mainly parenteral with the existence of other modes of transmission being more controversial. Sexual and perinatal transmission as well as family exposure have been suggested. Infectivity is high, for example, the risk of infection after a single needle-stick injury is 5-15% (53). Once an individual is infected with HCV a chronic low grade infection is the most frequent outcome (up to 80%), with debilitating chronic fatigue a very common complaint, and the risk of developing chronic liver problems including cirrhosis and hepato-cellular carcinoma after many years being high (54). Neither cure nor vaccination is available (55).

Testing for HCV is done mostly by serological testing, with a second generation test developed in 1991 having replaced the less sensitive first generation test. Molecular testing using PCR techniques is also possible. At least 5 distinct, but related, genotypes exist (56). HCV plasma viral load seems to be associated with HCV genotype, whereas HIV co-infection does not seem to influence the course of HCV infection (57).

Epidemiology of Hepatitis B and C

Multiple studies report high rates of infection with HBV among IDU with prevalence estimates between 38-89% (58,59). HBV prevalence is mostly related to duration of drug use, high-risk injecting and sexual behaviour, and the presence of HIV and HBV. The prevalence of HCV infection among IDU is also high: 50-86% according to different studies (58,60-64). In comparison, the prevalence in the general population is estimated to be around 1% in the US. Prevalence is usually related to length of drug use, high risk injecting behaviour, presence of HIV or HBV, and to a lesser extent to high-risk sexual behaviour.

Cohort studies of DU mainly focus on HIV rather than HBV or HCV incidence. However, a study from Amsterdam showed an HBV incidence rate of 9.1, and an HCV incidence rate of 10.1 per 100 person-years of follow-up between 1986-1989, in a partial out-of-treatment group (42). An Australian study (65) of an out-of-treatment group found an HCV incidence rate of 19.6 per 100 person-years between 1990-1992. An Italian study (64) in an in-treatment group found a HCV incidence rate of 6.2 per 100 person-years between 1992-93.

It has been suggested that infection with HCV most often occurs in the first four years of drug use (58,61,66).

These numbers are of considerable importance because it is quite possible that the net economic cost of HCV infection will become comparable to that of HIV infection. The pool of infected individuals is large, and the rate of complications over a protracted period is high. Chronic fatigue can reduce working capacity while liver cirrhosis leads to high health care system utilisation (67).

Prevention of viral infections among drug users

Since there is no cure for HIV infection, primary prevention remains essential. Since no vaccine is available, behaviour change is the only alternative. General preventive measures aimed at creating behaviour change include information or education campaigns via mass media, schools, or using peer-education techniques. HIV testing and counseling is promoted in several countries (USA, Sweden) as an important strategy in HIV prevention, whereas elsewhere (e.g. Netherlands) there is no

promotion of massive HIV testing. Since the presence of sexually transmitted diseases (STD) facilitates HIV transmission, STD control is an important part of HIV prevention.

Preventive measures more specific for DU imply prevention of drug abuse: primary prevention by education campaigns and secondary prevention by offering drug treatment possibilities. The law enforcement or war on drugs can be considered as a way of preventing people from using drugs, but there is no study that proves the effectiveness of this approach. On the contrary, prohibition appears to have been one of the major factors in the transition from smoking to injection of drugs, since this is the most economical way of consuming, with consequently an increased risk for HIV infection (4).

Opposed to law enforcement is the harm reduction approach. This public health paradigm is based on the following assumption: if it is not possible to stop a DU from using drugs, one should try to minimize the damage that this person does to him/herself, other persons and society at large (6,68). This approach is advocated in the Netherlands, the United Kingdom, Australia, Canada, and parts of Switzerland, as well as in some developing countries. HIV prevention measures respecting the harm reduction philosophy are needle/syringe distribution or exchange programmes, bleach distribution and methadone treatment. Often there are strong emotional rather than scientific motivations against harm reduction programmes, considered an incentive to use or inject drugs, and a first step on the slippery slope toward legalisation of currently illegal drugs. Much effort has been put into the evaluation of harm reduction programmes, but often these evaluations are hampered by the absence of a control group, a poor follow-up and/or selection bias, when asking volunteers to participate in behaviour or HIV testing studies (7,69). However, evaluations of needle/syringe exchange programmes have not provided support for the hypothesis that increased drug use in terms of frequency of injection or recruitment of new users has been stimulated (6,7,70). Other studies suggest a reduced risk of blood-borne infections in participants of needle exchanges, as well as a decreased sharing of equipment (6,47,70-72).

All HIV prevention campaigns aim at behaviour change. Several studies suggest a reduction in risk behaviour among DU and try to link this to declines in HIV incidence and prevalence (27,37,73-78). Some studies show that HIV infected DU show greater risk reduction than HIV uninfected individuals (79), but the data are inconsistent (80). Maintenance of safe behaviour will be the next problem (81). A few studies point out that despite low HIV incidence, HCV prevalence and incidence remain disturbingly high (42,58,59,65,70). This means that DU still share their equipment, probably with individuals they know to be HIV-negative. Interventions to prevent HCV should be applied early or before drug use begins, since infection usually occurs in the first four years of a person's drug career (61,65,66,82). HBV prevention should include vaccination campaigns.

Methadone Maintenance Treatment

Methadone programmes existed years before the HIV epidemic. During World War II methadone was developed as a strong analgesic. It is a long-acting opiate, taken orally once a day. In 1965 Dole and Nyswander demonstrated the usefulness of methadone as a substitute treatment for opiate addicts, diminishing craving for the drug (usually heroin), inhibiting the euphoric effects of additional heroin as well as reducing the social and legal problems associated with drug abuse (83). Many subsequent studies (including four randomised controlled trials) evaluating methadone maintenance treatment (MMT) have focused on its potential benefits: increases in retention of patients in treatment, decreases in illegal drug use, reduction in criminal behaviour, return to normal social life and employment combined with the safety of the treatment over the long term (84,85).

Probably MMT is the most evaluated form of treatment in the field of drug abuse treatment, but it continues to arouse professional and political controversy (85). In many countries the demand for MMT exceeds the availability. MMT is costly due to associated counseling and medical services as well as to the duration of treatment, but its cost-effectiveness (compared to drug-free treatment, imprisonment, etc.) has been proven (85). There is clear evidence of a considerable difference in efficacy of MMT programmes. The "best" programmes (as measured by decreased use of drugs,

decreased criminal activity and increased social productivity) appear to use higher doses of methadone (>60mg), offer more services (social, psychological, medical) and have stable experienced staff (85-88). There is a linear relationship between in-treatment performance and duration of time spent in treatment (20).

Since the start of the HIV epidemic the discourse on the role of methadone in the treatment of drug addiction has changed. MMT became a method of preventing HIV infection by reducing drug use and the frequency of drug injection and by attracting DU not ready to give up their drug use into treatment settings (86). In several countries MMT access increased (USA , Germany, Switzerland) or programmes were introduced (France). Effect of MMT on HIV acquisition has been evaluated in several studies, suggesting a protective effect of MMT (6,20,86), but randomised trials testing this hypothesis have not been published yet. Moreover, the conclusion is sometimes based only on the observation that there is a dramatic decline in number of injections per day after the start of MMT. In the absence of a control group, incidence rates are usually compared to historic cohorts. As well, several HIV prevention measures (information campaigns, needle exchange) in addition to MMT were implemented often in the same area at the same time. A study in Amsterdam suggested no protective effect of low-threshold methadone programmes, but the doses of methadone used were low (24). However, a nested case-control study in Rome showed a protective effect of long term MMT, with a risk for HIV seroconversion increasing 1.5 times with every 3 months spent out of treatment (89).

In vitro studies show that opiates inhibit immune functions. Long term parenteral use of street heroin is associated with abnormal laboratory tests of immune function, but there is no clear link with any particular clinical defect. When DU start MMT most studies show a return to normal laboratory values, suggesting that immune function changes are more related to life style factors and contaminants in street heroin than to opiates. Available evidence of effects of methadone on immune function or on the progression to illness in HIV infected DU remains incomplete. However, present evidence suggests that methadone does not significantly alter immune function, is safe for HIV infected individuals, and may actually lead to clinical improvement due to changes in life style factors and better medical follow-up (90,91). Especially for HIV

positive DU medical care can be enhanced by "onsite" primary care (92,93), and those on methadone treatment show better compliance with medical appointments and with treatment for HIV (94).

With regard to substitution treatment in general Seivewright (84) gives a summary of its aims. Over the short term the aim is to attract DU into treatment and relieve withdrawal symptoms. Over the long term the goals are to retain DU in treatment, reduce injecting, stabilise drug use, stabilise life style, reduce criminal behaviour, reduce HIV and HCV transmission and reduce the death rate.
Methadone is a substitute for heroin. However, many drug users use cocaine or crack, and are at high risk for HIV infection, in part due to very frequent injecting of the drug, and in part due to unprotected sexual relationships as result of sexual arousal and/or prostitution. Currently, there is no pharmacological treatment for cocaine, crack or amphetamine addiction, and results of other forms of treatment have been rather poor. The development of a vaccine, which would induce an immune response able to partially block cocaine-induced effects is in a preliminary phase (95). Improvement of care for cocaine users should be a priority in HIV prevention programmes.

Study setting

Description of Switzerland and the canton of Geneva.

Switzerland is a small middle-European country, bordering on Germany, France, Italy and Austria. Its total population is 7.8 million, and it is composed of 23 cantons. Legislation is partly federal, partly cantonal.

Geneva is a small canton with a total surface area of 282 km^2, divided between 45 communities, the city of Geneva occupying only 16 km^2. There are around 385,000 inhabitants, almost half of whom live in the city itself. Every workday more than 30,000 people cross the French border to work in Geneva, as well as 13,000 people from the canton of Vaud, north of Geneva.

On the west, south and east the canton is surrounded by borders with France. There is an international airport as well as an international railway station, making Geneva a privileged place for drug traffic. The proportion of foreigners living in Geneva is around 35%, two-thirds of whom have a permanent permit. Two-thirds of the population is between 20-64 years old, 15% is 65 years and over (96).

