HIV outbreak among injecting drug users in Finland

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To my family

ABSTRACT

Background and aims: An HIV outbreak among Finnish injecting drug users (IDUs) occurred in 1998. By the end of 2005, 282 IDUs were infected, most of them by recombinant virus CRF01_AE$_{Fin}$ of HIV. After a rapid spread, the outbreak subsided, and the prevalence of HIV among IDUs remained low (<2%). The purpose of the study was to describe the outbreak in order to recognise factors that have influenced the spread and restriction of the outbreak, and thus to find tools for HIV prevention.

Subjects and Methods: Data on IDUs newly diagnosed HIV-positive in the Helsinki University Central Hospital area between 1998 and 2005 was collected through interviews and patient documents. Study I compared markers of disease progression (CD4 cell count and viral load) between 93 Finnish IDUs and 63 Dutch IDUs representing two seroconverter cohorts infected by different subtypes of HIV. In study II, sociodemographic data and geographical distribution of 98 Finnish IDUs diagnosed in 1998-2000 was compared to data on 47 IDUs diagnosed in 2001-2003, and combined with the spatial distribution of employed males. In study III, risk behaviour data from interviews of 89 HIV-positive IDUs and 207 HIV-negative IDUs from the Riski cohort was linked, and prevalence and risk factors for unprotected sex were evaluated. In study IV, data on 238 newly diagnosed IDUs was combined with data on Finnish sub-epidemics among men who have sex with men (MSM) (n=396) and heterosexuals (n=279) between 1985 and 2005, and trends and risk factors for late HIV diagnosis (CD4 cell count <200/μL, or AIDS within 3 months of HIV diagnosis) were analysed.

Results: Shortly after HIV infection, Finnish IDUs infected with CRF01_AE$_{Fin}$ exhibited higher viral loads than Amsterdam IDUs infected with subtype B. Six months after seroconversion the predicted CD4 lymphocyte levels did not differ (535 cells/μL and 551 cells/μL, respectively), and there was no difference in CD4 development. The Finnish IDU outbreak spread and was restricted socially in a very marginalised IDU population and geographically in areas characterised by low proportions of employed males and low income. Up to 40% of the cases in the two clusters outside city centre had no contact with centre, where needle exchange services were available. Up to 63% of HIV-positive and 80% of HIV-negative sexually active IDUs reported inconsistent condom use within past 6 months. Unprotected sex was associated with steady relationships and recent addiction treatment. Compared to other transmission groups, HIV-positive IDUs were diagnosed

earlier in their infection. During 1998-2001 the median CD4 cell count was 490 cells/ μL, and only 6% of IDUs were diagnosed late. The sub-epidemics among MSM and heterosexuals were also detected relatively early in 1980's, with high median CD4 counts during the four first years of the outbreak (575 and 545 cells/μL, respectively) and low proportion of late diagnosed cases (13% and 18%, respectively).

Conclusions: The high viral load in early HIV infection may have contributed to the rapid spread of recombinant virus in the Finnish outbreak. The outbreak was restricted to a marginalised IDU population, and spatially to local pockets of poverty. To prevent HIV among IDUs, these pockets should be recognised and reached early by outreach work and distribution of needle exchange and other prevention activities. To prevent sexual transmission of HIV among IDUs, the results suggest that prevention programmes should be combined with addiction care services and targeted at every IDU. Among Finnish IDUs, early implementation of needle exchange and other preventive measures likely played a crucial role in reversing the HIV outbreak.

ABBREVIATIONS

AIDS	aquired immunodeficiency syndrome
ACS	Amsterdam Cohort Study
cART	combination antiretroviral therapy
CI	confidence interval
HAART	highly active antiretroviral therapy
HCS	Helsinki Cohort Study
HIV	human immunodeficiency virus
HUCH	Helsinki University Central Hospital
HCV	hepatitis C virus
IDU	injecting drug user
MSM	men who have sex with men
MMT	methadone maintenance treatment
NEP	needle exchange programme
NGO	non-governmental organisation
NIDR	National Infectious Disease Register
NSP	needle syringe programme
OR	odds ratio
OST	opiate substitution treatment
STARHS	serologigal testing algorithm for recent HIV seroconversion
UNAIDS	Joint United Nations Programme on HIV/AIDS
VCT	voluntary councelling and testing
WHO	World Health Organization

Contents

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original articles referred to in the text by their Roman numerals:

I. Kivela P, Krol A, Salminen M, Geskus R, Suni J, Anttila VJ, Liitsola K, Zetterberg V, Miedema H, Berkhout B, Coutinho R, Ristola M. High plasma HIV load in the CRF01-AE outbreak among injecting drug users in Finland. Scand J Infect Dis 2005;37:276-283.

II. Kivela P, Krol A, Simola S, Vaattovaara M, Tuomola P, Brummer-Korvenkontio H, Ristola M. HIV outbreak among injecting drug users in the Helsinki region: Social and geographical pockets. Eur J Public Health 2007;17:381-386.

III. Kivelä P, Krol A, Partanen A, Ristola M. High prevalence of unprotected sex among Finnish HIV-positive and HIV-negative injecting drug users. Scand J Public Health 2009;37:357-363.

IV. Kivelä P, Krol A, Salminen M, Ristola M. Determinants of late HIV diagnosis in different transmission groups in Finland from 1985 to 2005. Submitted.

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1. INTRODUCTION

HIV has caused one of the world's worst pandemics that has spread over all continents and poses a major challenge to global public health. Where heterosexual transmissions in Sub-Saharan Africa are declining first time in history, the epidemic among injecting drug users (IDUs) is still expanding, especially in Asia and East Europe.[1, 2]

The spread of HIV among IDUs is a complex issue influenced by behavioural, viral, social, political, geographical and economic factors. The parenteral transmission of HIV through infected blood is also more efficient than the sexual transmission mode.[3] In addition, IDUs share other routes of HIV transmission: sexual transmissions and indirectly, vertical transmissions from mother to child.[4, 5] Despite more than 25 years of studies, experience and evidence in HIV prevention among IDUs, the epidemic continues.

In Finland, HIV spread among men who have sex with men (MSM) in 1980's and among heterosexuals some years later. In contrast to many other Western countries that experienced IDU epidemics already in 1980's, the epidemic among Finnish IDUs spread as late as 1998. Thus, the Finnish outbreak is timely and geographically close to the large outbreaks of Eastern Europe, but the size of the outbreak remained small and it was limited mainly to the Helsinki metropolitan area.[6]

The rapid spread of the outbreak made it possible to identify seroconverters, cases where time of transmission can be estimated based on an earlier HIV-negative test. Among these cases, it is possible to study the natural history of HIV infection in the cohort. The whole epidemic was caused by the same recombinant strain CRF01_AE$_{Fin}$, which created a possibility to study differences in disease progression between CRF01_AE$_{Fin}$ and subtype B through international collaboration.[7] Helsinki University Central Hospital (HUCH) provides services in infectious diseases to about 80% of Finnish injecting drug users infected with the recombinant virus. The low threshold treatment system made it possible to collect information of majority of HIV-infected IDUs, and also to reach them for interviews. The data was collected from patient documents, and 151 HIV-infected IDUs were interviewed for the study.

The purpose of this study was to characterise the IDU outbreak in Finland in order to recognise factors that have influenced the spread and the restriction of the outbreak. Understanding the backgrounds and dynamics of this outbreak may help us to find tools for HIV prevention among IDUs.

2. REVIEW OF THE LITERATURE

2.1. Epidemiology of HIV

2.1.1. Global epidemiology of HIV

The first cases of aquired immunodeficiency syndrome (AIDS) were reported from United States (US) in 1981.[8] Human immunodeficiency virus (HIV) was recognised as the cause of AIDS in 1983, and the HIV antibody test became available two years later.[9, 10] By that time, HIV had already spread widely among men who have sex with men (MSM) and injecting drug users (IDUs) throughout Europe and North America.[11] However, recent phylogenetic analyses suggest that the virus began to spread in Africa more than 60 years earlier, near the beginning of the twentieth century.[12] In late 1980's HIV pandemic had reached all the continents and continued to grow.

The global epidemiology of HIV is unequal. The area of Sub-Saharan Africa is worstly affected. In many Sub-Saharan countries, HIV epidemics are *generalised,* i.e. self-sustaining in the population, and the prevalence of HIV in pregnant women is over 1% nationwide**.**[13] In 8 countries of Southern Africa, HIV prevalence exceeds 15%. More than 67% of HIV cases and 75% of AIDS deaths occurred in Sub-Saharan Africa in 2007.[1]

Most countries in the world have *concentrated* HIV-1 epidemics, i.e. HIV infection is detected in specific groups at risk, including MSM, IDUs, sex workers and their regular partners.[13] In large populations like South and Southeast Asia, the numbers of infected persons are high, even if the epidemic in the general population is low. The United States (US) is the country most heavily affected of the industrialised nations. In the US, the epidemic is concentrated in ethnic minorities and groups at risk, and there is a wide geographical variation in HIV prevalence within the country.[14] In Western Europe, HIV has spread mostly among MSM and IDUs. However, heterosexual transmissions have increased, many of them found among immigrants.[1] During 1997-2002 two thirds of all heterosexually transmitted HIV infections diagnosed in Europe were in people from countries with generalised HIV epidemics. This reflects the worsening of the HIV epidemic in Africa during the 1990s and changing world migration patterns.[15]

In Finland and in some other European countries the HIV epidemic is *at low level*, i.e. HIV prevalence remains under 5% in any defined subpopulations.[1,13]

Since 2000, the global percentage of people living with HIV has stabilised. The overall number of people living with HIV has increased to 33 millions as a result of new infections and beneficial effects of more widely available antiretroviral therapy.[1] In Sub-Saharan Africa, most national epidemics have stabilised or declined. In contrast, the most rapidly expanding epidemics are occurring in Central Asia and Eastern Europe.[1] In Eastern Europe, where severe epidemic emerged among IDUs in the late 1990s, the most affected countries are Russia and Ukraine.[1, 16]

2.1.2. Epidemiology of HIV among IDUs

Recent estimates suggest that 16 million people inject drugs worldwide and 3 million of these are HIV-positive.[17] The largest populations of HIV-positive injecting drug users are in Eastern Europe, East and Southeast Asia, and Latin America. Of the 148 countries where use of injecting drugs has been documented, 128 (86%) countries reported HIV infection among injectors. In 2007, countries with largest numbers of injectors were China, the US and Russia, where HIV prevalence among injectors was estimated at 12%, 16% and 37%, respectively.[17]

The geographical distribution of HIV among IDUs varies widely. In Russia, the reported prevalence of HIV infection among IDUs in different regions varied between 8% and 64%.[18] In 2005, the Chinese HIV epidemic among IDUs was reportedly concentrated mainly within seven of the country's 33 province-level divisions.[19]

The development of HIV epidemics among IDUs is diverse as well. Several cases indicate that the prevalence of HIV among IDUs exceeded 50% in short time.[20, 21] The closest example comes from Estonia, where HIV began to spread in 2000, resulting in prevalence of 62% among IDUs and the highest overall prevalence in Europe (1%).[22, 23] There are also cases where after years of low and stable HIV prevalence, the prevalence among IDUs suddenly rose to 25%.[24] On the other hand, a reversed and limited epidemic as the Finnish one has been described e.g. in Orrel, Russia.[25] Lately, countries with large concentrated HIV epidemics among IDUs have reported increased number of sexual transmissions.[1, 26]

2.1.3. Molecular epidemiology of HIV

Subtypes of HIV

HIV entered the human population through cross-species transmission from non-human primates in Africa.[27-29] The HIV-1 strains M (main), O (outlier) and N (non-M, non-O) likely represent different transmission events in Central Africa, while HIV-2 originated in West Africa. The major HIV pandemic is caused by HIV-1 group M strains, which have caused more than 90% of all infections.[30]

HIV exhibits enormous genetic variability. It evolves within the infected person and forms a constantly evolving quasispecies. On the other hand HIV evolves between virus strains in different epidemics, which has resulted in the development of subtypes.[31] Among HIV-1 group M strains, there are 9 subtypes (A,B,C,D,F,G,H,J and K).In addition, there are circulating recombinant subtypes (CRFs) which are constituted from different subtypes and are spreading in populations, and a variety of unique recombinant forms (URF) that are identified only from an single individual.[31]

Six strains dominate the global epidemic. Subtype A is prevalent in East Africa and in former Soviet Union, whereas subtype B is widespread and dominates epidemics in the Americas, Western Europe and Australia. Subtype C accounts for more than 50% of all infections concentrated in Southern and Eastern Africa and India. Subtype D circulates in East Africa. CRF 01_AE is the main strain throughout Asia, and CRF_AG dominates West Africa.[30] To date, molecular typing provides an important tool for tracking the HIV epidemic, mapping transmission networks and monitoring the dynamics of the epidemic.[32, 33]

Clinical significance of HIV subtypes

Even if there are clear genetic and functional differences between the strains of HIV, the clinical implications of subtypes in disease progression and transmission has been difficult to define.[34-39] The results of clinical studies without seroconversion data have yielded conflicting results **(Table 1A).**[40-48] In contrast, studies among HIV infected individuals with known dates of seroconversion have more consistently noticed differences between individuals infected with different subtypes **(Table 1B).**

A study in Senegal of 54 female sex workers reported that seroconverters infected with subtype A progressed clinically more slowly than those with non-A subtypes.[49] In a later cohort from the same study, CRF02_AG-infected women had significantly higher mean viral load during the early stage of infection than did the women infected with other subtypes.[50] In a cohort of seroconverters from Uganda, subtype A had lower viral loads and slower progression than subtype D.[51, 52] Data from a large cohort of seroconverters in Thailand suggest that viral loads in early HIV infection are higher in those IDUs infected with CRF01_AE$_{Fin}$ than in IDUs infected with subtype B but showed no difference in progression.[53] Ethiopian seroconverters infected with subtype C had lower viral loads in the first months after seroconversion than did Dutch seroconverters with subtype B.[54]

Despite the trend that seroconversion studies have found differences in viral loads or disease progression, all studies have their limitations. Most studies include small number of cases, short follow-up, different cohorts, and sometimes many subtypes grouped together (for example "non-A" subtype). The endpoints of the studies differ, and some studies lack viral load measurements. Comparisons of early viral load between studies are

Table 1. Studies that compare different HIV subtypes.

