



PhD thesis
Mette Vang Larsen
2011

HIV Infection and Injecting Drug Use in Denmark - Studies on Morbidity and Mortality



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Faculty of Health Sciences
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The present thesis is based on the following studies, referred to by their roman numerals in the text:

- Study I:** Impact of injecting drug use on mortality in Danish human immunodeficiency virus-infected patients: a nation-wide population-based cohort study. Larsen MV, Omland LH, Gerstoft J, Larsen CS, Jensen J, Obel N, Kronborg G. *Addiction*. 2010 Mar; 105(3): 529-35.
- Study II:** Impact of injecting drug use on response to highly active antiretroviral treatment in HIV-1 infected patients: a nation-wide population-based cohort-study. Larsen MV, Omland LH, Gerstoft J, Røge BT, Larsen CS, Pedersen G, Obel N, Kronborg G. *Scand J Infect Dis*. 2010 Dec; 42(11-12): 917-23.
- Study III:** Major but differential decline in incidence of *Staphylococcus aureus* bacteraemia in HIV-infected individuals from 1995 to 2007: a nation-wide cohort study. Larsen MV, Harboe ZB, Ladelund S, Skov R, Gerstoft J, Pedersen C, Larsen CS, Obel N, Kronborg G, Benfield T. *HIV Med*. 2011. *In press*.
- Study IV:** Impact of HIV on mortality in Danish drug users in drug abuse treatment – a nation-wide cohort study. Larsen MV, Hvidt C, Gerstoft J, Larsen CS, Jensen J, Obel N, Kronborg G. *Submitted*.

Preface

The studies included in this present PhD thesis were carried out between 2007-2011, while I was employed at the Department of Infectious Diseases, Copenhagen University Hospital Hvidovre as a medical doctor and a PhD student at Copenhagen University.

I am indebted to my supervisors and colleagues for their support and encouragement throughout the study period. Many thanks to my main supervisor Gitte Kronborg for her commitment to the project, her optimistic approach to life and her never failing belief that all would fall into place at last. Thanks for your never closed door, many cups of coffee and conversations of scientific questions, clinical issues as well as life itself. Thanks to Niels Obel for valuable knowledge on DHSC and statistical methods. Thanks to Thomas Benfield for guidance in doing research by showing me how to approach scientific questions with curiosity and perseverance. Thanks to Christian Hvidt for sharing his knowledge on drug abuse in Denmark. I also want to thank Steen Ladelund for invaluable statistic advice and help on SAS statistical software.

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It has been a privilege to work with data from DHCS and the Danish Staphylococcal database, which both are attributed to the continued work of many people and for which the studies for this thesis would not have been possible. Thanks to all co-authors and collaborators who have participated in the studies included in this thesis. I would also like to thank colleagues and fellow PhD students at the Department of Infectious Diseases and Clinical Research Center, Hvidovre Hospital as well as other DHCS PhD students for academic advice and social activities during my years as a PhD student.

Last but not least, thanks to my husband Dennis and my family for their love and support, especially when times were difficult.

Mette Vang Larsen, Hvidovre, March 2011

Abbreviations

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
BSI	blood stream infections
CA	community acquired
CD4	cluster of differentiation 4
CI	confidence interval
CRS	The Danish Civil Registration System
DHCS	The Danish HIV Cohort Study
DRDC	Danish Registry of Causes of Death
HA	hospital acquired/associated
HAART	highly active antiretroviral therapy
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HSX	heterosexual
ICD	International Classification of Diseases
IDUs	injecting drug users
IQR	interquartile range
IR	incidence rate
IRR	incidence rate ratio
MR	mortality rate
MRR	mortality rate ratio
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MST	methadone substitution therapy
MSM	men who have sex with men
NNRTI	non-nucleoside analogue reverse transcriptase inhibitor
NRTI	nucleos(t)ide analogue reverse transcriptase inhibitor
PI	protease inhibitor
PYO	person years of observation
RDT	The Registry of Drug Abusers Undergoing Treatment
RNA	ribonucleic acid
SAB	<i>Staphylococcus aureus</i> bacteraemia
<i>S. aureus</i>	<i>Staphylococcus aureus</i>
VL	viral load

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Introduction

Background

This project was initiated more than three years ago at the Department of Infectious Diseases at Copenhagen University Hospital, Hvidovre. Hvidovre Hospital is one of eight centres in Denmark treating and caring for individuals infected with human immunodeficiency virus (HIV). More than 1500 patients (1/3 of all Danish HIV patients) are regularly seen at the department and about 150-200 of the individuals are infected via injecting drug use, which is the highest number of injecting drug users (IDUs) seen in one centre. From daily clinical practice we had the feeling that HIV infected IDUs were a challenge to treat, as they not always had the same agenda as we, and that they had a higher mortality than other HIV infected individuals. Whether or not, this merely resembled the well-known challenges and risks for IDUs or if HIV infection was a contributing risk was unknown. Denmark has a supportive and free of charge, tax paid health care system and treatment of addiction is free and widely accepted. The main concept of this PhD project was that HIV infected IDUs could be (but maybe not were) well treated and that HIV was only one of many challenges that this group of individuals was facing.