Since the end of the nineteen-eighties, the economic recession has been felt in Geneva. Unemployment rates were always low compared to other European countries, but this difference is disappearing. The Geneva unemployment rate is always higher (5% in 1992) than the average Swiss unemployment rate (less than 2% in 1992). Unemployed Swiss residents or those having permanent permits can get income from social security.

The cost of living is high in Geneva, especially for houses (rented or bought) but also for primary consumption (food, clothes), transport and insurance. Until 1994 a "Medicaid" program existed for those not able to pay private medical insurance; now there are only private medical insurance plans. Although it is obligatory to have medical insurance, the proportion of uninsured people is increasing.

General

There is a mandatory notification of AIDS as well as of HIV cases in Switzerland. All new cases should be notified to the Federal Office of Public Health by the physician having prescribed the HIV test or diagnosing AIDS, with mention of sex, year of birth, canton of residence, and suspected risk factor for HIV. The proportion of people tested for HIV is high, a recent study suggests that 47% of the Swiss population has been HIV tested (half of them through blood donation, others voluntarily) (97).

Switzerland is among the European countries with the highest prevalence rate of AIDS cases. By the end of 1995 there had been 4996 cases of AIDS notified since the beginning of the epidemic, giving a cumulative incidence of 71.8 per 100,000 inhabitants. In 1995 the number of AIDS cases was 745 (or 10.7 per 100,000 inhabitants), with a range between the cantons of 0 to 27.9 AIDS cases per 100,000, with Geneva at the upper end of the range.

The total number of positive HIV tests declared was 21,363 at the end of 1995, of which 1028 were declared in 1995 alone. The range of HIV prevalence rates among cantons was 0 to 29.6 per 100,000 in 1995 (98).

Within Switzerland the Geneva canton has the highest HIV and AIDS prevalence, followed by other cantons with urban concentrations such as Zürich, and Basel. However, the number of new HIV infections per year decreased since 1991, from over 300 per year in 1991 to less than 200 per year since 1993 (99).

The main risk factors for acquiring HIV among AIDS cases in Switzerland are injecting drug use (38.8%), homo- or bi-sexual transmission (38.6%) and heterosexual transmission (16.5 %). Of all AIDS cases 77.7% are men. The profile of risk factors varies from canton to canton.

In Geneva, 658 cases of AIDS had been reported by the end of 1995. The predominant risk factors were IDU (41%) and homosexuality (40%). In fact IDU accounted for most new AIDS cases between 1989-91 (around 46%), but this proportion has decreased since then (99).

HIV prevention campaigns in Switzerland and Geneva

In 1986 a national STOP AIDS campaign started. There were three levels of intervention: general measures intended to inform and motivate the population as a whole, measures aimed at specific target groups (homosexuals, DU, adolescents), and in depth measures based on individual interactions (eg education of "mediators" such as teachers, doctors). The campaign, still continuing, has been extensively evaluated and is in general considered to be excellent, with respect to the process itself as well as to the results concerning knowledge, attitudes, risk behaviours, condom use and sales (100). The campaign has been complemented by preventive activities at the local level. In Geneva the 'Groupe SIDA' has organised HIV information campaigns at schools, in bars, for prostitutes, at music festivals, etc. It played an important role in the organisation of the bus for needle exchange, which has been going through the city every evening since the end of 1991.

In 1986 pharmacies were invited by the Cantonal Medical Office to make syringes available at low cost for drug users; many pharmacies participated. The police changed its policy with regard to carrying a syringe in 1992. The canton accepted a right of survival law for drug users in September 1991: every drug user who wants to stop using drugs should have the help to be able to achieve this, and every drug user who does not want to give up using drugs yet should receive the help necessary to survive. This means access to food, lodging, HIV prevention and substitution therapy. Access to methadone treatment was facilitated (101). In 1993 the Cantonal Medical Office started a hepatitis B vaccination campaign among drug users. Free vaccines became available at several drug treatment sites (usual price around 150 SF). It was expected that HIV and HCV prevention would be discussed with participants at the time of vaccination. Evaluation of this campaign is ongoing.

Evaluation of the impact of individual prevention activities is impossible, given the range of national as well as cantonal prevention measures under way at any time since 1986. Any evaluation will need to consider all the activities as a whole.

General

Drug abuse is mainly considered as a problem of the larger cities: Zürich, St. Gallen, Bern, Lausanne and Geneva. Zürich was known for its open drug scene called Platzspitz, a park where drug sale and use was tolerated. Although such a situation offers an interesting possibility from a harm reduction perspective, the park was closed in early 1992, as well as its less official successor Letten park in 1994 (102).
In the federated Swiss political system all cantons have their respective attitudes, programmes and regulations with regard to DU.

Legislation

In Switzerland all legal aspects of drug traffic and consumption are regulated in the Federal Law on Narcotics (1951). This law was repressive, forbidding all consumption, possession and traffic of soft and hard drugs. It has been modified several times to include regulation of methadone (and even heroin) treatment and to decrease penalties for consumption of drugs.
In Geneva since 1986, consumers of drugs have not been arrested, but have received fines. Although possession of syringes was considered proof of consumption, this policy changed in 1992, under pressure of HIV prevention campaigns (101).
Methadone treatment has been allowed since 1970. Heroin users desiring methadone treatment can, through the intermediary of their physician (private or in an institution), ask permission at the Cantonal Medical Office to receive methadone. Until 1991 eligibility criteria for methadone treatment were: opiate dependency of at least 2 years duration, having tried detoxification at least twice, and age over 21 years. For HIV prevention reasons, the criteria were changed into opiate dependency only.
A recent change in the law (May 1992) has allowed medically supervised prescription of heroin for a maximum of 250 cases deemed or judged to be extremely difficult. In several cities (Zürich, Bern) pilot programmes started in 1993, and Geneva (in the form of a randomised clinical trial) followed in October 1995. Extensive evaluation of these projects is currently being performed by the Federal Office of Public Health (102).

Drug use in Geneva

In their report on drugs published in 1990 (103) the police gave a detailed report on the evolution of the drug problem in Geneva. Between 1966 and 1968 the first hippies using cannabis entered the open drug scene. In 1968 lysergic acid diethylamide (LSD) had a certain but very temporary success. After 1970 drug traffic increased considerably as did the number of arrests and seizures: in 1968 25 persons were arrested and 50 kg of cannabis taken; by 1970 it was 60 persons and 4500 kg respectively. At that time, opium smoking and use of and oral morphine became fashionable. In 1972 heroin entered the market and became an increasing problem, especially after 1985. Heroin is now the drug favoured by Geneva drug users. Over the past few years cocaine use has increased, added to pre-existing heroin use. Multi-drug use is an increasing phenomenon since 1990. The drug market is rather active with numerous sources (Turkey, Yugoslavia, Portugal, Spain, Nigeria, etc.) making control difficult. Still, prices are high and drug enforcement efforts strong, so that the main route of consumption of heroin and cocaine is intravenous, since this is the most cost-effective way of consuming drugs. Recently there appears to be a trend among young drug users to smoke or inhale heroin (see below).

The population of DU, excluding marihuana users, is estimated by the police as well as by the socio-medical system to be around 2500 persons (101). However, it is not clear on what this number is based, systematic studies using capture-recapture methods not having been performed yet (104,105).

Medical and therapeutic care for drug users in Geneva.

Several public, private and mixed institutions are available for the care of DU. The public domain is represented by the Division for Substance Abuse of the Psychiatric Institute of Geneva University. It started its activities in 1981. At first only ambulatory treatment for detoxification, psychotherapy, social assistance, and street work were offered. In 1987 a 6 bed in-hospital detoxification unit was opened. Realising that only few DU were reached by this abstinence programme, short and long term methadone treatment was introduced in 1991. On-site medical care became available. This led to a considerable increase in DU requesting treatment and a decrease in time between start

of drug use to start of first treatment (106). In October 1995 a randomised clinical trial for the prescription of heroin treatment started. Injectable heroin was offered to a group of 40 chronic DU for whom MMT had failed.

In February 1996 a new 8 bed unit for DU with major psychiatric problems was opened. Public medical care is also offered at a specialised consultation service for DU at the outpatient department of the University Hospital.

Private practitioners offer medical care as well as methadone maintenance treatment. In 1986 51 different practitioners prescribed methadone. This increased to 88 in 1991 and has stabilised since. In 1993, together they took care of around 500 DU. Since 1994 private practitioners are allowed a maximum of 10 DU on methadone treatment under their responsibility. Finally, the Phenix Foundation (see below) is a private association offering integrated methadone treatment to around 400 DU.

The total number of official methadone treatment slots in Geneva has increased considerably during recent years: less than 300 in 1987, 800 in 1991 up to 1200 in 1994 (101). Medical insurance programmes pay for methadone treatment on a per consultation or contract basis.

Residential drug free treatment aiming at social and employment reintegration is offered in two institutions. One unit has a 3 month programme, another a 1 year programme. The total number of residence beds available recently increased from 12 to 24. Waiting lists used to be long.

Since October 1991 a bus circulates daily in the city offering exchange of syringes and needles, distribution of alcohol swabs and condoms, as well as information on HIV, hepatitis and drug treatment possibilities. After one year of operation around 100 persons were being seen each evening. This number decreased recently. It seems that young DU prefer smoking or inhaling heroin instead of injecting and that many DU are now receiving MMT (107).

There is no official shooting-room in Geneva.

The Phenix Foundation and the Geneva Methadone Cohort Study

At the end of the 1970s, Dr J.J. Déglon, a psychiatrist, was the first to open a large out-patient methadone treatment centre in Geneva: the "Ermitage Therapeutic Centre" (ETC). Up to 1987 it had a purely psycho-social orientation, working with psychiatrists, psychologists, nurses and social workers, and offering long term methadone maintenance linked with a psycho-social and employment reintegration program. No medical care was delivered to the patients; in the event of somatic problems they were referred to their treating physicians. It became obvious that, although many patients had problems related to HIV, hepatitis or other diseases, few went to their physicians. As well, at that time, many physicians were not well prepared to deliver adequate counselling and care to HIV positive patients. Dr. Déglon asked for support from Dr Hirschel, chief of the specialised outpatient HIV clinic of the Geneva University Hospital. This was the origin of the "Geneva Methadone Cohort Study" (GMCS). Dr. Hirschel and Dr. Perrin, head of the Central Laboratory of Viral Serology, agreed with the request, but asked for a regular collection and storage of data and specimens from HIV+ and HIV- patients for laboratory, clinical and epidemiological research purposes with the consent of the patients. They asked for permission to include all consenting HIV+ patients in the Swiss HIV Cohort Study. This study is a large observational study of HIV-infected patients of six Swiss University Hospitals (108).