A. Studies without seroconversion data.

Author, year	Subtypes	Study population, country	Subjects	Study period, follow-up	Result	Comment
Galai 1997 [40]	C vs. B	Ethiopian immigrants and Israeli men in Israel	77 vs. 91	1.2/1.7 years	-	No difference in CD4 or CD8 development. Viral load not measured.
Del Amo, 1998 [41]	B vs. non-B	Africans and non-Africans in the UK	1056 vs. 992	1982-1995	+	No difference in survival or progression to AIDS or death.
Neilson, 1999 [42]	C vs. A and D	Pregnant women from Kenya	225 vs. 87	cross-sectional	+	Higher viral loads and lower CD4 cell counts in subtype C.
Alaeus, 1999 [43]	A,B,C,D	1) Swedish patients 2) Ethnic Africans and ethnic Swedes	126 vs. 49 vs. 49	1994-1998 44 months	-	No difference in CD4 decline, viral load or disease progression.
Laurent, 2002 [44]	CRF02_AG vs. other subtypes	Patients from Senegal and Cameroon	207 vs. 128	1996-2001 26 months	-	No difference in survival, CD4 decline or clinical progression.
Kaleebu, 2002 [45]	A vs. D	Ugandan cohort recruited for vaccine study	1045	1995-1998 1.5 years	+	Faster disease progression to death and lower CD4 counts in subtype D.
Fischetti, 2004 [46]	CRF02_AG vs. other subtypes	Blood donor candidates and AIDS patients in Ghana	84 vs. 150	cross-sectional	+	Higher viral load in CRF02_AG among 84 asymptomatic patients.
Vasan, 2006 [47]	A,C,D and recombinants	Pregnant mothers in Tanzania	428	1995-1997 18-83 months	+	Faster disease progression to death, WHO stage IV and CD4 level <200 in subtype D compared to subtype A
de Brito, 2006 [48]	B-GPGR vs. B'-GWGR	Brazilian HIV patients admitted to the hospital	74 vs. 59	2002 cross-sectional	+	Higher CD4 counts, lower viral load, slower progression to AIDS and smaller risk to die in BGWGR

B. Studies with seroconverters.

Author, year	Subtypes	Study population, country	Subjects	Study period, follow-up	Result	Comment
Kanki, 1999 [49]	A vs. non-A	Female sex workers in Senegal	35 vs. 17	1985-1995 Up to 9 years	+	Higher risk to develop AIDS in non-A compared to A subtype.
Morgan, 2001 [50]	A vs. D	Ugandan cohort *	32 vs. 51	1996-1997 1 year	+	Higher viral load in subtype D.
Kaleebu, 2001 [51]	A vs. D	Ugandan cohort *	44 vs. 73	1990-1998 3 years	+	Higher risk for disease progression (stage 3, 4 or death) in subtype D. Viral load not reported, no difference in CD4.
Hu, 2001 [52]	CRF01_AE vs. B	IDUs in Thailand	103 vs. 27	1995-1996 24 months	+	Higher viral load during the first year after seroconversion in CRF01_AE. No difference in CD4 or CD8 development.
Rinke de Wit, 2002 [53]	C vs. B C vs. C´	Ethiopian factory workers vs. Dutch MSM and IDUs	20 vs. 127 vs. 68	1995-2001 4 years	+	Lower viral loads in C than in B during the first months. Lower viral loads in subtype C than in sub-cluster C´. Lower CD4 in C vs. B.
Sarr, 2005 [54]	CRF02_AG vs. non-CRF02_AG	Female sex workers in Senegal	13 vs. 10	1998-2002 13-51 months	+	Higher viral loads in the early stage of infection in CRF02_AG (significant during the second year)

*These studies include prevalent cases (non-seroconverters), not shown in this table

difficult due to differences in the seroconversion intervals. Furthermore, subtypes often cluster within risk and ethnic groups, and host genetics as well as co-infections may confound the results. Finally, subtype-related differences exist in the viral load assays.[55, 56]

Even if it is theoretically possible that novel subtypes with resistance properties could begin to circulate, there is so far no evidence that response to combination antiretroviral therapy (cART) would differ between the subtypes of HIV.[57-60] For vaccine development, the HIV diversity reflected in development of subtypes, is huge challenge.[61]

2.1.4. Epidemiology of late HIV diagnosis

Diagnosis of HIV and AIDS

Diagnosis of infection with HIV can be made by several different kinds of laboratory assays, in most cases by demonstrating the presence of HIV antibodies in the blood.[62] Antibodies against HIV usually become detectable 6-8 weeks after infection; by 12 weeks, nearly all infected individuals are HIV antibody-positive.[62, 63] The new generation of assays also incorporates HIV antigen detection, which shortens the window period with approximately one week.[64]

Diagnosis of AIDS is based on diagnosing one or more indicator diseases (AIDS-defining conditions, **Table 2**) in an HIV-infected individual.[65] In the US, the surveillance definition of AIDS also includes all HIV cases with CD4 cell counts of fewer than 200/μL, whereas the European definition is based only on the typical illnesses.[65, 66]

The reporting of newly diagnosed HIV and AIDS cases varies. To date, most industrialised countries report all newly diagnosed HIV infections as well as AIDS cases, whereas some countries still report only AIDS cases.[67] In resource-restricted settings where no HIV or AIDS case reporting exists, repeat prevalence surveys have served to monitor the HIV epidemic.[68]

Newly diagnosed HIV cases may have been transmitted recently or for years earlier. In HIV surveillance data, the incidence rates of newly diagnosed HIV cases not only reflect new transmissions, but also include individuals infected years before undergoing HIV testing.[69] The delay between the transmission and diagnosis of HIV can be roughly estimated using the CD4 count measured closest to the time of the HIV diagnosis. Since the CD4 cell count decreases over time after HIV infection, high CD4 counts suggest recent transmission, whereas lower counts most likely reflect old transmissions.[70]

During the past ten years, serological tests have been developed that recognise newly transmitted HIV infections (Serological Testing Algorithms for Recent HIV Seroconversion, STARHS).[71] These tests can recognise recent infections (seroconversion within 6 months), and have served to estimate the proportion of newly acquired infections in different populations. The

experiences of countries such as France and Germany suggest that despite their limitations, these tests seem helpful in HIV surveillance and in estimating the true incidence of HIV.[72-74]

Table 2. 1993 European AIDS surveillance case definition, list of indicator diseases.[66]

Bacterial infections, multiple or recurrent in a child under 13 years of age	Lymphoid interstitial pneumonia in a child under 13 years of age
Candidiasis of the bronchi, trachea, or lungs	Lymphoma, Burkitt's (or equivalent)
Candidiases, oesophageal	Lymphoma, immunoblastic (or equivalent)
Cervical cancer, invasive	Lymphoma, primary, of the brain
Coccidioidomycosis, disseminated or extrapulmonary	Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary	Mycobacterium tuberculosis, pulmonary in an adult or adolescent (>= 13 years)
Cyptosporidiosis, intestinal with diarrhea (duration >1 month)	
Cytomegalovirus disease, other than liver, spleen, or nodes in a patient over one month of age	Mycobacterium tuberculosis, extrapulmonary
Cytomegalovirus retinitis (with loss of vision)	Mycobacterium, other or unidentified species, disseminated or extrapulmonary
Encephalopathy, HIV-related	Pneumocystis carinii pneumonia
Herpes simplex: chronic ulcer(s) (duration >1 month) or bronchitis, pneumonitis, or oesophagitis in a patient over one month of age	Pneumonia, recurrent
	Progressive multifocal leukoencephalopathy
Histoplasmosis, disseminated or extrapulmonary	Salmonella (non-typhoid) septicaemia, recurrent
Isosporiasis, intestinal with diarrhea (duration >1 month)	Toxoplasmosis of brain in a patient over one month of age
Kaposi's sarcoma	Wasting syndrome due to HIV

Prevalence of late HIV diagnosis

In the era of cART, early diagnosis of HIV infection is essential to prevention, control and care. Delayed HIV diagnosis appears to be associated with 10-fold higher short-term mortality and at least 2-fold short-term costs.[75-78] Despite earlier initiation of cART, mortality is higher than for those diagnosed earlier.[79] Furthermore, the consequences and costs of late HIV diagnosis are multiplied at the epidemiological level: individuals unaware of their HIV infection for years may be a major source of new infections and thus could represent the driving force of the epidemic.[80-82]

During the past decade, epidemiology of late HIV diagnosis has become an important issue, and increasing number of studies and reviews have been published (**Table 3**).[83-112] The terms to describe delayed HIV diagnosis are

Table 3. Epidemiological studies from Western countries on delayed HIV diagnosis. Studies that include only inpatients are excluded.

Author, year	Country	Study period	Definition	Subjecs (n)	Prevalence	Median CD4	Data on late diagnosis in IDUs, comment
Guy, 2008 [83]	Australia	1993-2006	CD4<200 or AIDS [a]	12313	20% [e]		
McDonald, 2006 [84]	Australia	1985-2005	CD4<200 or AIDS [a]	336	16% [f]		
Begovac, 2008 [85]	Croatia	2001-2006	CD4<200 or AIDS	277	48%		
Plitt, 2009 [86]	Canada	1998-2003	CD4<200	526	28%		IDU not a risk factor
Krentz, 2004 [76]	Canada	1996-2001	CD4 <200	241	39%		IDUs diagnosed earlier than MSM or heterosexuals
Delpierre, 2008 [87]	France	1996-2006	CD4<200 or AIDS [b]	6805	38%		IDUs diagnosed later than MSM
Delpierre, 2007 [88]	France	1996-2003	CD4<200 or AIDS [c]	1077	33%		IDU not a risk factor
Lanoy, 2007 [79]	France	1997-2002	CD4 <200 or AIDS [d]	18721	36%		39%, IDUs diagnosed later than MSM
Lohse, 2005 [89]	Denmark	1995-2003	CD4<200	3941	39%		
Borghi, 2008 [90]	Italy	1992-2006	CD4<200 or AIDS [a]	844	39%	324	Median 445, IDU not a risk factor
Girardi, 2004 [91]	Italy	1997-2000	CD4<200 or AIDS [c]	968	29%		IDUs diagnosed earlier than other transmission groups
Sobrino-Vegas, 2009 [92]	Spain	2004-2006	CD4<200 or AIDS [c]	2564	37%		IDUs diagnosed later than MSM
Castilla, 2006 [93]	Spain	2000-2004	CD4<200 or AIDS [c]	1807	40%		IDU not a risk factor
Santos, 2004 [94]	Spain	1997-2002	CD4<200	470	48%		IDU not a risk factor
Wolbers, 2008 [95]	Switzerland	1998-2007	CD4<200	1915	31%		IDUs and MSM diagnosed earlier than heterosexuals
Lampe, 2007 [96]	UK	1999-2004	CD4<200, median	2386	27% [g]	345	
Chadborn, 2006 [97]	UK	2000-2004	CD4<200	10 503	42%		

Author, year	Country	Study period	Definition	Subjects (n)	Prevalence	Median CD4	Data on late diagnosis in IDUs, comment
Sullivan, 2005 [98]	UK, Ireland	2003	CD4<200	977	33%		
Chadborn, 2005 [75]	UK	1993-2002	CD4<200	14 158	31% [h]		
Sabin, 2004 [99]	UK	1996-2002	CD4<50	719	15%		MSM diagnosed earlier than other groups, only a few IDUs
Gupta, 2000 [100]	UK	1990-1998	CD4<200	9553	36%		32%
Easterbrook , 2000 [101]	UK	1986-1996	Median	5921		334	IDU not a risk factor
Keruly, 2007 [102]	US	1990-2006	Median	3348		371-276	IDUs diagnosed earlier than other transmission groups
Krawczyk, 2006 [103]	US	1996-2005	AIDS at HIV	1209	42%		
Duffus, 2006 [104]	US	1997-2005	AIDS at HIV [b]	4315	41%		
Grigoryan, 2009 [105]	US	1996-2004	AIDS at HIV [b]	27572	42% [i]		42% [i]
Mugavero, 2007 [106]	US	2002-2004	CD4<200	113	49%		
Lyons, 2008 [107]	US	1998-2003	CD4<200, median	277	38%	324	
Gandhi, 2007 [108]	US	1998-2002	CD4<200	4368	51%		
Dybul, 2002 [109]	US	2000	CD4<200	2223	36%		
Klein, 2003 [110]	US	1998	CD4<200	440	43%	254	47%
Samet, 2001 [111]	US	1994-1996	Median	206	37%	280	Median 331 IDU not a risk factor
Samet, 1994 [112]	US	1990-1992	CD4<200	251	30%		History of cocaine use associated with higher CD4

a AIDS within 3 months after HIV diagnosis
b AIDS within 1 year after HIV diagnosis
c AIDS at HIV diagnosis

d AIDS at cohort enrolment
e includes patients diagnosed overseas
f patients from sexual health clinics only

g 17% of patients on ART
h MSM cases only
i IDUs only

diverse (late presenters, late testers, late diagnosis), as are the definitions. Most often late diagnosed person (i.e. late presenter) is defined as a HIV case diagnosed with CD4 count below 200 cells/μL, or with an AIDS defining illness at HIV diagnosis

Broadly, two kinds of studies exist. Most recent studies include all newly diagnosed HIV cases in the defined area and use this number as denominator to calculate the proportion and study determinants of late HIV diagnosis **(Table 3).** There are also studies that use AIDS cases as denominator (i.e. report the proportion and determinants of late-diagnosed cases of all AIDS cases). The latter studies show illustratively that in the era of cART, late diagnosis explains an increasing proportion of AIDS cases and AIDS deaths in Western countries.[113-115] However, the studies that include AIDS cases as denominator cannot be directly compared to those that include all newly diagnosed HIV cases, since the interpretation of the results differs considerably.

Prevalence of late diagnosis varies between 20% and 51%. In Europe, the proportion of late-diagnosed cases is often between 30% and 45%. The percentages of late-diagnosed cases are naturally higher in those studies that use the definition "diagnosed with CD4 count<200 or AIDS", and lowest in those few studies that use the definitions "CD4 cell count <50/μL", or "diagnosed with AIDS". Universal definitions and monitoring of CD4 count at HIV diagnosis are warranted.[116] Late diagnosis tends to be even more prevalent in United States, and especially in developing countries, from where only few studies originate.[117-119] Published studies from Eastern Europe are not available. Interestingly, the few studies that include cases before and after introduction of cART have recorded no decrease in late HIV diagnosis between these periods.[75, 90, 102]

Risk factors for late diagnosis
In most previously published studies, cases diagnosed late were likely to be older, black or non-native, and not tested for HIV previously.[75, 76, 88, 90, 91, 102] In Australia, partners of individuals who came from high prevalence countries were at risk for late diagnosis.[83] In general, low perceived risk for HIV infection is a risk factor for late HIV diagnosis. Among non-migrant heterosexual population in France, late diagnosis was more frequent among longstanding couples and couples with children. Conversely, late diagnosis was less likely among individuals with large number of sexual partners.[88, 120] In some studies, living in a region with a low prevalence of HIV was a risk factor for late diagnosis.[75, 121, 122]

In many studies from Europe, MSM are diagnosed earlier than other transmission categories.[79, 96, 98, 100] Also IDUs often test positive early in their infection, but contrary results are also reported **(Table 3)**.[76, 91, 101] Moreover, many studies omit IDUs or the number of IDUs is small.

An Italian study showed that risk factors for late diagnosis are different from risk factors for late entry to HIV care.[91] IDUs were diagnosed earlier than other transmission risk groups, but IDU was a risk factor for delayed entry to care (56% of Italian IDUs delayed more than 6 months). In addition to IDUs, delayed entry to care was more common among those, who were not tested for HIV before, unemployed, and had received no HIV counselling after HIV test.[91] In an earlier study from Canada (1999), longer delays were reported among young, male and MSM cases.[123]

Strategies to encourage earlier HIV testing
To facilitate early HIV diagnosis, new HIV testing policies have been promoted. In 2006, CDC recommended routine HIV screening in all health care settings for patients aged 13-64 years, unless the local HIV prevalence is known to be less than 0.1%.[124]. New HIV testing guidelines are also considered in Europe, and the cost-effectiveness of increased or routine HIV testing in health care settings is discussed.[82] In the UK, new guidelines for HIV testing recommend HIV testing in a wider range of settings than is currently the case, and lists specific indicator conditions, where HIV test should be routinely recommended.[125]

2.1.5. HIV in Finland

HIV surveillance in Finland
HIV infection is a notifiable disease in Finland, reported by the diagnosing laboratories and physicians in each case**.** Reporting and case linking are tied to each individual's unique identity codes.[6] The European case definition for HIV and AIDS is used.[65] The National Institute for Health and Welfare maintains the National Infectious Disease Register (NIDR) for surveillance purposes.[126] The system records major transmission groups and has been in use without major changes since the mid-1980s.[6] In 2006, baseline CD4 cell count was added to the notification form filled by the reporting physician.

Blood and organ donations are universally screened for HIV in Finland. Also, pregnant women are offered HIV testing since 1997, and over 99% accept testing. Voluntary and free HIV testing is available in health centres throughout the country. In addition, HIV testing is offered in biggest cities at STD (sexually transmitted disease) clinics, NGO (non-governmental organisations) AIDS support centres, and within needle exchange programs for IDUs. Voluntary targeted unlinked- anonymous studies have served as additional data sources to address prevalence among MSM and IDUs.[6] Outside blood donor screening, approximately 150 000 HIV tests are performed every year with no significant changes in the number of tests over years (Department of Infectious Diseases Surveillance and Control, National Institute for Health and Welfare).