HIV and the epidemic in Denmark

The first cases of acquired immunodeficiency syndrome (AIDS) in Denmark were described in men who have sex with men (MSM) in 1982¹ not long after the disease was first recognised in Los Angeles, California.² Quickly it was also recognised that IDUs, along with haemophilic patients and children of mothers with AIDS, were also at risk for this new disease.³ A few years later the disease was linked to HIV.^{4,5} At present more than 4000 individuals in Denmark are alive knowing that they are infected with HIV, and over the last decade the total number of new HIV diagnoses has been constant at 2-300 new cases a year.⁶ It is suspected that approximately 1000 individuals are yet undiagnosed and therefore capable of continuing transmission of the disease.⁷ Transmission occurs mainly in MSM, heterosexuals (HSX) of whom a vast majority is of non-Danish origin and IDUs.⁸ Since 1997 highly active anti-retroviral treatment (HAART) has been available to all HIV infected individuals free of charge. Current guidelines prescribe HAART at CD4+ cell count below 350, acute HIV infection, clinical symptoms or pregnancy.⁹ During the study period also viral load (VL) and other limits for CD4+ cell count has been used. When initiating HAART the physician also estimates the readiness and willingness of the patient.

HIV in injection drug users

Worldwide

In most countries the HIV epidemic has spread rapidly among IDUs. For example in Spain the HIV epidemic is largely driven by infected IDUs who contribute to 50 % of the infected individuals.¹⁰ In the United States and Canada, isolated communities experience massive epidemics of HIV among IDUs – that is the case in Vancouver and Baltimore.^{11, 12} In recent years the infection has spread uncontrolled and with alarming speed among IDUs in Eastern Europe and the former Soviet Union, where it is estimated that up to 40-70% of IDUs are infected with HIV.¹³ Epidemics among IDUs are also a concern and major challenge in countries in South East Asia and Latin America.¹⁴ (Figure 1)

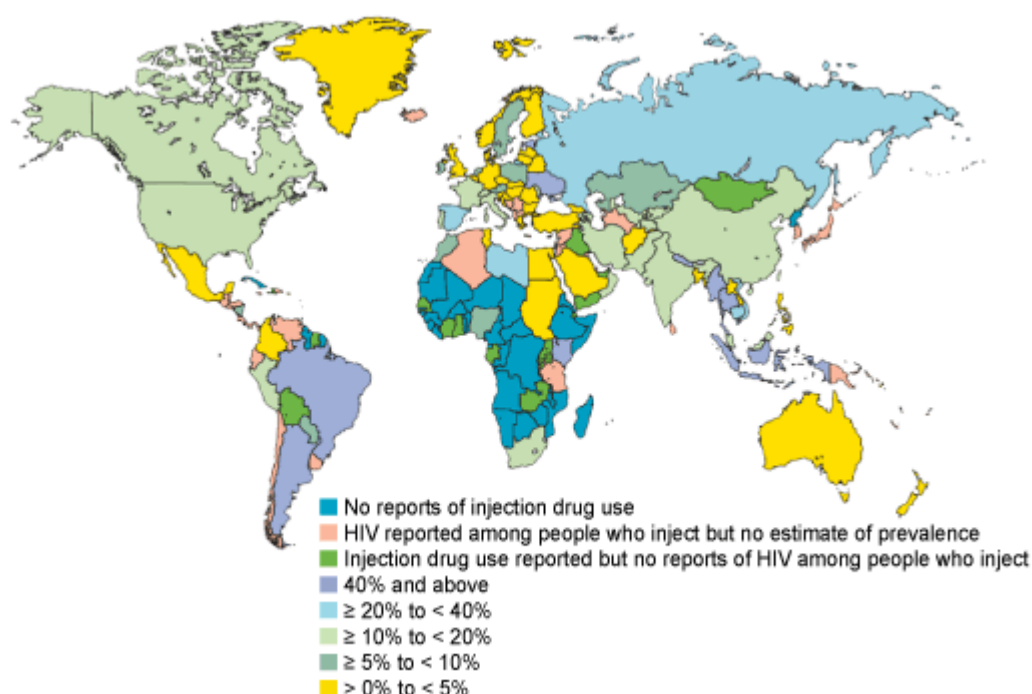


Figure 1: Prevalence of HIV infection among IDUs. Figure from ¹⁴ printed with permission from the authors and the journal. (Licence number 2615920712864)