At the beginning of 1988 Dr. Robert was asked to design and organise a biannual, voluntary HIV testing and counselling at the ETC, as well as to facilitate access to the HIV outpatient department. Groups of four physicians from this department were present two days at the ETC for HIV pre-test counselling and medical check-ups of those found to be HIV positive. During the testing days two specialised nurses from a private laboratory were available for blood taking from 6 am to 7 P.M.

Patients were seen again after two weeks by the same physician at the ETC for results of screening or CD4 count. Screening for hepatitis B and for hepatitis C, when it became available in 1989, as well as testing of blood count and liver enzymes were also performed. Vaccination for HBV was offered.

After 6 months the "testing-days" were repeated, and this until end of 1995. In 1989 Dr. Robert was replaced by Dr. Chamot. The organisation of the GMCS changed considerably after 1991, when Dr. Deglon decided to reform the ETC. Two new physicians both skilled in general medicine, psychiatry, HIV related problems and drug addiction treatments joint the ETC which was renamed "Phenix Foundation" (PF). Two new locations were opened. Medical care became available on site, facilitating patient care and preventive activities such as vaccination for hepatitis B. The two physicians became responsable for the pre- and post-test counselling for the testing days. Dr. Chamot was replaced by Dr. Broers in July 1991, who organised the testing sessions together with the physicians, was present during the testing days, and became the person responsible for data-management and feedback to the PF.
In November 1994, a fourth centre was opened and another physician was engaged. Between 1982 and 1994 the total capacity of the PF increased from 50 to 400 patients.

Clients were invited to participate in behavioural studies at two times between 1988 and 1995. In 1988 a questionnaire on HIV risk taking behaviour was administered by the study organiser, collecting data on sharing of syringes and use of condoms for the period before 1987 and for the period 1987 to 1988. In 1994, as part of a study in three different methadone treatment centres (total number of subjects 355) a different questionnaire was administered by the treating physician, collecting data on risk taking behaviour in the last six months before interview. These studies showed that before 1987 over 80% of DU were sharing syringes, sharing decreased to 29% (5% for HIV+ IDU) in 1988 (77) and decreased further to 9% (0% for HIV+) in 1993-94 (109). Consistent condom use increased over time from 4% before 1987 to around 30% in 1994. However, these data have not been used for the present study, since data collection was not done in a systematic way and different questionnaires were used. As well, data on exact sample size and sampling were not available for the study in 1988. Several publications have been produced by the GMCS, concerning virological, epidemiological as well as behavioural research (40,76,77,109,110).

Methadone treatment at the Phenix Foundation.

Heroin users requesting treatment at the PF are evaluated during an intake procedure and proposed a contract. The programme is divided into three successive phases:

1) Interruption of illegal drug use and restoration of good physical, psychological and social status. Duration: months to years; methadone dose high.

2) Weaning phase: decrease of methadone dose. Duration:6 months to over 2 years.

3) Prevention of relapse. Duration: variable. A weekly group session is offered as well as individual psychotherapy.

Overall duration of the treatment depends on the patient's personality and social and professional integration as well as the presence or absence of emotional support. Sometimes the programme may succeed in 1 year, but mostly treatment requires several years, with some patients requiring long lasting treatment. The average duration of treatment in the PF is 3-4 years, and the average methadone dose is 66 mg. Patients are excluded from the programme for several reasons: disappearance without notification, violence at treatment site, repeated cheating concerning urine or saliva analysis, unwillingness to pay for treatment and repeated violation of the therapeutic contract.

Relapses (heroin use during treatment) are not a criterion for exclusion from treatment, but rather a reason for prolongation of treatment and increase of methadone dose. Relapses are considered an unavoidable step in the recovery process. Methadone is given diluted in a syrup, to avoid intravenous use and sale on the black market. It is swallowed under supervision, in the beginning on a daily basis; for more stabilised patients one or several doses are given to be taken at home. Urine and saliva analysis for opiates, cocaine, benzodiazepines or barbiturates can be required from patients at any time without warning. Sometimes a marker such as phenobarbital is added to the methadone, or the temperature of the urine sample is measured to check for cheating. Frequency of testing varies between several times per week and once a month, depending on the stability of the patient.

Psychotherapy, on an individual, couple, family or group basis, is offered and strongly recommended, though not compulsory. Every patient has a short interview with at least one staff member at the time of methadone distribution.

Medical assistance has been available on site since 1991, and this has greatly improved both the quality and quantity of medical care and preventive measures such as vaccination programmes, screening for tuberculosis, and pentamidine inhalation as prevention for Pneumocystis Carinii pneumonia for HIV+ patients. Every patient has a comprehensive medical check-up when admitted to the programme.

Stability of staff, an important factor for the quality of methadone treatment (88), has been aimed for. Dr Deglon and his early coworkers are still there, but due to the enlargement of the programme and reallocation of patients to new centres there have been many new faces for the clients.

The budget of the PF is considerable: 2,200,000 Swiss Francs (SF) in 1991 (1 SF≡0.93 CAN$), SF 3,200,000 in 1995. Mean cost per treatment per week depends upon stage of treatment, but ranges from 40 to 60 SF. Ninety percent of the costs are covered by health insurance, which pays directly to the PF on a contract basis. To balance its budget, the PF gets some financial assistance from Public Health Agencies, and patients are asked to pay 10 to 20 SF per week themselves. This contribution also has a psychological value for the patient. People unable to pay can work one or more hours per week for the PF.

In 1988 (beginning of the GMCS) there were around 150 patients in treatment. This slowly increased to 400 patients in 1995 with a yearly turnover of around 20%. Most patients have housing and the average monthly income was SF 2710 in 1995. Whereas in 1988 a majority of patients was employed (80%) there was a substantial decrease in employed patients over the last few years, in correspondence with the overall Swiss economic picture. Still, compared to descriptions in American MMT programmes, the population studied here is relatively well off and socially integrated.

Aim of the Geneva Methadone Cohort Study and this thesis

The study was initiated in the context of a request to provide adapted medical care and information on HIV and hepatitis for drug users. It soon became clear that this group of DU on methadone treatment could provide an interesting data base for epidemiological, virological, behavioural and clinical research on HIV, hepatitis B and C and related medical problems. So, even when the necessity of providing medical care by the study physicians disappeared 3 years after the start of the study, it was decided to try to continue the GMCS. Public Health authorities in Geneva (the cantonal medical officer) even provided partial funding, since they were interested in the epidemiological data.

The aim of this thesis is to present and interpret the data on prevalence and incidence of HIV and viral hepatitis available from this cohort study, including the analysis of trends over time in prevalence and incidence rates, and comparison between genders, as well as between injectors and non-injectors. Based on data from the literature and on the timing of the introduction of the Geneva harm reduction policy, it was expected that the prevalence and incidence rates should decline over time. Injectors were expected to have higher rates of infections than non-injectors, but no gender differences were hypothesised.

The data presented are compared with available data from the literature, and the limitations of this study and recommendations for further research are discussed.

Data collection

All data come from the previously described Geneva Methadone Cohort Study (GMCS). This study is a collaboration between the Phenix Foundation (PF, Geneva's largest methadone treatment centre), the Division of Infectious Diseases (DID) and the Central Laboratory for Viral Serology (CLVS) of the University Hospital in Geneva. Seven hundred and six DU have been enrolled in this ongoing study since May 1988. This thesis describes results based on data collected until December 1995.

Data collection was slightly different between 1988 to 1992 compared to the period thereafter. In the first period of study several physicians of the DID as well as two nurses from a private laboratory were present at the PF during a two day period, every 6 months. Recruitment of participants was performed in the following way: two weeks prior to the testing days all patients were informed by letter about the study and invited to participate. Posters emphasising the dates were posted at several places at the PF, and assistants responsible for methadone distribution repeated this message the days before testing was done. Pre- and post-counselling was offered by the physicians of the DID and all blood samples were sent to the CLSV for analysis.

The main difference with the second period, when two physicians were permanently working at the PF, is that all patients were offered the possibility of participating in the study not only during the two testing days, but also more privately by taking an appointment with one of the physicians in the weeks before or after these days. Patient lists of those in treatment at the testing days were made available to the study co-ordinator allowing assessment of participation rates. Information on gender, age, year of starting methadone treatment, way of using drugs (intravenously or by inhaling/smoking) was routinely collected by the study co-ordinator for every new study participant. These data were taken from patient files containing a questionnaire filled out during an interview before the start of methadone treatment. This interview was routinely conducted by a psychiatrist or a psychologist of the PF. No information was collected on other patient characteristics at start of treatment, nor on the methadone doses used or results of urine or saliva testing during treatment, nor on the

reasons for the end of the treatment or the date of readmission. This means that for readmission the first entry in treatment as well as in the study was maintained as starting point and that the time out of treatment was included in the calculated individual total person time of follow-up.
The definition of an injection drug user in the context of this study was: any drug user who had used a syringe for taking drugs at least once in his/her life at the start of the MMT.

From every patient 4 tubes of blood were collected: for haematology (red and white blood count, thrombocytes), for biochemistry (creatinine, liver enzymes), for serology (HIV, HBC, HCV) and for storage. For HIV positive participants a supplementary tube for lymphocyte count (CD4, CD8) was collected. The blood samples were transported to the laboratory every 2 hours.