Epidemiology of HIV in Finland

Finland is a country with low prevalence of HIV (adult HIV prevalence <0.1%).[126] By the end of 2008, cumulatively 2410 HIV cases had been reported. Of these 520 developed AIDS including 285 who had died of AIDS.[126] After introduction of cART in 1996, AIDS cases declined until 2000, when a new increase was observed. Most of these AIDS cases are diagnosed close to HIV diagnosis, and may thus reflect the problem of delayed HIV diagnosis.[6]

In 1980's, HIV was transmitted among MSM, and the numbers of heterosexually transmitted cases were small. Toward 1990's, more heterosexually transmitted cases emerged. From the beginning of 1990's the incidence was relatively stable in both sexual transmission groups until the peak years 2006 and 2007 (**Figure 1**). The annual incidence rates of HIV in Finland (35 cases/million population) had in 2007 risen close to that of other Nordic countries (47-56/million), still being lower than in most Western European countries (50-100/million).[1, 6]

Figure 1. Newly diagnosed HIV cases in Finland among men who have sex with men (MSM), injecting drug users (IDUs) and heterosexual transmissions (National Infectious Disease Register, National Institute for Welfare and Health).
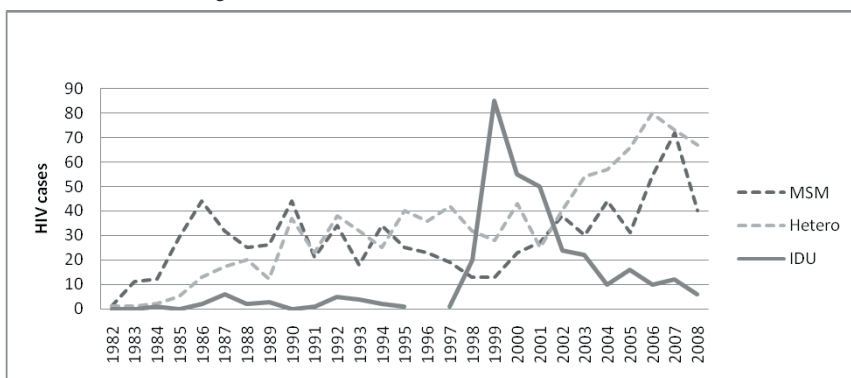
Of the heterosexual cases, 59% occurred among Finnish citizens, with a similar increase in both migrant and domestic cases. In addition, of cases among Finnish citizens, 38% have reportedly been travel-associated. Thus, only a minority of heterosexually transmitted cases reflect changes in the domestic epidemic. In contrast, Finnish citizens account for 89% of transmissions in the MSM group, in which one study has estimated the HIV prevalence to be 4.5% in 2006.[6]

In contrast to many other Western European countries, HIV outbreak among Finnish IDUs occurred as late as 1998. The number of new HIV infections among IDUs increased rapidly until 2000, when it began to decline. Between 1998 and 2008, 338 IDU cases were reported, over 80% of them from the Helsinki metropolitan area. The majority of infected IDUs (88%) were Finnish citizens.[6, 126]

Nearly all IDUs were infected with a recombinant subtype AE (CRF01_AE$_{Fin}$) of HIV, whereas only subtype B was found among the 28 single HIV cases detected among IDUs between 1983 and 1997.[7] Until the Finnish outbreak, CRF01_AE had been prevalent in the Far East but not in Western countries.[127]

The shape of the Finnish incidence curve in IDU epidemic is similar to many other IDU epidemics in 1990's, but the HIV prevalence among IDUs remained low. Between the years 1999 and 2003 more than 7000 samples from needle exchange programs (NEPs) and prisons were tested with a rapid HIV test (voluntary diagnostic test).[128] During the testing period the HIV antibody prevalence decreased from 6.7% to 0.4% in NEPs and from 2.4% to 0.3% among prison inmates with unknown serostatus. Based on prevalence surveys, the HIV prevalence among IDUs in the Helsinki metropolitan area was estimated at 1.2 % in 2007.[129]

Only 14 mother-to-child transmissions have been reported to the National Infectious Diseases Register, all but one of which occurred prior to arrival to Finland. Since 1985, no cases of HIV infection due to domestic blood transfusions or blood products have been reported in Finland.[6]

2.2. Factors influencing the spread of HIV among IDUs

2.2.1. Injecting behaviour

Injecting as a risk factor for HIV infection
Injecting behaviour that leads to HIV transmission has been studied since early in the epidemic.[4, 130] Sharing of needles and syringes was identified as a major route of HIV transmission among IDUs and became the primary focus of HIV prevention programmes in this population.[4, 131] In addition to needles and syringes, sharing drug paraphernalia (cooker, cotton and rinse water) was identified as a likely mode of HIV transmission.[132] Similarly, the HIV risk among IDUs in later epidemics in Thailand and Russia correlate with sharing needles and other equipment, and frequency of injection.[133, 134]

There are also differences in HIV risk factors between the studies and geographic areas, which reflects variation in risk behaviours, social context of risk behaviour, cultural differences, and differences in HIV prevalence.[135] In early epidemics in the US, HIV transmissions were associated with the use of "shooting galleries", unofficial locations where IDUs could rent or borrow needles and syringes and where the injection equipment was often used repeatedly and may have contained contaminated blood.[136] Correspondingly, some countries report a history of having injected drugs in prison the strongest predictor of HIV infection among IDUs.[137, 138]

Risk factors for sharing

Sharing of injection equipment is the most common measure to describe risky injection behaviour. Numerous studies have examined the determinants of sharing injection equipment. The type and frequency of drug use, multiple needle use, severity of drug addiction, unstable living, history of arrest, recent involvement in crime, and lower socioeconomic status have been found to associate with sharing injection equipment.[139-143]Also, sharing is more common among IDUs with multiple injection partners and among those who live or have sex with injection partners.[142, 144, 145] In sociological studies, many characteristics of social networks correlate with sharing injection equipment.[146]

Many attitudes: fear of police, low levels of perceived risk of infection with HIV, lack of knowledge of HIV transmission, and peer influences, influence the risk of sharing.[139, 144, 145] Furthermore, irregular use of NEP services and lack of exposure to AIDS interventions have been shown to be risk factors for sharing.[139, 147] In contrast, treatment contact with general practitioners has been associated with decreased risk for sharing injection equipment.[142, 148]

Most studies report lower prevalence of sharing among HIV-positive than among HIV-negative IDUs. In the Netherlands, the risk factors for sharing were largely the same among HIV-negative and HIV-positive participants.[147] Among HIV-positive active IDUs recruited to a secondary prevention intervention programme, admission to a hospital for drug treatment in the past 6 months, injecting with more than 1 person in the past 3 months, and having depressive symptoms were positively associated with lending syringes.[149] In a longitudinal analysis of the same study, about half of active injectors reported at least one sharing episode within past 6 months. Higher levels of psychological distress were associated with a greater likelihood of drug paraphernalia sharing.[148]

2.2.2. Sexual behaviour

Risk for sexual HIV transmissions among IDUs

Unprotected sex is a well-known risk factor for HIV among IDUs.[4, 150] However, sexual HIV risks have received less attention among prevention programmes targeted at IDUs.[151]

Where prevention programmes have successfully reduced injection-related risk behaviours, unprotected sex has become a major risk factor for new HIV infections among IDUs, especially in mature epidemics. A 19-year prospective cohort study of drug users in Amsterdam identified a decline in HIV incidence and injecting, but not in unprotected sex. New seroconversions since 1996 were related to having a heterosexual contact.[152] In a case control study from San Francisco, risk for HIV seroconversion was higher among MSM and young female IDUs, as well as female IDUs who

reported having traded sex for money. Thus, all the main risk factors for HIV transmission among IDUs in that study were sexual.[153]

Many studies have found the risk for sexual HIV transmissions to be high especially among female IDUs. In a study from Vancouver, HIV-positive sex partner was strongly and independently associated with HIV seroconversion, especially among women.[154] Similar results were obtained from 5 European cities: among IDU women the strongest risk factor for HIV infection was HIV-positive steady partner. In addition, commercial sex and newly diagnosed STIs were risk factors for HIV infection.[155] Among female IDUs in Baltimore, HIV incidence was twice as high among those who had recently had sex with an IDU.[156]

Risk factors for inconsistent condom use

The commonly used measure to describe the prevalence of unprotected sex is inconsistent condom use. Some studies measure inversely consistent condom use or indirect measures as STDs.[131] The prevalence of inconsistent condom use among western IDU populations varies between 40% and 70%.[152, 157-161] Inconsistent condom use has been found to be more common with main partners, when being high on drugs while having sex, and when believing that condom use will decrease pleasure.[162] In some studies, stimulant users, including crack smokers, have been found to engage in high-risk sexual behaviour, often while high on drugs.[162-164] Likewise, unprotected sex is associated with high alcohol consumption, especially among female IDUs.[157, 165] In contrast, the use of condoms has been associated with HIV positivity, having a casual sex partner, greater personal acceptance of condoms, and greater partner receptivity.[166-168]

2.2.3. Role of HIV prevention interventions

Needle exchange programmes (NEPs)

Evidence strongly suggests that NEPs are effective in HIV prevention among IDUs. An ecological study compared the HIV prevalence of IDUs in cities without NEPs to that of cities with NEPs. In the 52 cities without NEPs, HIV prevalence increased by 5.9% per year, whereas HIV prevalence decreased by 5.8% per year in the 29 cities with NEPs.[169]

NEPs are associated with reduced HIV incidence. Des Jarlais et al. have reported a 70% reduction in HIV incidence associated with NEP attendance in New York.[170] Many behavioural studies have shown significant reductions in needle sharing associated with NEP use.[147, 150, 171, 172] Two recent reviews summarise the existing evidence that NEPs are effective in reducing HIV and are unassociated with serious negative consequences, including increasing illicit drug use.[173, 174]

Even if condoms are provided in most NEPs, only a few studies have examined the effects of NEP use on risky sexual behaviour, and the findings

are inconsistent.[175] Some recent studies have reported a significant increase in condom use with the main partners of NEP users.[176, 177]

Among a large number of studies that show the benefits of NEPs, only a few studies have shown negative effects. In two studies from Canada, use of NEPs was associated with HIV positivity, possibly because of their appeal to high-risk IDUs. However, these studies have also been used to show that changing needles and syringes alone is insufficient: NEPs should be combined with comprehensive programmes that include counselling, support and education.[178, 179] To date, most NEPs provide HIV counselling and testing, condoms, HIV prevention education, and referrals to addiction treatment. In addition, some include STD screening and primary health care services.[180, 181]

Extensions of NEPs have also arisen in the form of medically supervised injecting centres. At these centres, IDUs can access sterile injecting equipment, inject pre-obtained illicit drugs under the supervision of nurses, and receive nursing care and addiction counselling.[182, 183] In Canada, these medically supervised safer injection facilities (SIFs) were introduced as a response to continuing HIV and overdose epidemics among IDUs, and have been shown to reduce needle sharing and unprotected sex.[161, 183]

Outreach

Outreach strategies aim to deliver information and services to IDU populations and to establish links between IDUs and health services. Of various models of outreach programmes, many are based on peers who deliver HIV prevention services targeting IDU social networks in community settings.[184] Outreach has been identified as one of three common prevention strategies contributing to low seroprevalence levels in cities where HIV has entered the IDU population.[185] The other two components were easy access to clean needles and syringes and rapid implementation of prevention activities.

One of the first studies to examine outreach programmes in relation to new HIV infections showed a decline in HIV incidence from 8.4 to 2.4 per 100 person-years. High-risk drug use behaviour declined from 100% to 14% compared to 50% among IDUs not in the outreach programme.[186] Numerous subsequent studies have shown outreach progammes to be an especially effective strategy for reaching out-of-treatment IDUs.[184] A significant proportion of IDUs exposed to outreach programmes change their behaviour, a trend associated with lower rates of new HIV infections.[184]

Opiate substitution treatment

Opiate substitution treatment have been shown to reduce the spread of HIV by reducing injecting drug use and sharing of injection equipment.[187-189] Most studies are conducted in Methadone Maintenance Treatment (MMT) programmes, but buprenorphine treatment has proved equally effective.[190]

Opiate substitution treatment also supports adherence to antiretroviral therapy and helps IDUs to achieve treatment results similar to those of other groups.[191] However, the lack of effective substitution treatment for stimulant injectors is a major problem in countries where stimulant use is common.[192] Furthermore, there is less definitive evidence that MMT prevents risky sexual behaviour.[187, 188] Even with reductions in the proportion of multiple sex partners or exchanges of sex for drugs and money, substitution treatments have had only limited effects on condom use.[188]

Behavioural interventions targeted at sexual behaviour

Where most HIV prevention interventions have been shown to decrease risky injection-related behaviour, many studies over the years have shown that these same interventions have little or no effect on sexual behaviour.[187, 193] However, a meta-analysis of 37 randomised controlled trials suggest that behavioural interventions are effective in reducing HIV risk behaviour among IDUs, including unprotected sex. The studies included group or individual interventions that provide an average of eight sessions for a one-month course targeted at both out-of-treatment IDUs and IDUs enrolled in outpatient or inpatient substance abuse treatment programmes.[194] Behavioural interventions were effective in reducing injecting-related and sexual risk-related outcomes as long as they targeted both high-risk drug and high-risk sexual behaviours, and included certain components that address behavioural skills. The effect of the interventions on condom use tended to diminish over time, which suggests the need for "booster sessions" or other additional strategies to maintain the initial effect.

HIV counselling and testing

HIV positivity has been shown to increase condom use among IDUs. In a prospective cohort study in Thailand, those IDUs who seroconverted during the study began to use condoms more consistently.[195] Despite the same serial interventions, HIV-negative IDUs failed to change their behaviour.

The same phenomenon has been described regarding injecting-related risks, and has been called "informed altruism" by des Jarlais et al.[196] In their study in New York, HIV-positive participants reduced their lending of needles and syringes (distributive sharing) more than did HIV-negative participants, but no differences occurred in borrowing (receptive sharing).[196] Several cohort studies and trend analyses indicate that many IDUs reduced their needle and syringe sharing after the HIV epidemic.[147, 197-200] However, it is difficult to distinguish the isolated impact of HIV diagnosis, counselling and testing from that of simultaneous prevention efforts. Furthermore, participating in studies may also serve as an intervention.[200]

Combination of different prevention efforts

It is well recognised that increased HIV testing, or providing only clean needles and syringes without other preventive measures, cannot prevent HIV epidemics among IDUs.[24] The term "harm reduction" is often used in association with NEP and opiate substitution treatment, and essentially means that reducing the adverse consequences of drug use is considered even more important than reducing illicit drug consumption.[201] The "harm reduction packages" introduced by the World Health Organization (WHO), however, include a much wider range of prevention components from needle and syringe programmes to antiretroviral therapy for HIV-positive IDUs (**Table 4**).[202] Such preventive efforts are linked to each other: NEPs offer condoms, HIV testing and referrals to addiction treatment, which again may include HIV testing, behavioural interventions, and other efforts.

Table 4. Comprehensive harm reduction package for injecting drug users (WHO 2009).

Needle and syringe programmes (NSP)
Opioid Substitution Therapy (OST)
Voluntary HIV Counselling and Testing (VCT)
Antiretroviral Therapy (ART)
Sexually Transmitted Infections (STI) prevention and condom programmes for IDUs and partners
Information, Education and Communication (IEC) for IDUs and their sexual partners through Outreach
Hepatitis diagnosis, treatment and vaccination (where applicable)
Tuberculosis (TB) prevention, diagnosis and treatment

Coverage

To prevent HIV among IDUs, interventions must reach adequate numbers of IDUs. Estimates indicate that only 5% of IDUs in the world currently have access to HIV prevention services.[203] The term "coverage" is used to describe the proportion of IDUs in the reach of effective intervention.[204]

A recent multi-method study investigating access to needles and syringes in three Russian cities indicates that fewer than 7% of IDUs have ever had contact with NEPs, as the vast majority used pharmacies to access injecting equipment.[205] In Pakistan, where HIV prevalence among IDUs has been rising since 2003, 32% of IDUs in the area of specific programmes, but only 17% of IDUs nationwide, reported ever having used harm reduction services.[206]

Syringe coverage for heroin injection was studied in 35 large metropolitan areas in the USA. Only 3 syringes were distributed per 100 injection events. Thus, only a small fraction of IDUs appeared to have contact with an NEP, and access varied greatly depending on where the IDUs lived.[207] Syringe coverage improved the longer the NEP was in operation. Moreover, government funding for NEPs contributed to successful NEP coverage.[207]

As these studies show, definitions of coverage vary between studies, and there are problems in measuring and defining acceptable levels of coverage for different intervention types. Including pharmacies and secondary syringe exchange as safe needle sources, and defining the size of the hidden IDU population (as a denominator of coverage) are only a few of the many challenges for the studies.[208] Nevertheless, the studies show that low coverage may explain the failures of harm reduction programmes in many areas.

Recently, UNAIDS (Joint United Nations Programme on HIV/AIDS) and the WHO have published recommendations for "high coverage sites", based on case studies from seven cities in developing and transitional countries. The report lists common features of these successful programmes where more than 50% of IDUs had been reached by one or more HIV prevention programmes.[209] The report concludes that the most significant finding is that high level coverage can be attained, also in developing as well as in transitional countries.

Even if effective risk reduction among IDUs has been achieved, no studies have reported the complete elimination of high-risk behaviour. Among active IDUs in the Amsterdam Cohort Study, the proportion of those who reported lending injection equipment dropped below 10% in five years among HIV-negative IDUs, and below 5% among HIV-positive IDUs, and borrowing dropped below 20% and 10%, respectively.[147]

2.2.4. HIV viral load

Viral load as risk factor for transmission
HIV transmission risk is strongly associated with HIV viral load, which is well documented in sexual transmissions and in mother-to-child transmissions.[210-214] The HIV viral load – and thus the transmission risk – is highest in the early stages of the infection.[215] In a study among serodiscordant heterosexual couples, the infectiousness was 26 times higher during the primary infection than during the asymptomatic phase of the infection, and 7 times higher in the late-stage infections.[215] Even small changes in the HIV viral load may influence the probability of transmission. The likelihood of transmitting HIV by heterosexual contact increases by 20% with every 0.3 log10 increment in the HIV viral load, 40% with a 0.5 log10 increment, and 100% with a 1.0 log10 increment in the HIV viral load, respectively.[216]

Whether these studies can directly be generalised to the IDU population remains unclear. However, since the main transmission mode among IDUs is parenteral, the plasma viral load could be expected to correlate with the transmission risk even more strongly than in heterosexual transmissions, in which HIV RNA in seminal fluid or vaginal secretion may differ from the HIV RNA measured in plasma.[217, 218]

Impact of HIV treatment

Since cART suppresses the viral load, the initiation of effective cART is followed by a reduction in the probability of transmission. This effect has been shown in mother-to-child transmissions and among discordant heterosexual couples.[219, 220] Similarly, a study among MSM in San Francisco showed a 60% decrease in infectivity after the widespread use of cART despite the increase in unprotected sex.[221]

In addition, ecological evidence suggests that ART can reduce transmission risk. Providing free cART to all HIV-infected citizens was associated with a 53% decrease in the estimated HIV transmission rate and contributed to the control of the HIV epidemic in Taiwan.[222] A recent congress report from Canada indicates that cART is also effective in preventing new transmissions among IDUs.[223] Community plasma levels among HIV-positive IDUs correlated with the community HIV incidence rate and strongly predicted HIV incidence independent of unsafe sexual behaviour and the borrowing of used syringes.[223]

Based on mathematical models, some researchers have suggested that universal voluntary HIV testing and immediate start of ART, combined with present prevention approaches, could profoundly impact severe generalised HIV epidemics.[224] Another modelling study from Canada studied the potential impact of expanded cART coverage on an HIV epidemic. The results indicate that the expanded and early administration of cART lead to substantial reductions in the growth of the HIV epidemic and in related costs.[225]

2.2.5. Spatial spread of HIV among IDUs

Spatial differences in HIV risk among IDUs

The geographical distribution of IDUs, HIV infected IDUs, and risk behaviour varies not only at country or city level, but also within cities and communities, which reflects and also creates different "risk environments" in relation to HIV risk.[226, 227]

One study from Vancouver evaluated neighbourhood ecological factors associated with drug use and HIV risk. The results indicated that geographical place of residence was independently associated with HIV infection among IDUs, even after adjusting for risky injecting behaviour.[228]

A study from St. Petersburg examined the spatial distribution of IDUs, of whom 30% were seropositive. The study combined the spatial distribution of HIV, sociodemographic data, and behavioural data on the study population. HIV-infected individuals were tightly clustered, and co-clustered with a high frequency of heroin injection, receptive syringe sharing, being under the age of 24, and living with parents. During the one-year follow-up period beginning in 2002, 20 new seroconversions occurred, of which more than half were located within or adjacent to the clusters.[229]

Geographical data have also been combined with data on social networks. In New Orleans, HIV-positive IDUs were located in areas predicted by low socioeconomic status and high density of alcohol outlets. After adjusting for other variables, however, the spatial structure was insignificant. The authors concluded that the possible "residual spatial structure" in adjusted analyses would have been attributable to core group members.[230] In Canada, the IDUs most central to their network engaged in risky injection practices in the locations where the highest prevalence rates occurred. Using social network analyses, this study showed how specific hotels within the locality of Winnipeg played a key role in generating opportunities for the transmission of HIV.[231]

Spatial data on IDUs and services

Spatial data and geographical information systems have also served to visualise and to study the distribution of IDUs and the distribution of services targeted at IDUs. A study among 597 IDUs from Baltimore showed that the type and frequency of drug use were associated with specific geographical areas, independent of neighbourhood characteristics.[232] In New York (1994-1996), 81% of street-recruited IDUs living near syringe exchange services typically used a syringe exchange, compared to 59% of those who lived more than a ten-minute walk away.[233] Recently, more research has been warranted on geographical place as well as on socio-spatial and political processes related to place that may help to determine were IDU-related HIV risk environments occur.[227]

2.2.6. Social, economic and political context

On an individual level, poverty is an independent risk factor for HIV infections.[234] In addition, several sociodemographic factors are known to be independent risk factors for HIV infection among IDUs: IDU groups with a low level of education, young IDUs, divorced or separated IDUs, and homeless IDUs are at greater risk for HIV infection.[235, 236]

Social and economic factors also have an impact at the population and country level. Studies have noted that IDU epidemics in transitional countries have emerged in eras of social, political or economic changes, which create a "risk environment" for HIV characterised by increased drug availability, increased injecting drug use, and a lack of sufficient coverage of evidence-based responses to HIV outbreaks.[237-239] In addition, also political barriers against harm reduction interventions such as NEP and opiate substitution, and stigma associated with IDUs may indirectly influence the spread of HIV.[239, 240]

The poor coverage of harm reduction programmes is not limited only to developing or transitional countries such as the former Soviet Union. In the US, for instance, political barriers to NEPs are commonplace, even if

the number of programmes has increased throughout 1990s.[181] In a cross-sectional analysis of 96 US metropolitan areas, the prevalence of HIV among IDUs was significantly higher in those areas where laws prohibit over-the-counter syringe sales. However, these laws were unassociated with lower population proportions of IDUs.[241] In a later study, the same researchers reported that a number of police employees, corrections expenditures and drug arrests were positively associated with the prevalence of HIV among injectors. The conclusion was that legal measures had little deterrent effect on drug injecting, and may even contribute to an increase in the number of HIV infections.[242]

Legislation has also prohibited NEPs in Sweden. A study that compared HIV incidence, prevention activities and legislation in Norway, Sweden and Denmark found that HIV incidence and prevalence in the early 1990s remained highest in Denmark, where NEPs were available, but where testing was reduced. In contrast, Sweden had strict legislation, but high testing rates; HIV incidence and prevalence there was lower. The researchers concluded in 2003 that HIV testing and counselling may be more effective than legal access to needles and syringes.[243] In 2006, however, the number of HIV positive IDUs in Stockholm rose, which resulted in changes in legislation that permitted needle exchange programmes.

3. AIMS

The purpose of this study was to characterise the Finnish HIV outbreak among IDUs in order to recognise factors that have influenced the spread and restriction of the outbreak, and thus find tools for HIV prevention and control.

The specific aims of this present work were as follows:

I.   To compare markers for disease progression (CD4 cell count and HIV viral load) between Finnish IDUs infected by the recombinant subtype $CRF01\_AE_{Fin}$ and Dutch IDUs infected by subtype B of HIV;

II.   To study the sociodemographic profile and spatial distribution of HIV-infected IDUs diagnosed in the beginning of the HIV outbreak and those diagnosed later;

III.   To study the prevalence and determinants of unprotected sex among HIV-positive and HIV-negative Finnish IDUs, and thus to examine the potential of the sexual transmission of HIV within and from this population;

IV.   To study the characteristics of and trends in newly diagnosed HIV cases in sub-epidemics among Finnish IDUs, MSM and heterosexuals, and to identify risk factors for late HIV diagnosis and delayed entry to HIV care.

4. METHODS

4.1. Comparison of CRF01_AE$_{Fin}$ and subtype B of HIV (I)

Study population and data collection

The study population comprised 93 HIV-positive IDUs who were confirmed to be infected with CRF01-AE$_{Fin}$, had at least one available CD4 cell count or viral load measurement, and had visited the outpatient clinic of the Infectious Disease Clinic at Helsinki University Central Hospital at least once prior to November 2001. Only individuals with a seroconversion interval of under two years were included. The Finnish cohort was compared to 63 IDUs from the Amsterdam Cohort Study (ACS) who met the same inclusion criteria, but the IDUs were infected with subtype B (**Table 5).**

For each Finnish participant, patient documents were used to establish age, sex, and main illicit drug used, the date of previous negative HIV antibody tests and the date of the first HIV-positive test, CD4 cell counts and viral loads, and AIDS-defining illnesses.

In the Amsterdam Cohort Study, participants were continuously recruited from 1985 onwards and were followed every four months. At every visit, they were interviewed for information on their health status, behaviour and illicit drug use; underwent a physical examination and had blood drawn for laboratory tests. IDUs included in the study were HIV-negative at entry and seroconverted during follow-up.[244]

Seroconversion was assumed to have occurred at the midpoint between the dates of the last negative and the first HIV-positive test. The date of the last HIV-negative test was documented for 58 (62%) Finnish individuals and for all 63 Dutch individuals. For the 35 (38%) Finnish IDUs without a date, it was estimated to be 1 July 1997 based on the following considerations. In March 1998, the first CRF01_AE$_{Fin}$ case was reported to the National Registry of Communicable Diseases. By the end of 1998, a sudden increase in the number of HIV-positive IDUs had been observed in prisons and at the Infections Disease Clinic of the University Hospital, whereas no HIV-positive IDUs had been identified in 1997 despite 919 HIV antibody tests performed only in prisons (Leena Arpo and Matti Ristola, personal communication). Finally, there was very low genetic interpatient variation between the CRF01_AE$_{Fin}$ sequences (< 0.5% in hypervariable regions).[7]

Table 5. Inclusion criteria of HIV-positive injecting drug users (IDUs) in the four sub-studies, study periods, and material combined or compared with the study population of Finnish HIV-positive IDUs. To be included in any of the sub-studies, the participants must have visited the Helsinki University Central Hospital at least once.

	Study population of HIV-positive IDUs	Compared or combined with
Study I Comparison of CRF01_AE$_{Fin}$ and subtype B	**93 IDUs** Infected with CRF01_AE$_{Fin}$ (1998-2001) • Seroconversion interval < 2 years • At least one CD4 measurement or viral load available	**63 Dutch IDUs** Infected with subtype B (1985-1996)
Study II Sociogeographical profile of HIV-positive IDUs	**176 IDUs** (1998-2003) • Socioeconomic and geographical data available	**Geographical distribution of employed males** in the Helsinki metropolitan area by zip codes (City of Helsinki, Statistics Unit)
Study III Unprotected sex among IDUs	**89 IDUs** Helsinki Cohort Study (2002-2004) • Seroconverters • Risk behaviour inverview available	**207 HIV-negative IDUs** Riski study (2000-2002)
Study IV Epidemiology of late HIV diagnosis in Finland	**238 IDUs** (1985-2005) • CD4 cell count available within 90 days of the first visit	**396 MSM and 289 heterosexual transmissions** (1985-2005)

Laboratory methods

At both sites, antibodies to HIV were determined by ELISA and confirmed by western blot. At every visit, T lymphocyte cell subsets were determined by using flow cytometry on fresh specimens. In Finland, the viral load was determined with the Amplicor HIV Monitor test version 1.5 (Roche Diagnostic Systems, Branchburg, NJ). The lower limit of primary quantitation was 400 copies/ml and later 400 or 50 copies/ml. In Amsterdam, the viral load was determined with NASBA, with a lower quantitation limit of 1000 copies/ml (Organon Teknika, Durham, NC). The genetic subtyping of patient viruses was determined by sequencing and phylogenetic analysis of the

env V3 region, and in Finland, also the gag p7 regions from patient plasma samples, as described elsewhere.[7, 245]

Data analysis and statistics

Simple descriptive statistics were used to describe the basic characteristics of the study population. Differences between the cohorts were tested using the chi-square test, Student's t-test or Mann-Whitney U test, as appropriate.

The random effects truncated probit model was used to compare the development of the HIV viral load over time after seroconversion. Values below the lower detection limit were treated as left censored; values above the upper detection limit were treated as right censored.[246] In this model, all viral load measurements were included, except for those points at which antiretroviral therapy was used and for those measured after AIDS diagnosis. Viral loads were log-transformed in statistical analyses. Each individual was allowed to have his or her own intercept and slope around an average population intercept and slope. For viral load, the slope was allowed to differ during the first six months. A Bayesian approach was used to estimate the parameters, beginning with non-informative priors. Posterior distributions were obtained with the Markov Chain Monte Carlo methods, using the WinBUGS programme. Three chains were generated, based on different sets of starting values. Parameter estimates are the medians of the posterior distributions. The range from the 2.5% to the 97.5% quantiles served to quantify the uncertainty in the parameter estimates. This range can be interpreted as a 95% confidence interval (CI) and was referred to as such. If the value zero was outside this interval, the effect was considered statistically significant.

To compare absolute CD4 cell counts and CD4 decline since HIV seroconversion, regression analysis for repeated measurements using a linear mixed model approach was used. Absolute CD4 cell counts were square root-transformed. The regression model, which was developed for the comparison of two cohorts, has been described in detail earlier.[247]

Statistical analyses were carried out using SPSS version 9.0 (Norusis; SPSS Inc., Chicago, IL, USA), SAS version 6.12 (SAS Institute Inc., Cary, NC, USA), and WinBUGS 1.3 (MRC Biostatistics Unit, Cambridge, UK).

4.2. Sociogeographical profile of HIV-positive IDUs (II)

Study population and data collection

The study population consists of 176 HIV-infected IDUs, on whom sociodemographic and geographical background data were available. Of the 213 IDUs who had visited the Infectious Disease Clinic at HUCH at least once prior to October 2003, 83% were included in this sub-study.