Laboratory methods

Blood specimens were tested for antibodies to HIV 1 and 2 (recombinant HIV1/2 enzyme immunoassay EIA, Abbott Laboratories, Chicago, IL), and positive specimens were confirmed by immunoblotting (Western blot, Dupont de Nemours, Geneva, CH). With regard to markers for hepatitis B, initial screening included testing for anti-HBc and Hbs Ag (EIA, Abbott). Antibodies for HCV were assayed in 1989-1991 using a first generation HCV antibody ELISA system (Ortho-Diagnostics, Raritan, New Jersey), which was replaced by a more sensitive second generation test in June 1991 (HCV EIA, Abbott). If available, stored sera from before 1992 were retested for HCV with the second generation test.
Until 1991 blood count and liver enzyme analyses were performed at a private laboratory, and viral serology at the Central Laboratory for Viral Serology (CLVS) of the University Hospital. After 1991 all testing was performed at the private lab and one tube of serum was sent to the CLVS for research activities. All confirmatory testing of positive HIV-ELISA tests by Western blot was performed at the CLVS. All data from both labs were made available to the study partners.

Data analysis and assumptions.

Data handling and analysis were performed using Foxpro (version 2.0) database, and SAS (version 6.10, 1994) and Epi-info (version 6, 1994) statistical softwares.

Prevalence

Prevalence rates for HIV, HBV and HCV infection at entry into the study were determined by sex, by injection behaviour, by year of entry in treatment, by year of birth as well as by age at start of treatment, based on first blood screening at study entry. The numerator was the number of positive tests, the denominator the total number of persons being tested (excluding those not tested). χ^2 tests were used to test for differences between proportions, a p-value of 0.05 was chosen as criterion of significance. Student's t-tests were performed to test for differences in means for continuous variables. Prevalence rates were calculated for the overall study population (injectors and non-injectors) and for the group of injectors only. To examine changes in prevalence per year of birth and per year of start of methadone, χ^2 tests for trend were used. The year of start of MMT instead of the year of entry in the study was considered as a variable, since this first variable contained all the information contained in the second, plus some additional information on the years before 1988.
The strength of time trends (birth and treatment-entry cohort effects) on prevalence rates was measured by odds ratios (OR). Cohorts were compared with respect to (assumed) level of exposure to HIV prevention campaigns. The groups were chosen based on the following assumptions: the HIV prevention campaigns started in 1986, substance abuse often starts in the late adolescence (111), and delay between the start of substance abuse and first MMT is usually at least 5 years (106,111). To analyse the birth cohort effect three groups were compared: those mainly not exposed to prevention before start of drug use (born before 1960 or age over 26 years at start of prevention campaigns), a mixed group (born between 1960 and 1967,), and those mainly exposed to prevention before starting drug career (born after 1967 or age 19 years or less at start of prevention campaigns). To analyse the treatment-entry cohort

effect the three groups were respectively: start MMT before 1988 (not exposed to prevention), between 1988 and 1991 (mixed group), or after 1991 (mainly exposed). A stratified analysis was performed, allowing adjustment of the treatment-entry cohort effect for year of birth (or age) at entry in MMT as well as adjustment of the birth cohort effect for the year of entry in treatment. Since none of the non-injectors was HIV infected, a stratification by injection behaviour was not possible, so the analysis was performed for all participants and for injectors only. The results of the stratified analysis were expressed by the Mantel-Haenszel odds ratios.

Incidence

Seroconverters for HIV (or incident cases) were those who tested HIV-negative at entry in the study, and who were detected as being HIV-positive on one of the subsequent visits. Seroconverters for hepatitis B were those who tested anti-HBc negative and became anti-HBc positive, seroconverters for hepatitis C they were those who tested initially anti-HCV negative with a second generation test becoming anti-HCV positive over time.

Incidence rates were calculated using a customised SAS program written by W. Meade-Morgan, used and validated in other studies of seroincidence (44,51). Instead of using as the assumed seroconversion date the mid-point between last negative and first seropositive test (as is done in most studies), this technique is equivalent to measuring incidence for each day in the 7.5 years of the study. This avoids the artificially low estimates at beginning and end of the study interval which occur while using the "mid-point" estimate (44).

The numerator of the incidence rate represents the sum of the fractions ascribed to that day for each seroconverter. Seroconversion is assumed to occur with uniform probability along the entire interval between the last negative and the first positive test dates. So, a patient with a last HIV-negative test on May 15, 1989 and the first HIV-positive test on May 14, 1990, will contribute a value of 1/365 to the numerator of the incidence rate for each date. The denominator of the incidence rate represents the sum of the number of HIV-negative individuals "under observation" and "at risk" on that day (those for whom that day occurred between their first and last negative tests) plus

a declining fraction of seroconverting persons in the interval between their last negative and first positive test. For such seroconverters, the contribution of "HIV-negative person-days" to the denominator of the incidence rate for each day in the interval during which they became HIV-positive is proportional to the amount of risk time remaining until the end of that interval. This allocation reflects the decreasing probability that the subject is still HIV-negative as the seroconversion interval elapses. Thus, for a 1-year seroconversion interval for example, a seroconverter will contribute to the incidence denominator approximately 364.5 per 365 person-days (PD) of HIV-negative observation to the first day of the interval, 182.5 per 365 PD on the mid-point day, and 0.5 per 365 PD on the final day, and intermediate values for the other days of the interval. The total of days contributed by each seroconverter equals one half of the actual number of the days in the interval between last negative and first positive tests. The same method was used for calculation of hepatitis B and C incidence. For all three viruses incidence rates were calculated for the total period, as well as for 6-month time period intervals, by gender and for injectors versus non-injectors. The rates were adjusted to denominators of 100 person-years (PY) of observation. Confidence intervals of the incidence rates were calculated according to the Poisson distribution (112). Comparison of incidence rates (for gender, injection behaviour) was performed using the methods for analysing density type of follow-up studies described by Kleinbaum, Kupper, Morgenstern (113).

As a test for a trend in incidence rates over time a Poisson regression has been suggested (42). Calendar year is then forced continuously in the model. The disadvantages of this method are as follows: it assumes a functional form for the relationship and it can give a significant result if there is a threshold effect without a real trend. Therefore it was decided not to conduct significance tests for the trend in incidence, but to describe the form of the trend by looking at the graph (see Results section).

Results

Description of the study population and prevalence

A total of 706 patients were included in this study between 1988 and 1995. The total number of patients being followed at the Phenix Foundation during that period was 802, so the overall participation rate was 88.0%. The reasons for non participation were refusal or being in treatment only during the period that fell in between two study periods, but these reasons have not been recorded, nor have the characteristics of these non-participants.

Table 3 gives some characteristics of the study population. Of the 706 participants, 160 (22.7%) were female. Average age at entry in the programme was 27.0 years (range 17.4-48.4 years), and significantly higher for injectors compared to non-injectors. Eighty-three percent had injected drugs at least once, 17 % had never injected. The overall prevalence rate for HIV was 18.9%, for HBV 45.0% and for HCV 58.3%. As can be expected all prevalence rates were significantly higher for IDU compared to non-IDU. None of the 119 non-IDU was infected with HIV. The crude odds ratios for prevalent infection while comparing IDU and non-IDU could not be calculated for HIV, and were 17.1 for HBV (95% confidence interval 7.5-40.8) and 30.7 for HCV (95% confidence interval 14.1-69.5).

There was no difference in the proportion of injectors among women and men (83.3% versus 82.7%). Also there was no significant difference in the prevalence rates for either virus between men and women (not in table).

Co-infections were common: all of the HIV+ participants were co-infected with either HBV or HCV, 87.9% were co-infected with both. One hundred and nine participants (all injectors) were positive for all three viruses, 243 participants (of whom 140 were injectors) were negative for all three viruses. The prevalences of antibodies to the 3 viruses were all significantly correlated (cf. Table 4 for the odds ratios).

The average age at start of MMT among the HIV infected participants was 28.1 years (SD 5.2), among the HIV uninfected participants it was 26.8 years (SD 5.5). This was a significant difference (t-test, p=0.01). When comparing the average ages of the HBV infected (28.7 years) to the HBV uninfected (25.7 years), or of the HCV infected (28.1

Table 3. Characteristics of the study population at study entry.

	Total (n=706)	IDU (n=576)	non IDU (n=119)	p
male	**77.3 % (546/706)**	77.4% (446/576)	78.2 % (93/119)	0.86
female	**22.7 % (160/706)**	22.6 %.(130/576)	21.8 % (26/119)	0.86
average age (SD)	**27.0 year (5.4)**	27.3 years (5.42)	25.5 years (5.28)	<0.01
HIV +	**18.9 % (133/703)**	23.2 % (133/574)	0 % (0/119)	<0.01
HBV +	**45.0 % (304/675)**	53.4 % (296/554)	6.3 % (7/111)	<0.01
HCV +	**58.3 % (399/684)**	69.8 % (391/560)	7.0 % (8/114)	<0.01

note: Total numbers differ due to missing data: for injection behaviour 11 missing, for HIV status 3, for HBV status 31, for HCV status 22, for gender 0, for year (and age) of entry in treatment 4.

Table 4. Odds ratios and 95% confidence intervals of associations between prevalence rates, at treatment entry, of 3 viruses

	n	% HIV+	%HBV+	%HCV+
Total	706	18.9	45.0	58.3
HIV +	133		90.7	97.6
HIV -	570		34.4	49.6
HIV unknown	3		0	0
OR			**18.6**** [1]	**41.9**** [2]
95% CI			9.6-36.6	13.7-207.9
HBV+	304	38.5		91.2
HBV-	371	3.3		32.6
HBV unknown	31	12.9		40.9
OR		**18.6****		**21.6**** [3]
95% CI		9.6-36.6		13.3-35.2
HCV+	399	31.1	69.5	
HCV-	285	1.1	9.6	
HCV unknown	22	27.3	53.8	
OR		**41.9****	**21.6****	
95% CI		13.7-207.9	13.3-35.2	

**p<0.01, those with unknown serological status are excluded in the computation of odds ratios

N.B. The reader should note that these odds ratios correspond to the following prevalence ratios:

[1] 2.64 (90.7/34.4) [2] 1.97 (97.6/49.9) [3] 2.80 (91.2/32.6)

years) to the HCV uninfected (25.4 years), both were significantly different (t-test, $p<0.0001$).