Since the first three cases of the HIV outbreak among IDUs in the Helsinki metropolitan area were detected, HIV-positive patients were interviewed regarding their history of injecting drug use, income, housing, education, work, history of addiction care, and imprisonment. Because many of the first cases were noticed to occur in clusters, IDUs were also asked in which areas they had been living or using drugs around the time of their first HIV-positive test result or at the time of infection. Participants could list up to four different geographical areas.

During the HIV-positive IDUs' first visits to the Infectious Disease Clinic, data were initially collected by a social worker through semi-structured interviews for sociomedical purposes. After September 2002, these same data were obtained as part of a cohort study among HIV-positive IDUs. The CD4 cell counts were collected from the hospital data system. The CD4 cell measurements within 100 days of the IDUs' first HIV-positive test results were included.

The socioeconomic data describing the spatial structures of the city in the Helsinki metropolitan area were obtained from the City of Helsinki Statistics Unit. The indicator used was the percentage of employed males aged 25 to 64. This age limit aimed to exclude students and the elderly.[248]

Data analysis and statistics

To detect possible differences in the sociodemographic characteristics of the 176 participants, the early HIV-positive IDU cases newly diagnosed between 1 April 1998 and 31 March 2000 (n=98) were compared to recent cases (n=47) diagnosed between 1 April 2001 and 31 March 2003. To obtain maximum contrast, 31 cases between the groups were excluded. The analyses were also repeated without exclusion of the cases, and the data were divided in two by 30 September 2000.

To describe the geographical dynamics of the HIV outbreak in the Helsinki area, the areas where the IDUs reportedly lived or used drugs were converted into zip codes. The geographical distribution of the areas where the HIV-positive IDUs had been living or using drugs was projected onto maps showing the spatial differences in male employment.

Simple descriptive statistics were used to describe the basic characteristics of the study population. Differences between early and recent cases were tested using the chi-square test, Student's t-test or Mann-Whitney U test, as appropriate. Statistical analyses were carried out using SPSS version 10.0 (Norusis; SPSS Inc., Chicago, IL, USA). The geographic distribution of the HIV cases was analysed using MapInfo Professional version 7.0 (MapInfo Corp., Troy, NY, USA).

4.2. Unprotected sex among IDUs (III)

Study populations and data collection

This study combines data from two cohort studies on IDUs from the Helsinki metropolitan area (**Table 4).** The HIV-positive participants were recruited from among HIV-positive IDUs who were referred to the HUCH between 1998 and 2004, and who had a seroconversion interval of less than two years. Of 225 IDUs, 89 (39.6%) were included in this prospective study, known as the Helsinki Cohort Study (HCS). The intake interviews were conducted over the years 2002, 2003 and 2004.

The HIV-negative participants (n=207) came from the Riski study.[249] Participants were recruited from among needle exchange programme users in three Finnish cities over the years 2000, 2001 and 2002. In our study population, we included only subjects who were interviewed in the Helsinki metropolitan area, and who were found to be HIV-negative in an oral fluid test. The original study design has been described in detail elsewhere.[249]

In both cohorts, only participants 18 years of age and older were included. All the interviews were conducted according to a standardised questionnaire. Questions about sociodemographic background, detailed drug use, and risky injecting and sexual behaviour were the same in both cohorts. Questions regarding behaviour and use of services referred to the six months immediately prior to the interview. The participants were also interviewed regarding any sexually transmitted diseases diagnosed, their use of needle exchange services, and their use of addiction care services (inpatient, outpatient, and through which institution) as well as hospitalisations and periods of imprisonment.

Data analysis and statistics

The combined anonymous data set includes baseline data on the two cohort studies and consists of 296 cases. The outcome was inconsistent condom use, defined as having unprotected sex with any sexual partners within the past six months (used condoms never, sometimes or most of the time). Consistent condom use was defined as always using condoms.

Simple descriptive statistics served to describe the basic characteristics of the study population. Risk factors for inconsistent condom use were analysed with logistic regression using forward and backward selection procedures. In multivariate analyses, risk factors for inconsistent condom use were analysed based only on those participants who reported having sexual partners within the past six months. The analysis was carried out with SPSS 14.0 (Norusis; SPSS Inc., Chicago, IL, USA).

4.4. Epidemiology of late HIV diagnosis in Finland (IV)

Study population and data collection

The study population comprised 934 newly diagnosed HIV-positive patients in the HUCH area between the years 1985 and 2005. The included individuals were over 16 years of age, had visited the clinic at least once, and had a CD4 cell count available between the HIV diagnosis and within 90 days of their first visit to the clinic. All patients were antiretroviral naive. By the end of 2005, NIDR had received 1211 notifications of HIV cases from the HUCH area. Of 1083 patients who had visit the Aurora Hospital at least once, 86% were included. Individuals referred by other hospitals that provide care for HIV infection were excluded as were 16 cases whose first visit took place prior to the July 1985 introduction of the HIV test in Finland (Jukka Suni, personal communication).

Sociodemographic data, possible earlier HIV-negative tests, date of first HIV-positive test, place of HIV diagnosis, date of referral and first visit to the clinic, AIDS-defining illness, death, and end of follow-up were recorded in the dataset. The data were collected from patient documents up to 1997. After 1997, data were available from the observational clinical database of the Infectious Disease Clinic and were complemented with patient documents. CD4 cell counts were available from patient documents, referrals, as well as from the hospital data system. Follow-up data (AIDS-defining illnesses and deaths) were included until the last visit prior to January 2006 or death.

Data analyses and statistics

Late diagnosis was defined as having a first CD4 count below 200 cells/μL or having AIDS (according to the 1993 European AIDS case definition) within 90 days of the HIV diagnosis.[65] Delayed entry to care was defined as having first visited the clinic more than six months after the HIV diagnosis. Newly diagnosed was defined as those referred directly to the Infectious Disease Clinic at HUCH after their first HIV-positive test.

Health care-related diagnosis was defined as having had the first HIV-positive test performed in primary health care (health centres, private doctors or occupational health care) or in secondary health care (hospital wards or outpatient clinics). Non-health care-related diagnosis included HIV diagnoses made at prisons, NEPs, immigrant centres, drug treatment or non-governmental AIDS support centres. Sub-epidemics were defined according to transmission mode (heterosexual, MSM, IDU).

Study period was divided into five four-year intervals based on the year of HIV diagnosis (1August 1985-1989, 1990-1993, 1994-1997, 1998-2001, 2002-2005). The four-year interval was selected in priori based on the fact that the epidemic among IDUs began in 1998. The analysis was repeated using the year 1997 as an alternative cut-off in order to analyse the possible

effect of cART. The interval 1985-1989 was defined as the *first stage* of the sub-epidemic among MSM and heterosexual cases. The other periods were defined as *subsequent stages* of the epidemic.

SPSS 15.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Chi-square tests, t-tests and Mann-Whitney tests served to test for differences between the groups. The multivariable logistic regression model served to identify factors independently associated with late HIV diagnosis and delayed entry to care. For data validation, the analysis was repeated using a 90-day cut-off for time between the HIV diagnosis and the first CD4 count.

4.5. Ethical aspects

The Helsinki Cohort Study among HIV-positive IDUs was approved by the Ethics Committee, Department of Medicine. The Riski study was approved by the Ethics Committee of Epidemiology and Public Health, Hospital District of Helsinki and Uusimaa. The Ethics Committee of Epidemiology and Public Health approved the combination of the cohorts. The participants have provided their written informed consent to participate in the studies.

5. RESULTS

5.1. Comparison of CRF01_AE$_{Fin}$ and subtype B (I)

General characteristics
No significant differences occurred between the 93 Finnish and the 63 Dutch IDUs in mean age at HIV seroconversion (32 vs. 32 years), gender (72% vs. 59% male) or years since beginning injecting drug use (9 vs. 10 years). The main narcotic substance used was amphetamine for 51% of Finnish IDUs, whereas in Amsterdam, 57% injected speedballs (heroin together with cocaine).

The median seroconversion interval was longer in Finland than in ACS (12.8 months vs. 3.9 months, p<0.05). The seroconversions occurred between 1997 and 2001 among the Finnish IDUs, and between 1986 and 1996 among the Dutch IDUs. In the Finnish study cohort, the maximum number of HIV seroconversions occurred in 1998 **(Figure 2).**

The follow-up was restricted to 48 months in the ACS, but the median HIV-positive follow-up was still slightly shorter in Finland (24.3 vs. 29.8 months). During the follow-up, four Finnish IDUs died, and one was diagnosed with AIDS, whereas in the ACS, seven had AIDS, and five died.
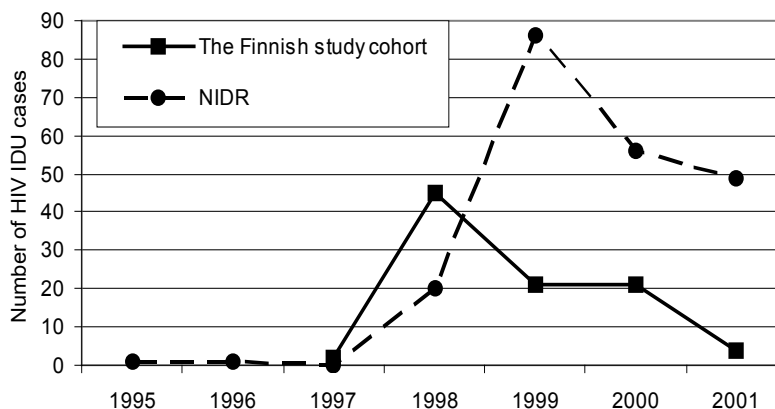

Figure 2. The estimated year of HIV seroconversion for the Finnish study cohort, and the year of first positive HIV test result for all injecting drug uses (IDUs) as reported to the National Infectious Disease Register (NIDR), National Institute for Welfare and Health, Finland.
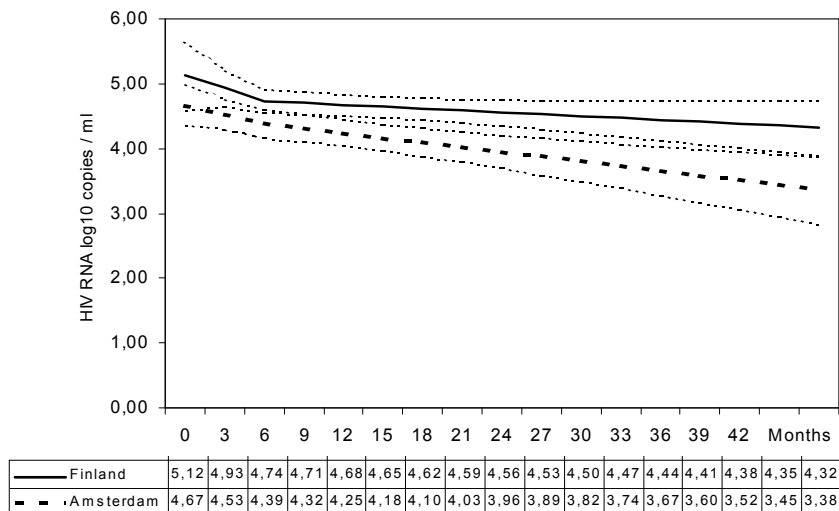
CD4 cell decline and HIV viral loads

The median number of CD4 measurements per individual was four (range 0-15) in Finland and six in the ACS (range 1-13). For both sites, the median number of viral load measurements was four (0-14).
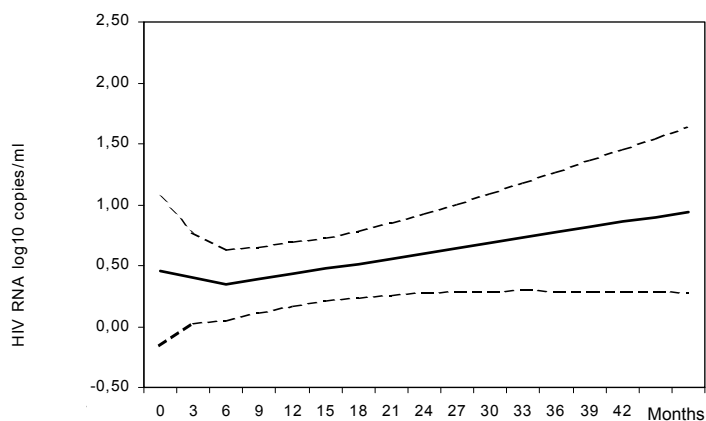
No statistical difference occurred in CD4 cell level or in CD4 cell decline between the Finnish and the ACS cohort during the 48-month follow-up period. The predicted CD4 decline after six months since seroconversion was 67 cells/μL per year in the Finnish cohort and 64 cells/μL per year in the ACS. The predicted CD4 lymphocyte levels six months after seroconversion were 535 and 551 cells/μL, and after 24 months, 425 and 446 cells/μL, respectively.

In the random effect truncated probit model, Finnish IDUs exhibited higher viral loads throughout the follow-up period **(Figure 3).** When analysis was repeated only for those 24 Finnish seroconverters with a narrow seroconversion interval (<6 months), the difference in the viral load between the Finnish and Amsterdam narrow seroconverters was statistically significant from 12 to 48 months after seroconversion.

When the analysis of viral loads was repeated including all the measurements after the administration of ART or after AIDS diagnosis, the proportion of participants with one or more excluded measurements was the same in both cohorts (10%). In this analysis, the model shows still higher viral loads in the Finnish cohort, and the difference between the cohorts was significant from 6 to 24 months after seroconversion. After correcting for gender, the difference between the cohorts remained comparable in magnitude and significance.

A

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	Months
Finland	5,12	4,93	4,74	4,71	4,68	4,65	4,62	4,59	4,56	4,53	4,50	4,47	4,44	4,41	4,38	4,35	4,32
Amsterdam	4,67	4,53	4,39	4,32	4,25	4,18	4,10	4,03	3,96	3,89	3,82	3,74	3,67	3,60	3,52	3,45	3,38

B

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	Months	
HIV-RNA difference	0,45	0,40	0,34	0,39	0,43	0,47	0,52	0,56	0,60	0,65	0,69	0,73	0,77	0,82	0,86	0,90	0,94
95% confidence interval, higher	1,06	0,77	0,63	0,66	0,69	0,74	0,79	0,86	0,93	1,01	1,09	1,18	1,27	1,36	1,45	1,55	1,64
95% confidence interval, low er	-0,16	0,03	0,05	0,12	0,17	0,21	0,24	0,26	0,28	0,29	0,30	0,30	0,30	0,30	0,29	0,29	0,28

Figure 3. A) HIV RNA loads (log copies/ml) in Finland and Amsterdam. **B)** HIV RNA load difference (log copies/ml) between the Finnish and the Amsterdam cohort. Random effect model allowing for left and right censored data, 95% confidence intervals.

5.2. Sociogeographical profile of HIV-positive IDUs (II)

General characteristics

Of all the 176 HIV-positive IDUs, the mean age was 33 (16-63 years), 86.4% were living in Helsinki city, and 72.2% were male. Only 1.9% were employed at the time of the first interview, 22.4% had been working within the past five years, and for 43%, the main source of income was social security. The number of homeless (no official address) was 65.3%, and 82.0% had fewer than nine years of education, 15.1% were living with a partner, and 35.3 % had children (<18 years), but only 10.5% of them were living with their children; 43.5% had been admitted to a psychiatric hospital care at least once.

The sociodemographic characteristics of the 98 early and the 47 recent cases appear in **Table 6.** The recent cases were significantly older, and had used injecting drugs for a longer period than had the early cases. There were no significant differences between the early and recent cases in the proportion of young drug users (age <25 years, 14.3% vs. 6.4%) or in the proportion of IDUs who had begun injecting for fewer than five years prior to their first visit (26.7% and 14.6%, respectively).

Additional analyses that either exclude cases interviewed more than one year after HIV diagnosis or include cases between April 2000 and March 2001 yielded similar results.