Time trends

Age at start of MMT slightly increased between before 1984 and until 1990-91, and decreased afterwards (cf. Table 5). The proportion of non-injectors increased over time, from 2.5% for those entering treatment before 1984 to around 30% for those starting treatment in recent years (test for trend $p<0.001$). The proportion of females did not change over time.

Prevalence rates decreased over time for all three viruses. The overall HIV prevalence per 6 month study session decreased constantly over time, from 36.6% in May 1988 to 8.7% in December 1995 (χ^2 test for linear trend 92.9, $p<0.001$).

The prevalence rates at entry into the study for HIV, hepatitis B and hepatitis C were considered by year of birth, by year of entry in methadone treatment, as well as by age at start of treatment (cf. Tables 5, 6, 7 and graphs 1 and 2).

Prevalence rate peaked for HIV for those born between 1956-1960, for HBV and HCV for those born before 1956, as well as for those entering treatment in 1984-1985. They declined considerably for the younger birth cohorts and for those starting methadone after 1985. For example comparing DU born before 1961 to those born after 1970, the prevalence rate of HIV decreased from 29.1% to 2.0%, of HBV from 71.3% to 2.2%, of HCV from 83.6% to 17.9% (cf. Table 6, tests for trend all significant). This means that those starting treatment at a younger age as well as DU from more recent birth and treatment cohorts were less likely to be infected with all three viruses. Comparing injectors only to the whole study group, prevalence rates for all three viruses were always higher for injectors, but showed the same tendencies of decline over time (all tests for trend significant). The prevalence rates of HCV remained disturbingly high, even in the youngest birth cohorts: 17.9% for those born after 1970, 27.6% for the injectors of this group. Prevalence rates of all 3 viruses increased with increasing age at start of treatment (cf. Table 7).

Table 5. Trends in mean age (in years) at start of treatment, proportion of injectors and females, prevalence rates of HIV, HBV and HCV infection at entry into study; related to year of start of methadone treatment. Prevalence rates are given for the total study population and for injectors only (between brackets).

year start methadone	n	mean age	% injectors	% females	%HIV+ (inj)	%HBC+ (inj)	%HCV+ (inj)
<1984	40	24.4	97.5%	17.5%	35.0 (35.9)	82.5 (84.6)	92.5 (94.0)
1984-85	34	25.4	97.1%	14.7%	52.9 (54.5)	88.2 (90.9)	93.9 (96.9)
1986-87	62	25.7	98.4%	29.0%	33.9 (34.4)	73.8 (75.0)	90.0 (91.5)
1988-89	135	27.3	93.2%	21.5%	26.7 (29.3)	56.4 (60.7)	78.2 (84.3)
1990-91	143	28.3	87.1%	25.9%	17.5 (20.5)	47.4 (53.5)	57.6 (64.7)
1992-93	129	26.5	66.4%	19.4%	7.0 (10.8)	20.7 (26.7)	36.3 (52.5)
1994-95	159	26.7	70.3%	23.3%	4.5 (6.4)	20.1 (28.0)	29.8 (42.5)
χ^2 test for trend		*	58.2**	0.161 n.s.	71.7** (46.7**)	132.9** (89.5**)	145.4** (135.0**)

* correlation coefficient r=0.69, p=0.087; **p<0.01.

Table 6. Trends in prevalence rates of HIV, HBV and HCV infection at entry into study, related to year of birth. Prevalence rates are given for the total study population and for injectors only (between brackets).

year of birth	n	%HIV+ (inj)	%HBV+ (inj)	%HCV+ (inj)
<1956	65	20.0 (20.3)	73.0 (77.6)	83.9 (89.5)
1956-1960	186	32.3 (32.3)	70.7 (74.7)	83.5 (89.2)
1961-1965	195	25.1 (30.2)	50.0 (58.4)	63.4 (75.8)
1966-1970	160	5.6 (7.5)	22.3 (27.6)	37.7 (46.3)
>1970	100	2.0 (3.3)	2.2 (3.6)	17.9 (27.6)
χ^2 test for trend		63.0** (26.0**)	165.9** (121.9**)	157.8** (111.3**)

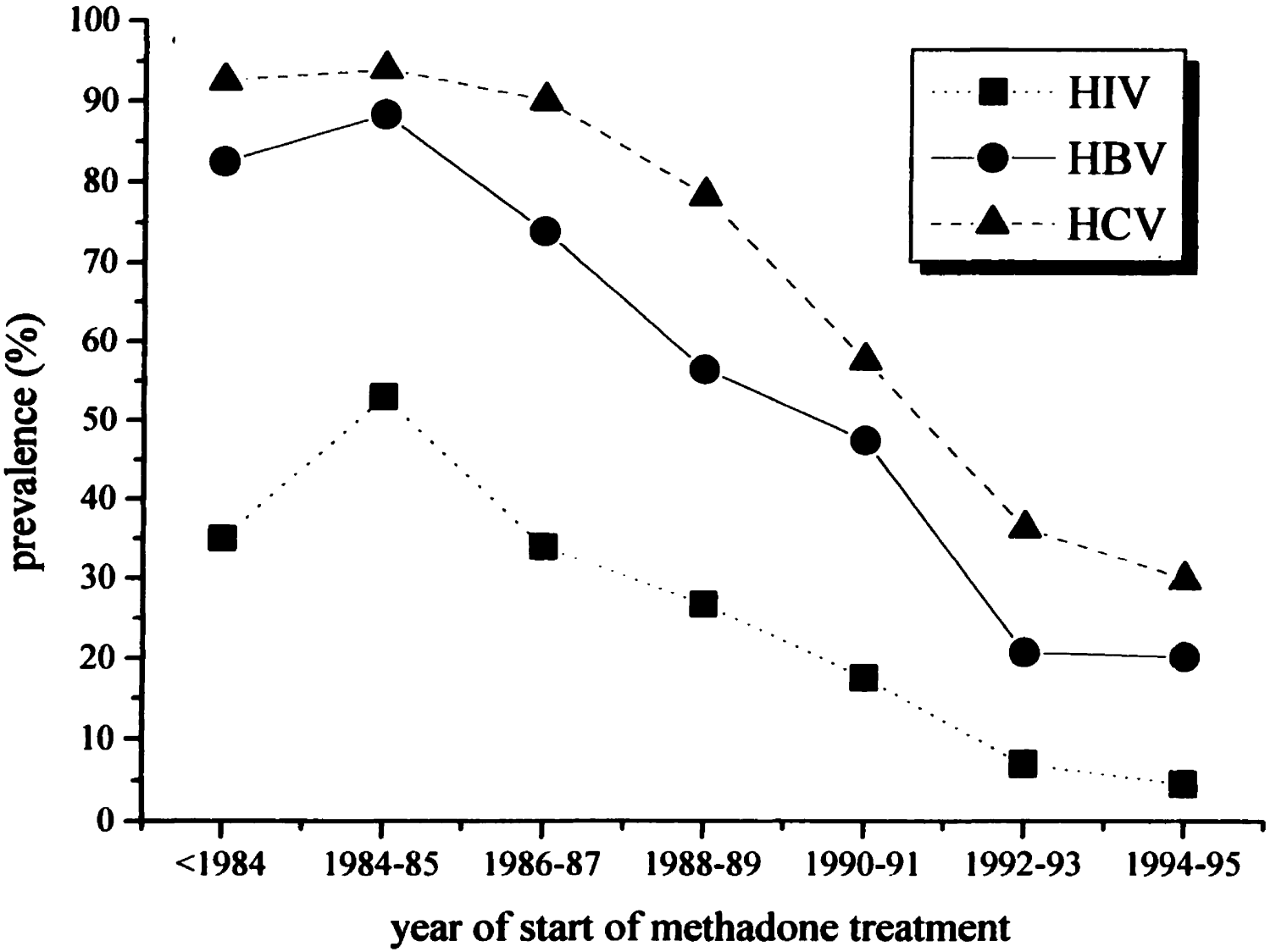
**p<0.01

Table 7. Prevalence rates of HIV, HBV, HCV infection related to age at start of methadone treatment for all participants.

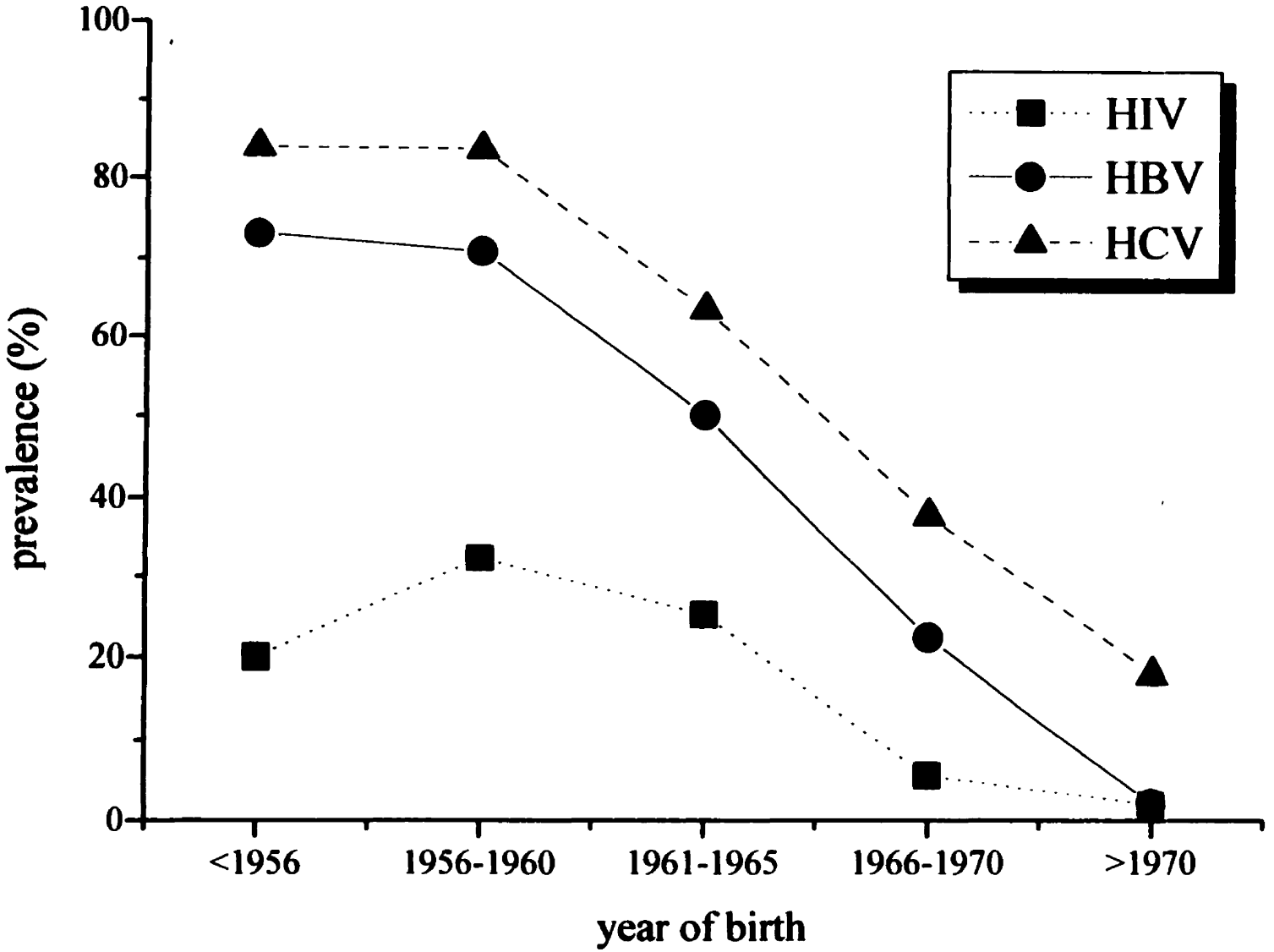
age at start methadone	n	HIV%	HBV%	HCV%
≤ 20 years	46	9.8	11.9	23.3
20-25 years	262	16.5	34.7	49.6
25-30 years	204	20.1	51.5	64.4
30-35 years	133	21.8	56.3	67.2
>35 years	57	22.8	66.6	83.0
χ^2 test for trend		4.5*	45.1**	44.1**

* p<0.05 **p<0.01.

Graph 1. Prevalence rates per year of entry into treatment for all participants



Graph 2. Prevalence rate per year of birth for all participants



Separating by birth cohort as well as by treatment entry cohort in 3 groups corresponding to different presumed levels of HIV education before the start of the drug using career, odds ratios of prevalent HIV (HBV, HCV) infection at study entry were calculated. The crude and adjusted analyses were done separately for the whole study population and for the group of injectors. (cf. Table 8, 9, 10 for crude and Mantel-Haentszel odds ratios). For the birth cohort effect analysis those born after 1966 (corresponding to the group mainly exposed to HIV prevention education before start of drug use) were considered as the reference group. For those born between 1960 and 1966 (mixed exposure to HIV prevention education) the crude odds ratio for prevalent HIV infection was 13.4, the (for year of entry into MMT) adjusted odds ratio was 5.2 (cf. Table 8 and 9). For injectors only the odds ratios were 11.2 and 5.2 respectively. For those born before 1960 (not exposed to HIV prevention education) the crude odds ratio was 18.0, the adjusted was 5.8 (injectors 13.0 and 5.1 respectively). None of the 95% confidence intervals included 1. The same conclusions can be drawn for HBV and HCV infection.

For the treatment-entry cohort analysis the group who started MMT after 1991 (mainly exposed to education before start of drug use) was considered as reference group. Comparing those starting MMT between 1988-1991 (mixed exposure to education) to those starting MMT after 1991, the crude odds ratio for prevalent HIV infection was 4.7 (for injectors 3.7), whereas for those starting MMT before 1988 (not exposed to prevention) the crude odds ratio was 10.7 (injectors 7.5). The adjusted odds ratios were 2.3 and 4.7 for all participants, 1.9 and 3.6 for injectors only. The same tendencies were observed for prevalent HBV and HCV infection. Only two of the 95% confidence intervals included 1 (cf. Table 10).

Incidence

Of the 570 initially HIV uninfected patients 65 were admitted in 1995 (recent patients) and for 103 no follow-up was available (cf. Figure 1). This means that the overall follow-up was 70.5%, or 79.6% (402/505) for those entering the study before 1995.

Table 8. Crude odds ratios (and corresponding 95% confidence intervals) of prevalent infection at study entry, per birth cohort and per treatment-entry cohort (MMT).

	HIV		HBV		HCV	
	all	**injectors**	**all**	**injectors**	**all**	**injectors**
born after 1966 n=224	1	1	1	1	1	1
born 1960-1966 n=212	**13.4** 4.6-44.1	**11.2** 3.8-37.1	**8.5** 4.9-15.0	**7.1** 3.9-12.8	**6.2** 4.1-9.5	**6.0** 3.7-9.6
born before 1960 n=200	**18.0** 6.1-59.8	**13.0** 4.4-12.2	**30.8** 16.7-56.7	**24.6** 12.8-47.5	**18.9** 11.2-32.0	**15.4** 8.4-27.9
MMT after 1991 n=288	1	1	1	1	1	1
MMT 1988-1991 n=278	**4.7** 2.6-8.8	**3.7** 2.0-6.9	**4.2** 2.8-6.3	**3.5** 2.3-5.5	**4.3** 3.0-6.2	**3.3** 2.2-5.1
MMT before 1988 n=136	**10.7** 5.6-20.8	**7.3** 3.8-14.2	**15.6** 9.1-27.1	**11.9** 6.6-21.4	**22.8** 11.3-47.2	**17.4** 7.7-40.7

Table 9. Mantel-Haentszel odds ratios (and corresponding 95% CI) of prevalent infection at study entry, for birth cohort adjusted for year of entry into MMT (for all study participants and injectors only)

	HIV		HBV		HCV	
	all	**injectors**	**all**	**injectors**	**all**	**injectors**
born after 1966	1	1	1	1	1	1
born 1960-1966	**5.2** 2.1-15.7	**5.2** 2.1-15.8	**3.1** 1.8-5.7	**3.6** 2.0-6.7	**2.7** 1.7-4.4	**3.1** 1.8-5.3
born before 1960	**5.8** 2.5-20.5	**5.1** 2.0-16.7	**10.0** 5.8-19.7	**9.9** 5.1-19.0	**7.5** 4.3-13.8	**7.4** 3.7-13.9

Table 10. Mantel-Haentszel odds ratios (and corresponding 95% CI) of prevalent infection at study entry, for treatment-entry cohort (MMT) adjusted for year of birth (for all study participants and injectors only)

	HIV		HBV		HCV	
	all	**injectors**	**all**	**injectors**	**all**	**injectors**
MMT after 1991	1	1	1	1	1	1
MMT 1988-1991	**2.3** 1.2-4.7	**1.9** 0.9-3.9	**2.0** 1.2-3.4	**1.8** 1.1-3.2	**2.2** 1.5-3.6	**1.6** 1.0-2.8
MMT before 1988	**4.7** 2.6-9.8	**3.6** 2.0-7.6	**4.6** 3.1-8.6	**4.1** 2.6-7.9	**6.1** 3.6-11.1	**5.0** 2.5-10.0

Figure 1. Overview of the study

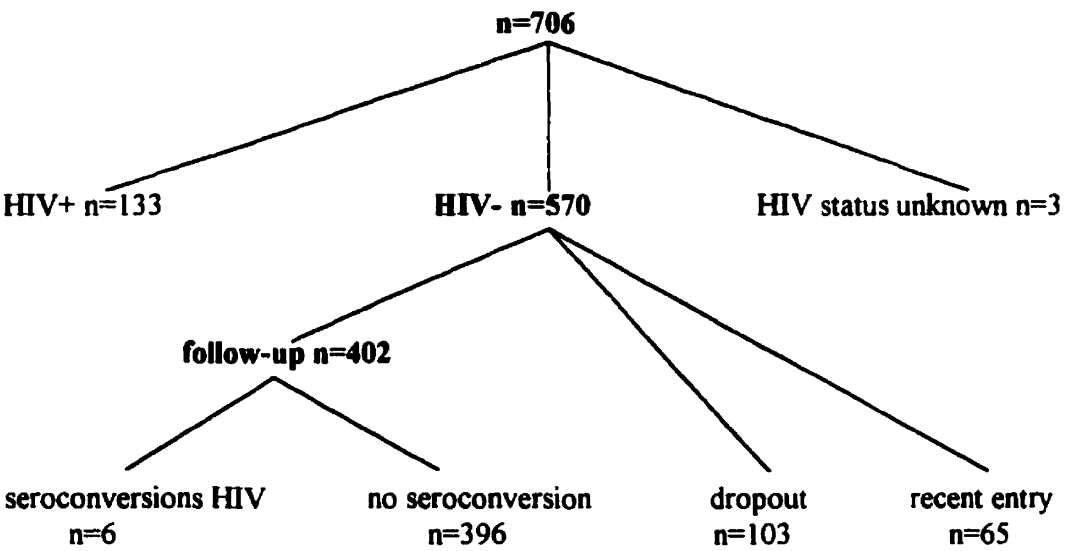


Table 11. Characteristics of HIV negative individuals with follow up versus dropouts

	with follow up	drop outs	test
n	402	103	
average age (SD)	26.8 (5.1)	26.2 (5.3)	t-test 1.05, p=0.29
% women	20.1 %	31.1 %	OR 0.56, p=0.02
% methadone entry before 1992	58.1 %	50.5 %	OR 1.36, p=0.16
% IVDU	82.4 %	74.0 %	OR 1.65, p=0.06
% HBC+	30.6 %	28.9 %	OR 1.55, p=0.07
% HCV+	55.2 %	43.2 %	OR 1.62, p=0.02

Drop outs were more often female and less infected with HCV at study entry, otherwise there were no significant differences between the follow-up and the drop out group (cf. Table 11).