Table 6. Sociodemographic characteristics of early and recent HIV-positive injecting drug user cases in the outbreak in the Helsinki metropolitan area (early cases: first HIV-positive test between 1 April 1998 and 31 March 2000; recent cases: first HIV-positive test between 1 April 2001 and 31 March 2003).

	Early cases n=98	Recent cases n=47	p value
Age (years, mean, range)*	32 (16-56)	36 (20-62)	<0.05
Male (%)	70.4%	78.3%	0.323
Main drug amphetamine	74.1%	77.8%	0.670
Duration of injecting (years, mean, range)*	10.7 (0-32)	14.3 (1-37)	<0.05
Homeless	66.3%	66.0%	0.966
In employment	2.2%	2.4%	0.801
History of imprisonment	74.7%	72.3%	0.762
Lack of further education (≤9 years)	83.8%	84.4%	0.919
History of addiction rehabilitation or detoxification or both	61.7%	70.5%	0.109
First CD4 count (cells/μL)	579	431	<0.01

* at the time of the first HIV-positive test

Sociogeographical distribution of HIV-positive IDUs

The reported geographical areas where the IDUs lived or used drugs during the time of their HIV diagnosis appear in **Figure 4.** Among recent cases, only one additional area (suburb of Myyrmäki) was mentioned. When the distribution of employed males was compared to the distribution of areas mentioned by the IDUs, a consistent pattern emerges: all IDU clusters outside the city centre are located in areas with low male employment rates.

When examining the two largest geographical clusters outside the downtown separately, 39% (15/38) of the persons who lived or used drugs in the suburb of Maunula, and 40% (8/20) of those in the suburb of Malmi, did not mention the centre of Helsinki as one of the areas.
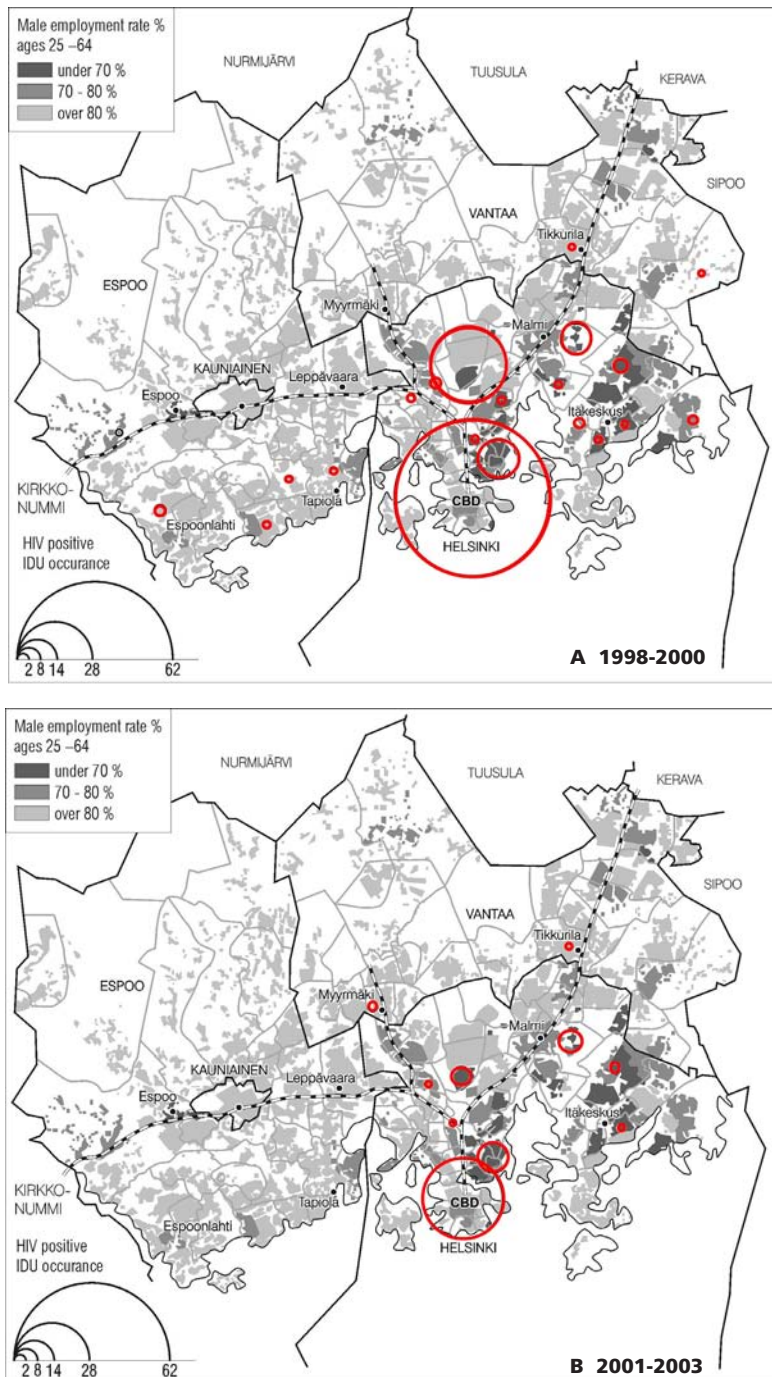
Figure 4. Geographic areas in the Helsinki metropolitan area, where the HIV-positive injecting drug users (IDUs) lived or used drugs during the time of the HIV diagnosis, and male employment rate. Map A shows the areas reported by the early cases, map B the areas reported by the recent cases of the outbreak (1-4 observations / person).

5.3. Unprotected sex among IDUs (III)

General characteristics

Several significant (p<0.05) differences emerged in the characteristics of the HIV-positive and HIV-negative IDUs. The HIV-positive IDUs were older (median age 36 vs. 26 years), more often unemployed (98% vs. 89%), and hepatitis C antibody-positive (96% vs. 51%) than were the HIV-negative IDUs. The main drug was amphetamine for 52% of the HIV-positive participants and for 36% of the HIV-negative participants. Of the HIV-positives, 78% had a history of imprisonment and 72% reported injecting in the past six months, whereas the proportions among the HIV-negatives were 38% and 100%, respectively.

Of the HIV-positive IDUs, 28% had undergone inpatient addiction treatment (with or without outpatient treatment), 56% had undergone outpatient treatment only, and 26% had used no addiction treatment services, whereas the proportions among the HIV-negative group were 57%, 10% and 33%, respectively. At the time of the interview, 18% of the HIV-positive IDUs were on methadone substitution treatment and 2% on buprenorphine substitution treatment, whereas the proportion in the HIV-negative group was 0.5% and 7%, respectively.

Of the HIV-positive IDUs, 18% reported having lent needles, syringes or other injecting equipment at least once in the past six months. Borrowing or lending injection equipment was reported by 62% of the HIV-negative IDUs.

Sexual behaviour

The sexual behaviour of the HIV-negative and HIV-positive IDUs appears in **Table 7.** The HIV-negative participants were more often sexually active than were the HIV-positives (87% vs. 70%). Inconsistent condom use was reported by 63% (39 of 62) of the HIV-positive and 80% (144 of 181) of the HIV-negative sexually active IDUs. Of the HIV-positive IDUs, 33% had multiple sex partners compared to 42% of the HIV-negative group. Among the male IDUs, 2% of the HIV-positive participants and 4% of the HIV-negative participants reported having sex with other males.

Table 7. Sexual behaviour of HIV-positive and HIV-negative injecting drug users in the past six months.

Variable	HIV-positive (n=89) Helsinki Cohort Study	HIV-negative (n=207) Riski study
Number of partners		
0	28 (31.5%)	26 (12.6%)
1	32 (36.0%)	93 (44.9%)
2-6	26 (29.2%)	77 (37.2%)
>6	3 (3.3%)	10 (4.8%)
Partner type		
Steady partner only	27/62 (43.5%)	89/181 (49.2%)
Casual partner only	26/62 (41.9%)	26/181 (14.4%)
Steady and casual	8/62 (12.9%)	56/181 (30.9%)
Commercial sex partner	6/62 (9.7%)	15/181 (8.3%)
Inconsistent condom use with*		
Steady partner	26/35 (74.3%)	127/155 (82.5%)
Casual partner	15/34 (44.1%)	48/82 (58.5%)
Commercial sex partner	0/(0%)	9/30 (30.0%)
Any type of partner	39/62 (62.9%)	144/181 (79.6%)
No condom/last occasion with*		
Steady partner	15/35 (42.9%)	101/155 (65.2%)
Casual partner	10/34 (29.4%)	38/82 (46.3%)
Commercial sex partner	0/(0%)	4/15 (26.7%)
Sexually transmitted infections diagnosed	8 (9.0%)	4 (1.9%)

* Percentages of those who have a partner

Factors associated with inconsistent condom use

In univariate analysis, inconsistent condom use was more common among HIV-negative IDUs than among HIV-positive IDUs, and was more common in steady relationships in both groups. In addition, inconsistent condom use was more common among those IDUs who had received inpatient addiction treatment within the past six months than among those who had received no such treatment (p<0.10). In multivariate analysis, the association between addiction treatment and inconsistent condom use differed according to HIV status. For the HIV-positives, inconsistent condom use was associated with in- and outpatient treatment, whereas for the HIV-negatives, inconsistent condom use was associated only with inpatient treatment **(Table 8).**

In this study, inconsistent condom use showed no independent association with age, gender, marital status, number of sex partners, commercial sex, STIs, drug use frequency, NEP use, or duration of injecting. Furthermore, inconsistent condom use showed no association with education, unstable living, unemployment, recent imprisonment (within the past 6 or 12 months) or number of imprisonments. Among those who reported no drug use, but had sexual partners, 56% (9/16) reported inconsistent condom use.

When the logistical regression analysis was repeated to include those IDUs who reported having no sexual partners in the past six months, the results were similar. Likewise, the results remained the same after excluding the 16 HIV-positive IDUs who had known HIV-positive partners, and after excluding the 22 participants who reported no drug use in the past six months.

Table 8. Factors related to inconsistent condom use in the past six months. Because of interaction between substance abuse treatment and HIV status, odds ratios (OR) appear separately according to HIV status. Injecting drug users (IDUs) who reported having had no sex (n=54) were excluded.

Variable	Inconsistent condom use	OR (95% CI) in the multivariate model
Partner type		
Steady partner only	98 (84.5%)	5.6 (2.4-13.4)
Casual partner only	28 (53.8%)	1.0
Steady and casual	49 (76.6%)	2.6 (1.1-6.4)
HIV-positive IDUs (n=60)	39 (65.0%)	
Substance abuse treatment		
Inpatient	12 (80.0%)	6.0 (1.7-143.0)
Outpatient only	25 (65.8%)	9.0 (1.4-60.4)
No treatment	2 (28.6%)	1.0
HIV-negative IDUs (n=179)	143 (79.9%)	
Substance abuse treatment		
Inpatient	82 (82.0%)	1.7 (0.7-4.1)*
Outpatient only	10 (66.7%)	0.4 (0.1-1.5)
No treatment	51 (79.7%)	1.0

* OR 4.2 (1.2-15.2) compared to the outpatient group

5.4. Epidemiology of late HIV diagnosis in Finland (IV)

General characteristics of newly diagnosed HIV cases

Of all 934 cases, 26% were IDUs, 31% heterosexuals, and 42% MSM. The transmission group for 11 cases was either other or unknown. The characteristics of the study population divided into four-year calendar periods of HIV diagnosis appear in **Table 9**. The study population represents 77% of IDU, 66% of MSM and 42% of heterosexually transmitted HIV cases reported to the National Infectious Disease Registry nationwide between 1985 and 2005 (n=1597).

Table 9. Characteristics of newly diagnosed HIV patients and proportion of late diagnosed HIV cases in the study.

Characteristic	Period of HIV diagnosis					
	1985-1989 n=122	1990-1993 n=139	1994-1997 n=155	1998-2001 n=279	2002-2005 n=239	All n=934
Age, median, years (IQR)*	31 (25-37)	31 (26-38)	33 (28-40)	34 (28-40)	36 (30-42)	33 (28-40)
Male	90%	76%	68%	73%	81%	77%
Finnish nationality	89%	83%	72%	90%	82%	84%
Previously tested	20%	44%	45%	48%	56%	45%
HIV-negative test within 2 years	17%	31%	22%	32%	29%	28%
Late-diagnosed cases						
IDU	2/8 (25%)	1/3 (33%)	0	11/181 (6%)	17/46 (37%)	31/238 (13%)
Heterosexual	4/22 (18%)	13/59 (22%)	25/78 (32%)	12/51 (24%)	22/79 (28%)	76/289 (26%)
MSM	11/88 (13%)	21/75 (28%)	32/77 (42%)	15/47 (32%)	22/109 (20%)	101/396 (26%)

*Interquartile range

Late diagnosis among newly diagnosed HIV cases

Of all cases, 195 (21%) presented with a CD4 count of fewer than 200 cells/µL, 59 (6%) with a CD4 of <50 cells/µL, and 80 (9%) presented with AIDS. Altogether, 211 (23%) were classified as late diagnoses (CD4 <200 cells/µL, or AIDS within three months of HIV diagnosis). Within the first year after HIV diagnosis, 98 (11%) were diagnosed with AIDS. The median CD4 count was 419.

The proportions of late-diagnosed individuals and predictors of late diagnosis in the multivariate model appear in **Table 10.** Individuals diagnosed late were more often older (≥40 years), male, non-IDUs, non-Finnish, and less likely to be tested before. Late-diagnosed individuals were more often diagnosed in primary health care or in secondary health care than in STD clinics.

Late diagnosis was rare before 1990 and between 1998 and 2001. These four-year periods overlapped with the early stages of identifiable sub-epidemics: the MSM and heterosexual sub-epidemic prior to 1990, and the IDU outbreak in 1998-2001 **(Figure 5)**. When multivariate analysis was repeated using the variable "stage of the epidemic" instead of calendar periods, the later stage of the outbreak was found to be a strong independent predictor (OR 4.3, 95% CI 2.5-7.4) for late diagnosis. The cART era failed to change the proportion of late-diagnosed cases among heterosexual and MSM transmissions. The IDUs were excluded from this analysis, since the outbreak occurred after introduction of cART.

Table 10. Prevalence and predictors of late HIV diagnosis.

Variable	Late diagnosed cases (%)	Adjusted OR (95% CI)	p value
Nationality			<0.05
Finnish	164/78 (21%)	1.0	
Non-Finnish	47/153 (31%)	1.7 (1.1-2.8)	
Age at HIV diagnosis			<0.001
<30	47/304 (16%)	1.0	
30-39	78/371 (21%)	1.5 (1.0-2.3)	
>=40	86/259 (33%)	2.6 (1.6-4.1)	
Transmission group and gender			<0.01
IDU female	2/58 (3%)	1.0	
IDU male	29/179 (16%)	5.2 (1.2-23.3)	
Hetero female	30/155 (19%)	3.5 (0.7-16.0)	
Hetero male	46/134 (34%)	6.1 (1.3-27.8)	
MSM	101/396 (26%)	7.2 (1.6-31.9)	
Calendar period			<0.001
1985-1989	17/122 (14%)	1.0	
1990-1993	37/139 (27%)	2.3 (1.2-4.6)	
1994-1997	57/155 (37%)	3.7 (1.9-7.2)	
1998-2001	38/279 (14%)	1.3 (0.6-2.6)	
2002-2005	62/239 (26%)	2.2 (1.1-4.1)	
Stage of the epidemic *			<0.001
First	26/291 (9%)	1.0 *	
Later	185/643 (29%)	4.3 (2.5-7.4)*	
Previously tested HIV- negative			<0.001
Yes	70/422 (17%)	1.0	
No	141/512 (28%)	1.9 (1.4-2.8)	
Site of HIV diagnosis			<0.001
STD clinic	8/94 (9%)	1.0	
Primary health care	54/258 (21%)	2.5 (1.1-5.6)	
Secondary health care	97/275 (35%)	5.2 (2.3-11.6)	
Non-health care	45/280 (16%)	2.1 (0.9-4.9)	
Unknown	7/27 (26%)	3.4 (1.1-11.1)	

*Multivariate analyses repeated by replacing the variable "calendar period" by "stage of the epidemic".
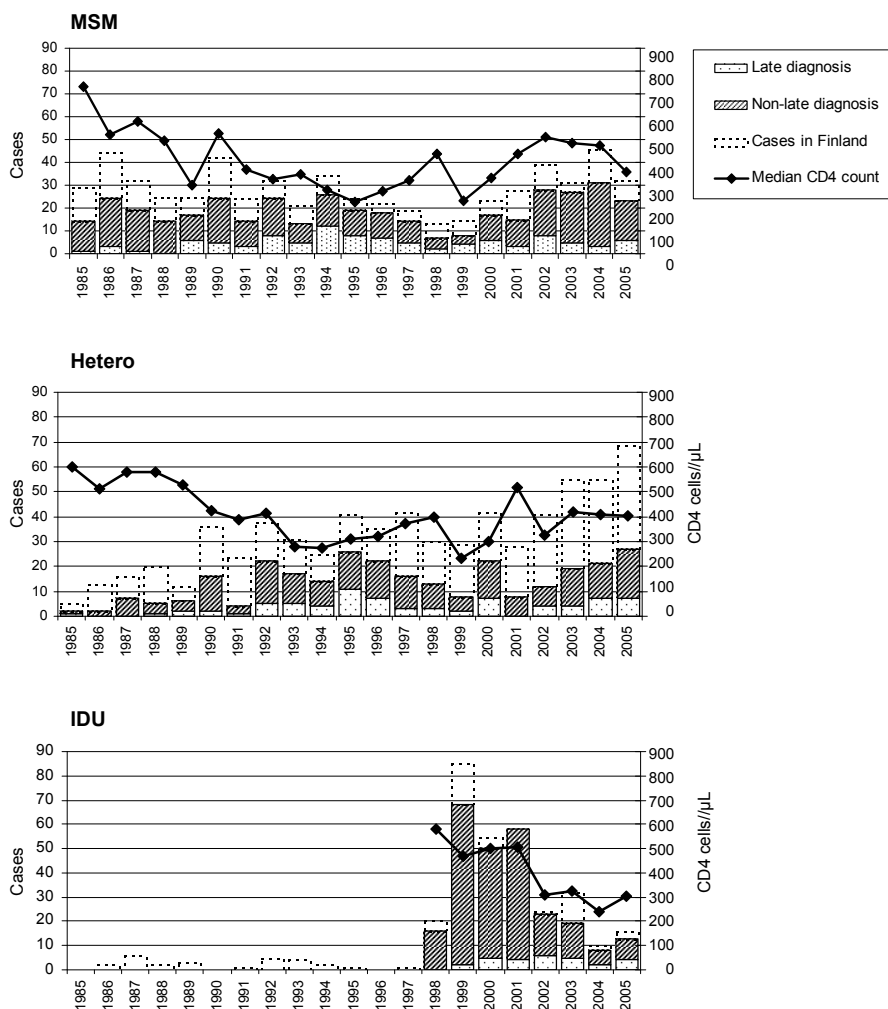
MSM

Hetero

IDU

Figure 5. Median CD4 cell count, annual number of newly diagnosed HIV cases, and number of late-diagnosed HIV cases in sub-epidemics among men who have sex with men (MSM), heterosexuals, and injecting drug users (IDUs) in the HUCH area, and annual number of HIV cases reported to National Infectious Diseases Register from Finland.

Site of HIV diagnosis

Of the heterosexually transmitted cases, 71% were diagnosed as HIV-positive in primary or secondary health care settings, whereas the proportion among MSM and IDU groups was 56% and 40%, respectively. Prisons, needle exchange sites or drug treatment facilities diagnosed 49% of the HIV cases among IDUs **(Table 11).**

Despite the stable proportions over calendar periods in all diagnoses made in health care settings, primary health care diagnosis decreased from 35% to 13% among late-diagnosed cases.

Table 11. Sociodemographic characteristics, testing behaviour and delays in HIV cases among injecting drug users (IDUs), heterosexuals, and men who have sex with men (MSM).

Characteristics	IDU	Hetero	MSM
	n=238	n=289	n=396
Age, median, years (IQR)*	35 (28-41)	31 (27-40)	34 (28-40)
Male	76%	46%	(100%)
Finnish nationality	96%	62%	93%
Testing status			
Previous HIV-negative test available (%)	50%	38%	48%
HIV-negative test within 2 years	36%	21%	28%
Site of HIV diagnosis			
Primary health care	18%	34%	29%
Secondary health care	22%	38%	27%
STD clinics	3%	6%	17%
AIDS support centre	0%	5%	13%
Prisons	23%	1%	0%
NEPs	20%	1%	0.3%
Drug treatment	6%	0%	0.3%
Immigrant centre	0%	4%	0%
Other	5%	9%	11%
Unknown	3%	3%	3%
Delays (median, days)			
HIV-positivity to referral	15	14	14
Refererral – First visit	32	16	17
HIV-diagnosis – first CD4	44	33	34
HIV-diagnosis – first visit	59	34	35

*Interquartile range

Delayed entry to HIV care

The median delay from the HIV diagnosis to the first visit at the Infectious Disease Clinic was 1.3 months. The delay was shortest for female heterosexuals (median 1.1 months) and longest for male IDUs (median 2 months). Of all cases, 11% were delayed for more than six months, and 4% for more than two years. Of the IDUs, 20% were delayed for more than six months.

In the multivariate model both, female IDUs (OR 5.0, 95% CI 2.0-12.1) and male IDUs (OR 3.9, 95% CI 1.9-7-9) were more likely than MSM to enter HIV care late. Delayed entry to care was more common prior to 1998, and was also associated with non-Finnish ethnicity (OR 2.3, 95% CI 1.3-4.11).

6. DISCUSSION

Finland's geographical location between the East and West is reflected in the spread of HIV. Whereas Western-type sexual epidemics spread in the 1980s, the Finnish outbreak among IDUs spread late, but explosively, similar to the concurrent outbreaks in the former Soviet Union. However, this study describes characteristics of one of the few IDU epidemics to revert very quickly, and where the prevalence of HIV among IDUs remained low.

Finland's relatively isolated northern geographic location may also have contributed to the late introduction of HIV in Finland, which allowed the early detection of the epidemics that appear in this study. This early detection, followed by early response, may have contributed to the low HIV prevalence in the country.

Perhaps most importantly, this study shows the geographical spread and restriction of the HIV epidemic among IDUs on a smaller scale, at the city and neighbourhood level. The results show that in low prevalence countries, high-risk groups may be concentrated in deprived areas, or "pockets of poverty", and poses a strong argument in support of outreach work, the decentralisation of services, and rapid responses.

Even if this study covers only some of the factors that may have influenced the spread of HIV, it allows discussion of the spread and restriction as well as the risk for further spread of the HIV outbreak among Finnish IDUs in light of the results, surveillance data, and published studies available from other countries. Study IV also creates an opportunity to compare this IDU outbreak with other Finnish sub-epidemics among MSM and heterosexuals.

6.1. Rapid spread of the outbreak (I,II)

The spread of HIV among Finnish IDU was even more rapid than official statistics suggest. This study shows that the majority of seroconversions occurred as early as in 1998, whereas the peak in incidence in the Finnish reporting system occurred in 1999. Since the median CD4 counts were high in the early years of the outbreak, the sharp rise in new HIV cases cannot be due only to increased testing, but rather reflects a recent increase in new transmissions.

The HIV viral load is associated with infectivity.[210-214] The viral load is high in the early stage of the infection, which renders recently infected IDUs particularly infectious and enables the rapid spread of HIV. In this

study, the viral load was higher in the Finnish cohort infected with subtype CRF01_AE$_{Fin}$ than in the Dutch IDU cohort infected with subtype B, which may have facilitated the explosive spread of CRF01_AE$_{Fin}$ among Finnish IDUs.

The results indicate that the period of higher probability of transmission may be longer in CRF01_AE$_{Fin}$-infected persons, at least compared to individuals infected by subtype B. Viral loads declined in both subtypes, but the decline was slower in the Finnish cohort, and the difference between the subtypes increased during the two-year follow-up.

According to results from Uganda, the risk for transmission is 26 times higher during the primary infection than later in the course of HIV infection, but only for a three-month period.[215] Among heterosexuals, the impact of this early period was considered short in relation to the long asymptomatic phase of the infection. However, the early period carries greater weight among IDUs, since the number of high-risk situations and sharing partners may be large, and the probability of transmission associated with unsafe injecting is higher than with sexual contacts.[3]

Since the difference in viral load between the subtypes was relatively modest, we must take into account the possible impact of different quantitation assays. Previous versions of the assays are known to underestimate viral loads in non-B subtypes. In the present study, both cohorts were analysed with an assay that is sensitive to the prevalent subtype: NASBA for subtype B and Amplicor for subtype CRF01_AE$_{Fin}$. Our own analysis and calculations based on previous studies indicate that had Amplicor 1.5 been used for both cohorts, the viral loads for subtype B would have appeared slightly lower, and thus the differences between the cohorts even greater.[250-252]

A recently published study suggests that relatively small changes in viral loads may affect the transmissibility of HIV.[216] The researchers estimated that the likelihood of transmitting HIV through heterosexual contact increases by 20% with every 0.3 log10 increment in HIV RNA. The mean viral load difference between the Finnish and the Dutch cohorts varied between 0.34 and 0.94 log10, and the lower 95% confidence interval exceeded 0.2 log10 after the first year of follow-up. Thus, the observed higher viral load in the Finnish cohort may have contributed to the rapid spread of the outbreak.

The results of the present study are in accordance with the results of a cohort study in Thailand, where higher viral loads were found during the early period of HIV infection among persons infected with CRF01_AE than among those infected with subtype B; both were analysed with Amplicor 1.5.[52] In Thailand, subtype AE has also spread more rapidly than subtype B has, even if both were introduced to the IDU population.[253] Similar differences in viral loads in the early stages of HIV infection have been observed in other comparisons between seroconverter cohorts (i.e. studies that allow comparison of the cohorts in relation to the time since estimated transmission).[50, 53, 54] However, studies lacking seroconversion data seem

unable to detect such differences between subtypes, since these appear only in the early stages of HIV infection.[40-45]

In addition to high viral load and infectiousness in early infection, other factors have also been associated with the rapid spread of HIV among IDUs. The lack of information about HIV and restricted access to clean needles and syringes combined with a high number of susceptible individuals in the naive IDU population have fueled HIV epidemics in many countries.[254, 255] Rapid spread may also be associated with situations that create fast risk-partner changes (e.g. "shooting-galleries" where IDUs may share needles and syringes with many IDUs in a short period of time).[255]

In the Helsinki metropolitan area, the number of IDUs was estimated to be as high as 7400 in 1998, and high incidence of hepatitis C (HCV) infections reflects the existence of risky injecting behaviour among this large susceptible IDU population. Qualitative information obtained during the structured interviews of this study also indicate a lack of information about HIV and other blood-borne diseases. Probably most importantly, this study describes the limited access to clean equipment in the beginning of the outbreak.

NEP was implemented with limited resources in the city centre in 1997, and the other NEP centres were opened after 1999. In this study, two clear clusters of IDUs emerged outside the city centre. Up to 40% of the HIV-positive IDUs who lived or used drugs in these clusters had no contact with the city centre of Helsinki. Thus, NEP failed to reach these geographical pockets of infection.

In addition to the insufficient geographical coverage of NEPs, the numbers of exchanged needles and syringes was only 74 000 in 1998, compared to 1 108 000 in 2003.[256] Since neither the amount of equipment distributed by pharmacies nor the number of IDUs in the area increased during that period, the coverage of the equipment was far from adequate during the first years of the outbreak, when the majority of transmissions occurred as early as in 1998.

The number of exchanged equipment can also serve as a surrogate for other prevention activities since these were included in Finnish NEPs, known as the Low Threshold Health Service Centers, from the beginning.[256] Those IDUs unreached by clean needles and syringes were also less exposed to information, education, low-threshold testing, counselling and referrals to drug treatment.

Conversely, access to clean equipment and other services improved rapidly, and is most likely one of factors that contributed to the limitation of the outbreak.

6.2. Rapid restriction of the outbreak (II)

In many countries, HIV incidence among IDUs peaks when the prevalence of HIV is high, and thus the number of susceptible IDUs in the population decreases. In the Helsinki area, this saturation effect fails to explain the limitation of the outbreak, since the number of IDUs was estimated to be as high as 7400 in the area, and fewer than 300 of them became infected with HIV.[257, 258]

However, the results of the present study indicate that the outbreak was saturated in a core group of marginalised IDUs. Firstly, those IDUs infected with HIV in the later stage of the outbreak (2002-2003) were significantly older, had lower CD4 levels, and had used injecting drugs for a longer time than had those IDUs diagnosed in the beginning of the outbreak. Thus, they may at least partly represent the same core group as the early cases, only diagnosed later. Secondly, the HIV-infected IDUs were older and more marginalised than were the HIV-negative IDUs interviewed in the Riski study, which was conducted at needle exchange stations.[249] Even if the selected material of the Riski study does not represent all IDUs, those results support the view that the sociodemographic profile of HIV-infected IDUs differed from that of the average IDU population in the area. Thirdly, this present study also shows the spatial clustering of HIV-positive IDUs. In the lack of specific network data, these clusters of IDUs found outside the city centre can be considered indirect signs of networking between the IDUs: the 40% of individuals in clusters who had no contact with the city centre may also have had limited contact with other IDUs outside the clusters.

Compared to the situation in Russia, the sociodemographical profile and spatial distribution of the HIV-infected Finnish IDUs contrast sharply.[229] In Helsinki, the HIV-infected IDUs were older, more marginalised, frequently homeless, and often had a history of imprisonment, addiction care, psychiatric care, and a long history of injecting drug use. The cases diagnosed in later stages of the outbreak were just as marginalised and came from the same neighbourhoods as did the early cases, and no new clusters were detected during the five-year study period. Only 10% of the cases were young (<25 years), and the proportion of young IDUs decreased during the study period.

In St. Petersburg, the HIV-infected IDUs were not only spatially clustered, but also co-clustered with a high frequency of heroin injection and receptive syringe sharing, and – most notably – being younger than 24 years of age and living with their parents. [229] Similarly, in Estonia, most HIV-infected IDUs belonged to the 15- to 24-year age group.[23] Young IDUs may be more likely to transmit HIV further, because they are often more sexually active and may have little knowledge of HIV and safe injecting.[235, 259]

Some studies suggested in the 1990s that HIV may enter the IDU population through marginalised groups of IDUs.[260, 261] This study shows

that the Finnish epidemic spread in only a limited fashion outside this marginalised core group. However, HIV-negative IDUs were engaging in high-risk behaviour, as reflected in the high incidence of HCV and in the interviews of the Riski study among HIV-negative IDUs conducted shortly after the outbreak.[126, 249] Without interventions, HIV would most likely have spread among the larger IDU population and caused a "second wave" of the outbreak within the area.

Nevertheless, several interventions were implemented, which may have contributed to the containment of the HIV epidemic. The first NEP began in 1997 and offered clean needles, syringes, condoms, and health counselling and testing for HIV and hepatitis. In addition, pharmacies were encouraged to continue selling needles and syringes to IDUs. In response to the first HIV cases detected among IDUs, public information about a possible outbreak was disseminated through the media, and specifically at the NEP stations. The frequency of HIV testing increased, especially in prisons and at NEPs. Notably, almost one in three HIV infected IDUs was diagnosed at prisons during the first two years of the outbreak.