Average follow-up in the treatment group for those for whom a second HIV test was available was 2.7 years (minimum 5 months, maximum 7.5 years). Of these, 6 seroconverted for HIV (5 men, 1 woman), 5 for HBV (3 men, 2 women) and 12 for HCV (6 men, 6 women). Incidence rates per 100 person years of follow-up (with 95% confidence intervals) were 0.6 (0.2-1.3) for HIV, 2.1 (0.7-4.9) for HBV and 4.2 (2.2-7.4) for HCV (cf table 12). One male client seroconverted for HIV and HCV (at different times), nobody seroconverted for more than 2 viruses.

There was a higher incidence rate of hepatitis C among women (9.6% versus 2.7% for men), but this difference was not statistically significant ($p=0.06$) (cf. table 13). The incidence rate of HBV infection was also slightly (and not statistically significant) higher for women (3.5 versus 1.7%). There was no gender difference for HIV seroconversion. Incidence rates for HIV and HCV were higher in injectors than non-injectors, but not significantly so.

Time trends in incidence

HIV incidence decreased constantly over time; in the last two years of the study there were no more seroconversions for HIV (cf. Table 13 and Graph 3). HBV incidence peaked between May 1990 and April 1991, before decreasing rapidly to 0 in 1994. The significance of these trends has not been tested for the reasons cited in the Methods section. HCV incidence fluctuated over time but remained high compared to HIV and HBV incidence rates.

Table 12. Incidence rates (seroconversions per 100 persons-years) and 95% confidence intervals of HIV, HBV and HCV infection.

	seroconversions/person-years	incidence rate (95% CI)
HIV	6/1045	**0.6** (0.2-1.3)
HBV	5/236	**2.1** (0.7-4.9)
HCV	12/282	**4.2** (2.2-7.4)

Table 13. Trends in incidence rates (seroconversions per 100 person-years) of HIV, HBV and HCV infection.

	HIV incidence rate	HBV incidence rate	HCV incidence rate
May '88-April '89	2.0	0.0	4.5
May '89-April '90	1.6	3.3	3.1
May '90-April '91	0.9	4.3	2.2
May '91-April '92	0.2	2.3	6.1
May '92-April '93	0.5	1.4	4.8
May '93-April '94	0.1	1.4	2.4
May '94-April '95	0.0	0.0	3.4
May-December '95	0.0	0.0	9.2
women	0.5	3.5	9.6
men	0.6	1.7	2.7
p-value	1	0.70	0.06
iv drug use	0.6	2.0	5.9
non-iv drug use	0	2.7	1.1
p-value	0.99	1	0.13

Discussion

This observational cohort study describes the prevalence and incidence rates of the viral infections HIV, hepatitis B and hepatitis C in a group of 706 DU on methadone maintenance treatment in Geneva, Switzerland. The period of study was May 1988 to December 1995.

The main findings are that there was an important decline in the prevalence rates of the 3 viruses over time. The incidence rates of HIV and HBV were low; the incidence rate of HCV was high.

The strengths of this study are the high participation and the relatively high follow-up rate, as well as the long period of follow up.

There are several important limitations of this study. The data available on characteristics of participants were limited, the only data collected being sex, date of birth, date of entry into the programme, age at start of treatment and way of using drugs. No systematic data were available on drug career, risk taking behaviour and personality disorders at study entry, nor on methadone dose, use of other drugs or behaviour change at follow up, nor on reason of end of treatment. Also the measure of intravenous drug use was rather crude. The participants who entered treatment before 1988 represent the survivors, so there is a possibility of selection bias.

Study population.

The average age at entry fluctuated for the different years that subjects started MMT, with a peak between 1990-91. The lower age in older treatment cohorts could be due to a selection bias, older persons having died or stopped MMT before this study started in 1988 (see below). The lower age in recent cohorts probably reflects the change in cantonal MMT eligibility criteria in Geneva after 1991. At that time new MMT possibilities were created, and the former criteria of heroin dependence of at least 2 years and 2 previous withdrawal attempts were no longer necessary to receive MMT. Waiting lists for MMT have almost disappeared, and the average delay between initiation of dependence and first demand of treatment has decreased (106).

The proportion of lifetime injection, based on self reporting, was high (83%). Under- or over-reporting of lifetime injection can not be excluded. However, several studies suggest that self-reports of HIV risk behaviour by IDU are reliable (114,115). No distinction was made in this study between an IDU having injected once in his or her lifetime or someone having injected several times daily for many years. The proportion of injectors decreased over time in this study. This corresponds to declining choice of this mode of drug administration observed in recent years in Geneva at needle exchange and other treatment sites (106,107).

It is not possible to say if this study group is representative of the general population of DU in Geneva. We can assume that in general those seeking treatment are not the same as those actively using drugs. Several studies conclude that treatment status as well as type of treatment are related to sample characteristics, but this is not consistently related to HIV infection risk behaviour. In an Australian study (116) those never in treatment had a lower level of HIV risk-related injecting behaviour compared to those currently or previously in treatment. An American study found that in-treatment IDU were older, better educated and less often members of ethnic minorities (suggesting lower HIV-risk) then out-of-treatment IDU recruited at counselling centres or in jail (117). Extrapolation of data from this study to the general population of DU should be done with extreme caution. This caveat applies even more so to the incidence data compared to prevalence data, since the prevalence data reflect the risk taking behaviour of those out of treatment and the incidence data reflect the risk taking behaviour of those remaining in treatment.

Prevalence

Data on the prevalence rates of antibodies to HIV, HBV and HCV showed common patterns of decline over time. Prevalence rates were expressed per year of entry into MMT as well as per year of birth. An initial increase in prevalence rate was noted: for those starting MMT in 1984-85 compared to those who started before that time the prevalence rate was higher and decreased afterwards. Similarly those born before 1956 were less infected then those born between 1956-1960, and infection rates declined for following birth cohorts. All tests for trend were significant.

The initial increase could be due to a selection bias we might call a "healthy drug user" effect. Since this study only started in 1988 the infected drug users from the oldest cohorts could have died from AIDS, AIDS related or other diseases before the start of the study. The resulting study group would then consist of a relatively healthy population. An alternative explanation is that around 1985 health concerns raised by the AIDS epidemic initially brought high risk DU into treatment, resulting in a higher HIV prevalence at that time.

The decline in overall prevalence after this initial increase could be due to:

- Selection bias within the study sample due to differential refusal. This cannot be excluded, but it is unlikely that this could explain the main effects observed in this study. Participation rates were high, estimated at almost 90% during the whole study period.
- Confounding due to an increase in the proportion of non-injectors. As mentioned before, the proportion of non-injectors increased from less then 3% for the oldest cohort to around 30% in more recent cohorts. Prevalences for all 3 viruses were significantly lower for non-injectors and none of them was infected with HIV. However, when the group of injectors only was analysed separately the decrease in prevalence remained significant.
- Misclassification of HIV, HBV, HCV status. There is a window period of up to 3 months after HIV infection before the HIV antibody test is positive. Testing for HIV antigen early after infection is feasible but was not done in this study. For HBV and HCV infection a similar window period exists. Otherwise sensitivity and specificity of all three tests are high. In any case, should there have been misclassification, it is unlikely to be different in the various time periods, so this would not explain a change in prevalence over time.
- Vaccination, for HBV infection only. HBV vaccine has been available for over 10 years. All study participants were offered vaccination once in MMT, this was more systematically performed after 1991 compared to the years before. In 1994 the Cantonal Medical Office started a free vaccination campaign for drug users. Since the prevalence rates reflect an individual's risk behaviour before the start of MMT,

it is unlikely that the prevalence rates for HBV infection were influenced by vaccination practices, but incidence rates could have been.

The most likely 2 explanations for the decrease in prevalence rates are:

- Admission of lower risk DU in recent years and decrease in out-of-treatment time. These data are not available, however average age at start of treatment decreased after 1991 (see above). There have been no reports in Geneva suggesting that DU have started using drugs at younger age, so this suggests that delay between start of dependency and start of MMT in this group decreased over time, as has been observed elsewhere in Geneva (106).
- A real change in behaviour of injecting drug users, more "safe sex, safe drug using". In this study systematic data on HIV and hepatitis related behaviour at the start of treatment are missing, with only some cross-sectional surveys having been performed (77,90,109). These studies showed that over 80% of participants were sharing injection equipment before 1987, this declined to 5% for HIV positive and 29% for HIV negative individuals in 1989, and in 1994 these numbers were 0% et 9% respectively. Increased condom use was noted as well. This reduction in HIV risk behaviour over time has been described in other studies as well (74,75,78,81,118,119).

Calculation of odds ratios gives a more direct estimate of the risk of prevalent HIV and hepatitis infection for different birth and treatment-entry cohorts.
Recent cohorts (born after 1967, started MMT after 1992) were likely exposed to HIV prevention campaigns before the start of a drug using career. Oldest cohorts (born before 1960, started MMT before 1988) consist of individuals who probably had started using drugs before prevention campaigns started. The cohorts in between were probably a mixture of prevention-exposed and -unexposed DU. The crude odds ratios for HIV infection, for middle and oldest versus recent birth cohort, were 13.4 and 18.0, for treatment-entry cohorts (early and middle versus recent), they were 4.7 and 10.7, respectively. Among injectors only the crude and adjusted odds ratios were slightly lower (as can be expected), and still highly significant, with the exception of the adjusted odds ratio for the middle vs. recent treatment-entry cohort. The fact that

the odds ratios for treatment-entry cohorts are smaller than for birth cohorts is probably due to the fact that in 1991 the admission criteria for methadone treatment changed and many "old and recent" DU entered into treatment. There is thus a dilution of the birth cohort effect. The odds ratios adjusted for year of treatment-entry or year of birth are all lower than the crude odds ratios, suggesting that part of the protective effect is due to a decrease in time between initial dependency and first MMT.

Odds ratios for HBV and HCV infection show the same tendencies. Comparison of odds ratios of the whole group with injectors only shows that only part of the cohort effect is due to a reduction in the proportion of injectors. All odds ratios indicate however that there is an important decrease in the probability of being HIV/HBV/HCV infected for younger DU, independent of injection behaviour.

Incidence

Follow-up was available for almost 80% of participants who entered the study before 1995. This follow-up rate is high compared to many studies (cf. Table 2).

Incidence rates were calculated using the Mead Morgan method which does not assume seroconversions at mid-point between last negative and first positive tests. (44,51). Rather it is assumed that there is an an equal risk of seroconverting on any day between tests when the seroconversion occurred. The advantage of this method is that it gives a generally similar but smoother and more realistic estimate than the mid-point assumption, which itself gives an artificially low estimate of incidence at the beginning and the end of the study interval.

The overall HIV incidence rate was 0.6 per 100 person years of follow up, the HBV incidence rate was 2.1, and the HCV incidence rate was 4.3. The HIV incidence is low compared to other studies of DU (see Table 2), but it should be kept in mind that this study was done in a treatment setting. Heroin use in this group still occurs, but at a considerably lower rate than before treatment. Since data on HIV incidence in a real control group (DU before or out of treatment in Geneva) is missing it is not possible to say to what extent this low incidence is due to the treatment itself. However, Garbino

(120) at the Division of Infectious Diseases attempted to identify risk factors for the acquisition of HIV, HBV and HCV. He collected data up to April 1995 and found among 74 drop outs of the GMCS one seroconversion for HIV, one for HBV and six for HCV. The incidence rates per 100 person years of follow-up were respectively 0.7 for HIV, 1.8 for HBV and 12.5 for HCV. In this selected out of treatment group the HIV seroconversion rate appears to have remained low. The fact that among young DU HIV prevalence is low suggests that there is a treatment-unrelated independent cohort effect of low HIV incidence in recent years, perhaps related to the other HIV related prevention campaigns.

Neither injection behaviour nor gender were identified as risk factors for HIV seroconversion. It should be kept in mind that the sample consisted of a predominantly male and injector population, consequently the groups of women and non-injectors are small (n=160 and 119) and estimates of incidence rates in these subgroups less accurate.

The low number of HIV seroconversions did not allow any multivariate statistical analysis. However, all HIV seroconverters were interviewed about their risk behaviour. Five of them were IDU, for one of them drug using behaviour was unknown. Two seroconverters (1 female) reported both unprotected sexual intercourse with partners with unknown serology and exchange of used syringes. Two seroconverters denied the exchange of used seringes, but admitted to unprotected sexual intercourse, one with casual partners, one with a known HIV seropositive partner. Two seroconverters denied the possibility of sexual transmission, but admitted to the exchange of used syringes. The two cases had been diagnosed as borderline personalities, and had been taking risks while injecting cocaine with friends. One of them committed suicide 5 months after seroconversion.

In summary, of six seroconverters two had possible sexual exposure, two had exchanged syringes, and two had both risk factors. These cases suggest the existence of subgroups among DU with high HIV risk, such as cocaine users, those with psychiatric comorbidity and those with HIV seropositive partners.

The decline in HIV-incidence over time is encouraging. Nevertheless the challenge of maintaining behaviour change over the long term remains problematic (121,122).

HBV incidence in this cohort should have been zero, since HBV vaccination was proposed to all study participants. Reasons for refusal or non-compliance with vaccination have not been searched for. Most HBV seroconversions occurred before the reorganisation of the medical service at the Phenix Foundation, so it could be that part of the reason for lower than expected vaccination rates was due to insufficient medical supervision. Again, the time trend indicating no HBV seroconversions in the last 2 years is encouraging.
HBV seroconverters have not been interviewed systematically. However, among the 5 persons who seroconverted for HBV 4 were injectors (80.0%) compared to 70.0% of those who did not seroconvert for HBV (OR 1.71, p=0.63).

Less encouraging are the findings with regard to HCV infection. The incidence rate per 100 person years was 4.3, with no decline over time. This means that at the PF, which has around 350 patients of whom at present around 200 HCV remain uninfected, there are still approximately 9 new cases of HCV occurring every year, and this is in an informed group. In Geneva, with an estimated 2500 DU (half of them in MMT, at least half of them HCV infected) we can expect at least 54 new cases of HCV due to drug use per year. Garbino's data (120) suggest that among out-of-treatment DU the HCV incidence is higher, so the number of cases is probably even higher.
Among the 12 HCV seroconverters 11 were injectors (91.7%) compared to 58.8% of those who did not seroconvert for HCV (OR 7.7, p=0.02). Systematic data on the sharing of injection equipment are lacking.

An interesting finding was the higher rate of HCV seroconversions among women (9.6 per 100 person years compared to 2.7 in men), although this difference did not reach significance (p=0.06). Gender differences for HCV incidence have not been reported elsewhere. Some studies showed a higher HIV incidence (49,50) or higher HIV prevalence (27) among women, others (29,34,123) showed no gender difference. One study found a higher incidence for HBV, but not for HIV and HCV, among women (42). The Montreal study found a higher HIV incidence among men (31).
Dwyer et al (86) explored gender differences in HIV risk practices. They found, in a cross-sectional survey of a population of mainly out-of-treatment IDU, that female

injectors were more likely to report sharing needles, injecting heroin more often in a given month, and sharing with someone they later found out was HIV seropositive. They were also more likely to have had more sexual partners, to have been engaged in prostitution, and to have had a sexual partner who was currently an IDU. It would be interesting to investigate further a possible gender difference in risk behaviour.

Selective loss to follow-up can induce bias if either high- or low-risk individuals are involved. In this sample drop-outs were more often female, and less infected by HCV, with no other differences being found. Again, not enough data on behavioural aspects were available to conclude whether a bias in incidence estimates was introduced and whether such a bias leads to an under or over estimation.

The prevalence as well as the incidence of hepatitis B and C were high compared to HIV. Other studies also show that among DU infections with HBV and/or HCV occur relatively frequently compared to infection with HIV (cf. Table 2). Some investigators have proposed using HBV/HCV incidence as a more sensitive outcome measure in studies of HIV prevention activities (124). Others state that the drug injecting population in general becomes rapidly saturated with these two viruses, creating uncertainty as to the potential sensitivity of HBV/HCV as a surrogate marker for HIV (59). In the Dutch study van Ameijden et al (19,42) documented a decreasing HIV incidence while HBV and HCV incidence remained stable. HIV prevalence at study entrance was also lower than HBV/HCV prevalence (30 vs. 7%). The authors state that IDU at risk for HIV at study entrance might differ from those at risk from HBV/HCV, and that as a result monitoring acute hepatitis infection may not reflect the spread of HIV.

HIV incidence was low in this study. HBV incidence was 3.5 times higher and HCV incidence 7 times higher than HIV incidence. Should the conclusion be that DU in this cohort are still practising risky injection or sexual behaviours and that HIV prevention has failed? Or should it be that HIV prevention has maintained its goals but prevention of hepatitis should be improved? An hypothesis, based in part on clinical experience, would suggest that sharing of injection equipment and paraphernalia as well as unprotected sexual relations still occur, but mostly with stable and/or known HIV

negative partners. Knowledge about HIV and one's HIV status among drug users is in general quite good, and DU have changed their behaviour accordingly (4,27,36,74). However, there is much confusion about hepatitis. Often DU do not know their HBV/HCV status, or assume they are protected against all hepatitis after having received a HBV vaccination. Even among HIV uninfected DU prevalence of HCV is high, so if sharing of injection equipment within this group occurs, the risk of infection with the very virulent HCV is high. Testing of this differential knowledge hypothesis by a simple cross-sectional survey is clearly warranted.

Conclusion

As Stimson writes (125) the main methodological difficulty in the analysis of policy and practice with respect to drug use and HIV infection is to draw links between event and outcome. In particular it is difficult to assess the impact of interventions on the health behaviour of DU, and to assess the link between behaviour changes and trends in HIV infection.

This study showed an important decline in the prevalence rates of HIV, HBV and HCV infections at start of methadone treatment in later birth cohorts of drug users. This is consistent with a major change in risk taking behaviour even before treatment starts, partly by a shift from injecting drugs to smoking or inhaling and partly by the adoption of safer injecting behaviour. However, a change in the factors selecting DU into treatment should also be considered as an explanation for this trend.

In Geneva several HIV prevention measures were undertaken in addition to the national information campaigns after 1986. Syringes became available in pharmacies in 1987. A bus exchanging syringes and needles started its activities in 1991. Methadone treatment became widely available. Drug treatment programmes changed their policies in order to attract more clients. Although a causal link cannot be drawn between these interventions and the declining prevalence over time as well as the low incidence of HIV infection in the study sample, the success of the Geneva public health policy and an important behaviour change among DU are clearly suggested. Data from this study should be combined with data from other sources (AIDS case incidence, needle-exchange, other drug treatment centres) to confirm this conclusion.

Many new cases of HCV infection still occur, warranting marked improvement of HCV prevention strategies. The focus of public health intervention should shift to a combined focus on HIV and hepatitis.
Identification of individuals at high risk for infection such as partners of infected persons, females, and those with psychiatric diagnoses could be useful if it were accompanied by an appropriate intervention to assist individuals to change risk taking

behaviour. Maintaining safe behaviour is another issue. With the impending threat of a cocaine epidemic which is gaining momentum, the surveillance of trends in behaviour and in viral infection rates in DU should continue in Geneva.

Glossary of abbreviations

AIDS= acquired immune deficiency syndrome

CI=confidence interval

CLVS=Central Laboratory of Viral Serology

detox=detoxification center

DID=Division of Infectious Diseases

DU=drug user(s)

ETC=Ermitage Therapeutic Centre

FU=follow up

GMCS=Geneva Methadone Cohort Study

HBV=hepatitis B virus

HCV=hepatitis C virus

HIV=human immunodeficiency virus

IDU=intravenous drug user(s)

IT=in treatment setting

LSD=lysergic acid diethylamide

MMT=methadone maintenance treatment

n.a.=not available

non-IDU=non injecting drug user(s)

OT=out of treatment setting

PF=Phenix Foundation

SD=standard deviation

STD=sexually transmitted disease(s)

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