A study by Des Jarlais et al. described prevention activities and risk behaviour in cities where HIV was introduced to the IDU population, but the prevalence remained low (<5%).[185] The three most common components of prevention were present in all five cities: the implementation of prevention activities when HIV prevalence was still low, easy access to sterile injection equipment, and community outreach to IDUs. As described above, the two first components were also present in the Helsinki metropolitan area.

Some of the interventions began after the outbreak peaked, and have thus played no role in reversing the trend in HIV incidence. They may have influenced continued positive development, however. Since December 2000, the day centre for HIV-positive IDUs offers a free low-threshold methadone programme, clean injection equipment, food, addiction care services, infectious disease specialist services, medication and social services. The centre has also improved adherence to antiretroviral therapy, which can reduce the risk of transmission by decreasing the viral load.[219-221] Furthermore, separate daily services have encouraged networking among HIV-positive IDUs, and may also have reduced their contact with HIV-negative IDUs. One of the indirect indicators of this is the low proportion of HIV-positive clients in anonymous seroprevalence studies conducted in other NEPs despite the fact that a majority of HIV infected IDUs remain active drug users.

Outreach programmes began in 2001, and have educated peer workers who distribute information, clean equipment and condoms for hard-to-reach IDUs outside the city centre. Peer work as well as HIV and health education programmes targeted at IDUs have been implemented in prisons as well.

Early detection of the outbreak and early diagnosis of HIV may also have led to similar positive changes in risk behaviour as reported in other studies

among IDUs.[195, 196] In this study, HIV-positive IDUs reported significantly less risky injecting and unprotected sex than did HIV-negative IDUs. Unfortunately, this study has no pre-outbreak behavioural data.

The Finnish HIV outbreak among IDUs occurred in a fairly stable socioeconomic and political situation compared to those in Estonia, Russia, and in many other transitional or developed countries. Although barriers to the acceptance of harm reduction programmes were common, the outbreak of HIV facilitated the diffusion of NEPs in the Helsinki metropolitan area, as well as in other parts of the country.[262] Compared to many Western countries where the HIV incidence among IDU peaked as early as in the 1980s, much more evidence-based data on HIV prevention was now available, which could be put into action without significant delay.[263]

6.3. Risk for further spread of HIV among Finnish IDUs (III)

Examples where HIV has spread again after years of stable HIV prevalence do exist.[24] On the other hand, also in cities that succeeded in reverting HIV outbreaks, residual risk behavior has been reported. This study included no detailed analysis of injecting behaviour and determinants of risky injecting among HIV-positive and HIV-negative IDUs. It does, however, show that among the 296 IDUs included in the sexual risk behaviour analyses, up to 18% of HIV-positive IDUs reported at least one lending episode, and 62% of HIV-negative IDUs reported having borrowed or lent equipment at least once in the past six months.

The residual injection risk behaviour among HIV-positives is in line with that of other studies.[147] The observed prevalence of risky injecting, combined with the HCV incidence of more than 350 cases from the HUCH area and the rising HCV incidence in northern Finland, indicates that a risk for HIV spread exists through unsafe injecting. Sharing is unlikely to become less common among those IDUs excluded from the Riski study, which was conducted within NEPs. Thus, the continuation, distribution and development of NEPs and of other prevention activities are of great importance.

Several studies have shown the growing impact of sexual transmission on HIV epidemics among IDUs, especially in settings where prevention activities have successfully decreased injection-related risks.[152, 153] This study shows that unprotected sex was common among Finnish IDUs. Up to 70% of IDUs reported inconsistent condom use, which is in line with the results of earlier studies.

Compared to the study populations of many other studies, this study population was more marginalised.[152, 157-160] On the other hand, this study also shows the high prevalence of risky behaviour despite the wide range of services available: HIV-positive IDUs were followed up in the Infectious

Disease Clinic, and HIV-negative people were active NEP users. In addition, the majority of IDUs in both groups had used addiction care services. However, structured HIV prevention targeted at sexual behaviour is offered to HIV-positives only during the first clinic visits. Of HIV-negatives, a minority reported that they had received counselling at NEPs about sexual behaviour.[249] There exists a clear need to combine structured and repeated interventions targeted at sexual behaviour with these services offered for IDUs.

Having a steady partner is a known risk factor for unprotected sex among IDUs.[264] In contrast, the association between recent addiction care and inconsistent condom use found in this study is an unexpected result. It must be noted that this sub-study was not designed to evaluate the effect of addiction care. Where most previous studies have been conducted during drug treatment and have had no positive effect on high-risk sexual behaviour, our study population consisted of active injectors. Despite this possible selection bias and small sample size, the results suggest the need for further studies, since similar results were obtained recently in a larger study among SIF users in Canada.[161]

A more qualitative approach may help us to understand whether this higher-risk behaviour possibly reflects the chaotic life situation of IDUs prior to entering treatment, increased networking among IDUs in drug treatment, or increased sexual activity after such treatment. Nevertheless, the high prevalence of unprotected sex poses a risk for HIV to spread sexually among IDUs, and poses a huge challenge for health and addiction care workers who work with this difficult patient population.

6.4. Characteristics of the IDU outbreak compared to sexual epidemics in Finland (I, IV)

When the characteristics of the IDU outbreak are compared to the Finnish epidemics among MSM and heterosexuals, some clear differences stand out. As discussed previously, the IDU outbreak spread later, spread faster, and was contained faster than were the epidemics among MSM and heterosexuals.

Comparable to a study from Italy, Finnish IDUs were diagnosed earlier in their infection, but their delays in receiving HIV care were longer than for the MSM and heterosexually transmitted cases.[91] The IDUs were also more likely to test HIV-negative earlier. Of particular importance, the IDUs were more often diagnosed at sites, such as NEPs, drug treatment or prisons, that may actively offer HIV testing combined with other services while up to 70% of heterosexuals and 60% of MSM were diagnosed in health care settings. Being diagnosed in non-health care settings as well as in STD clinics was also independently associated with earlier diagnosis, at least more so than in primary or secondary health care.

However, some interesting similarities also exist between the IDU epidemic and the sexual sub-epidemics in Finland. The data show that the spread of HIV was detected early not only among IDUs, but also in sexual epidemics in the 1980s. In the IDU outbreak, only 6% of patients were diagnosed with low CD4 levels during the first four-year period. The median CD4 count of all IDUs diagnosed between 1998 and 2001 was 490 cells/μL whereas the predicted CD4 count of seroconverters in study I was 468 cells/μL 12 months after seroconversion. The recent spread of HIV was confirmed by the introduction of a novel, genetically homogenous HIV clone in the IDU population and in only a few HIV cases diagnosed among IDUs in previous years.[7]

Notably, the proportion of late-diagnosed cases was low also in the first stage of the sub-epidemics among MSM and heterosexuals, and the median CD4 count was even higher than in the beginning of the IDU outbreak (545 and 575 cells/μL, respectively). This early detection of each sub-epidemic allowed early responses, and provides one possible explanation for the low prevalence of HIV in Finland.

The other common feature in all epidemics was the increasing proportion of late-diagnosed cases in later stages of the epidemics. Late diagnosis was rare in the first four-year period of each sub-epidemic, but became more common thereafter. Regardless of transmission group, the subsequent, later stage of the epidemic was an independent risk factor for late diagnosis.

Devoting so much attention in the literature to late diagnosis and its avoidance may lead to the assumption that a low proportion of late-diagnosed cases is a favourable epidemic situation. However, in our data, the lowest proportions of late-diagnosed cases coincided quite naturally with the early phases of the spread of HIV to respective transmission groups. Illustratively, in the last four-year study period, the proportion of late diagnosis was highest (37%) in the rapidly contained outbreak among IDUs, and lowest (19%) in the MSM sub-epidemic characterised by a rising incidence. A low proportion of late-diagnosed cases can be a desired outcome of prevention and testing policies, but combined with rising HIV incidence, may also signal new transmissions.

6.5. Strengths and limitations (I-IV)

This study has several advantages. The study population covers a large majority of the whole HIV outbreak among Finnish IDUs and is the first study to describe the spatial spread and containment of an IDU outbreak over time. It also includes data on all newly diagnosed HIV cases in the HUCH area, representing 65% of all HIV cases in Finland. The study period, which included the early stages of all sub-epidemics, enabled recognition of the stage of the epidemic as a risk factor for late HIV diagnosis. In addition, the

virological sub-study contributes data to the debate on clinical differences between the HIV subtypes, and suggests the possible role of this recombinant subtype in the rapid spread of the IDU outbreak.

This study nevertheless has limitations that must be considered. Firstly, this study covers only some of the wide range of factors that influence the spread of HIV, whereas many known and unknown factors remain beyond its scope. Thus, the results can neither to prove the effects of different factors or interventions nor to weigh their impact against the spread of HIV.

In addition, the individual sub-studies have their limitations. The different quantitation assays used in the comparison of the two subtypes are discussed here earlier. Regarding the study on sexual behaviour, the small sample size, the missing data regarding HIV status of one's partners and the different selection criteria of the two study populations limit the conclusions. In the study on the spatial spread of HIV, data on the spatial distribution of HIV-negative IDUs and data on networking between HIV-positive and HIV-negative IDUs would have added much to the analysis. In addition, the inclusion criteria vary between the sub-studies, and may limit the generalisation of the results. Finally, the reason for HIV testing was recorded only for IDUs, not for all newly diagnosed cases in the study that described trends in late HIV diagnosis.

6.6. Implications (I-IV)

This study demonstrates the importance of outreach work and other preventive efforts that target the hard-to-reach population of marginalised IDUs. The HIV outbreak occurred in socioeconomically defined areas, which – except for the city centre – were characterised by high unemployment rates and low income (i.e. the most deprived neighborhoods in the Helsinki region).

Friedman et al. described in 1995 that in low prevalence countries, HIV may be concentrated in socio-behavioural pockets of infection. The present study shows that these social pockets are located in pockets of poverty within the region. To prevent outbreaks, these pockets must be identified and reached, ideally before the spread of HIV. In addition to outreach and other peer work, this may include the decentralisation of NEP and of other services, and collaboration between the health care and the local social sector.

These results can be generalised to similar countries and areas with low-level epidemics, and to some extent to other concentrated IDU epidemics as well. Studies show that large geographical differences in prevalence of HIV also exist in those countries where HIV is highly concentrated among IDUs. In high prevalence settings, far more resources are clearly needed to curb the outbreak. However, to identify and to reach marginalised IDUs in

deprived neighborhoods is an important challenge in all settings.

The second implication of this study is the prevention targeted at the sexual behaviour of IDUs. Inconsistent condom use is common among HIV-positive and HIV-negative IDUs, and was associated with steady relationships and with recent addiction care. This creates a risk for HIV spread, but also highlights opportunities for prevention. A large majority of IDUs had previously used addiction care services, which suggests combining HIV prevention with these services.

Although many studies report the difficulty in changing sexual behaviour, behavioural interventions are shown to be effective, especially when they include certain behavioural skills components.[194] Behavioural interventions may also be easier when combined with addiction care than with NEPs, since such interventions require several sessions, and when in treatment, IDUs are likely to be off drugs and more receptive to the interventions. However, interventions are also needed to facilitate safer sex among out-of-treatment IDUs. Since unprotected sex was unassociated with markers of marginalisation, commercial sex or gender, the results underscore the need to target the interventions structured for every IDU. Furthermore, the steady partners of IDUs should be actively offered intervention and HIV testing.

Thirdly, to facilitate early HIV diagnosis, this study suggests increasing of HIV testing. An increase in routine HIV testing actively offered as a part of health care, and new low-threshold testing opportunities are needed, especially for heterosexuals who are often diagnosed late. For MSM, this study also suggests strengthening primary prevention measures because of increasing HIV incidence despite increases in previously tested cases.

Public awareness of HIV, of promising prognoses and the importance of early diagnosis should be raised, as should such awareness among physicians and other health care personnel. Anonymous, low-threshold HIV testing should be easily available in all health care settings. In addition, it is important to continue and to develop alternative testing possibilities, such as through NGOs.

Despite these needs to develop and increase HIV testing in Finland, this study does not support the view that late diagnosis would be more common in countries with low-level HIV epidemics, which is an important background for new testing policies. Lower proportions of late diagnosed cases are reported only from Australia, another country with a low-level epidemic.[83]

Finally, there are some lessons learned regarding HIV surveillance and similar studies. Including baseline CD4 data in HIV surveillance has been recommended and has begun in 26 countries in Europe, and a common definition for late diagnosis is under discussion.[265] This study shows that local data on the epidemiology of late HIV diagnosis is valuable, since trends and risk factors vary between countries and studies. The 20-year study period also shows that the proportion of late-diagnosed cases reflects not only

the problem of late HIV testing, but also the stage of the local epidemic. The stage and the age of the epidemic must be taken into account when interpreting surveillance data and studies on late HIV diagnosis, especially in cross-country comparisons. The goal must be early diagnosis rather than a low proportion of late diagnoses.

6.7. Future considerations

In the future, monitoring the baseline CD4 cell counts of the national HIV surveillance data makes it possible to recognise groups at risk for late diagnosis in Finland, and shows in which geographical areas and transmission groups HIV testing must be improved. In order to recognise recent infections and thus groups and areas that require targeted prevention programmes, baseline CD4 cell count data on newly diagnosed HIV cases can be complemented with serological tests that recognise recent HIV infections (STARHS).

According to a comment by Wilson and Halperin published in the August 2008 issue of *The Lancet*, the key research question in concentrated epidemics is "How to reach vulnerable groups with high coverage of high-quality targeted interventions?".[266] This study provides some answers, though leaving many questions unanswered. To know more about the spatial distribution of HIV-negative IDUs in Finland, about the mobility, characteristics, behaviour and networking between different sub-populations of IDUs, as well as to obtain more qualitative information about the risky sexual behaviour of IDUs would be important. Furthermore, the sexual partners of IDUs as a high-risk group for HIV should also be included in studies and interventions.

Moreover, IDUs are only one of the vulnerable groups. Study IV shows the growing number of newly acquired HIV infections among MSM, and the relatively large number of immigrants among heterosexual transmissions, both groups at risk for late diagnosis. At the same time, one in three HIV infections among Finnish heterosexual males – excluded from the "vulnerable groups" – is diagnosed too late, reflecting the paradox that those with no perceived risk are at greater risk for late diagnosis.[120] In low-prevalence countries, it is thus important not only to target high-risk areas and populations early with interventions and research, but to expand low-threshold HIV testing widely outside those settings.

7. CONCLUSIONS

I.   Shortly after HIV-1 infection, Finnish IDUs infected with the recombinant subtype $CRF01\_AE_{Fin}$ had higher viral loads than did the Amsterdam IDUs infected with subtype B. This higher viral load may have contributed to the rapid spread of the outbreak.

II. The Finnish HIV outbreak was socially restricted to a marginalised IDU population, and spatially to local pockets of poverty. To prevent HIV among IDUs, these pockets should be identified and reached early through outreach work and through the decentralisation of NEPs and other prevention activities.

III. Unprotected sex is common among both HIV-positive and HIV-negative IDUs, and enables HIV and other sexually transmitted infections to spread among Finnish IDUs. Inconsistent condom use is common in steady relationships, and is related to recent addiction treatment. Since the majority of IDUs receive addiction treatment services, this provides an important opportunity to reach IDUs for HIV prevention, which should also focus on sexual behaviour. Developing a structure and opportunities for testing the partners of IDUs may play an important role in the early diagnosis of new HIV transmissions.

IV. The proportion of late-diagnosed cases varies between the sub-epidemics and time-periods, and reflects not only the continuing problem of delayed HIV testing, but also the dynamics of sub-epidemics. IDUs are diagnosed as HIV-positive earlier than are other transmission groups, but are at greater risk for entering care late. The low proportion of late-diagnosed cases and the high median CD4 level in the early years of each sub-epidemic suggest that sexual epidemics were also detected early, which may have contributed to the low prevalence of HIV in Finland.

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Pia Kivelä

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