Denmark

In Denmark the first cases of HIV infection among IDUs were registered in 1984¹⁵ and many more were diagnosed in the mid 1980's, after the HIV antibody test became available.¹⁶ Of all Danish individuals diagnosed with HIV approximately 10% are infected via injecting drug use.⁸ In the early years of the epidemic up to 15% of newly diagnosed were IDUs,¹⁷ but in the last 10 years this proportion has decreased remarkably and now newly diagnosed IDUs accounts for less than 5% of

the incident HIV-cases.⁶ (Figure 2) The prevalence of HIV among IDUs has always been low in Denmark compared to many other countries.¹⁴ The estimated prevalence of HIV in IDUs is 2.1¹⁸-4%¹⁹ compared to an overall prevalence of HIV of 0.09% among adults in the general population.⁶

The decline in number of HIV diagnoses among IDUs is unexplained. It is unclear if the newly diagnosed are individuals who have been infected for long, but have not been tested, or if they represent newly infected individuals i.e. if the HIV epidemic among IDUs in Denmark is dying out or if there is ongoing transmission among IDUs. Facing the problem of addiction and drug abuse, Denmark early on decided on harm reduction methods. In Denmark it is possible to buy needles and syringes from pharmacies,²¹ and in the mid to late 1980's, when it became obvious that HIV could be transmitted via blood, nationwide campaigns were launched, in which needles and syringes were handed out for free. Today tools are provided free of charge from a variety of places: pharmacies, street workers, health care centres, drug abuse treatment centres etc. Recent papers have focused on sexual transmission among IDUs, as unsafe sex-practices are also common among IDUs.²²⁻²⁵

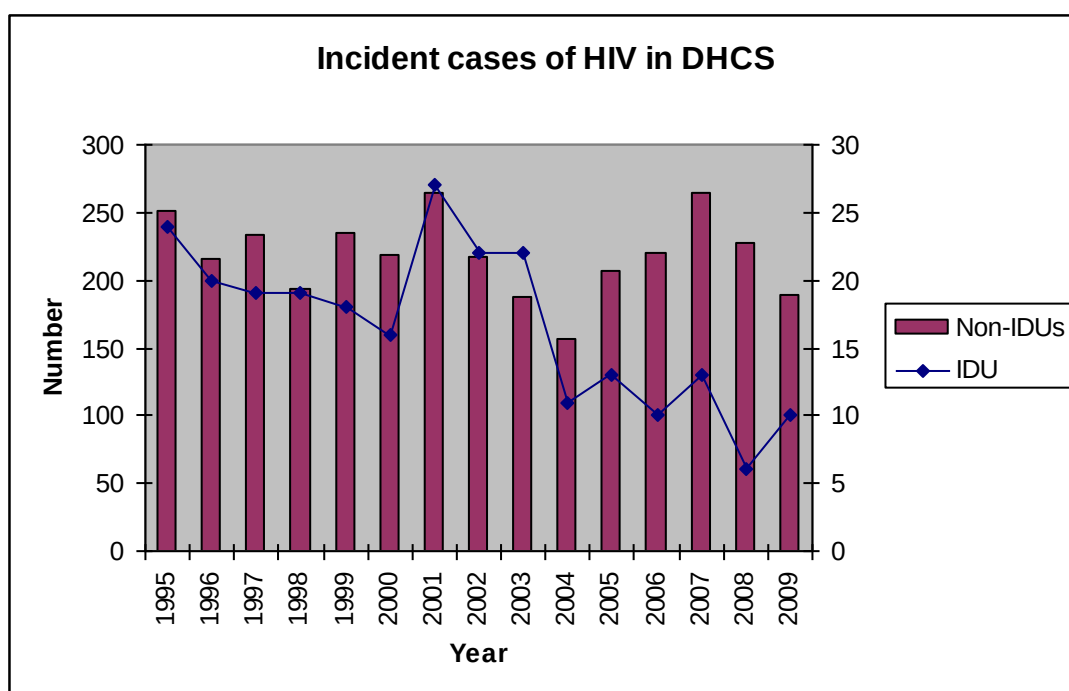


Figure 2: Incident cases of IDUs and non-IDUs diagnosed with HIV from 1995-2009 and registered in DHCS. Adapted from Obel N.⁶

Injection drug use in Denmark

In the report “The drug situation in Denmark” from 2010 the National Board of Health estimates that there are 33.000 drug users in Denmark of whom 11.000 only use cannabis.²⁶ Of the remaining 22.000, an estimated 13.000 are injecting their drugs and are therefore at risk of acquiring HIV due to needle sharing. During the last decade both a real and proportional decline in heroin/opioids users has been seen, opposed by an increase in the use of cannabis and central stimulating agents. The exact number of IDUs is difficult to estimate, since most injected drugs are illegal in Denmark.²⁶ Treatment for drug abuse is free and widely accepted. For opioid addiction treatment methadone substitution therapy (MST) is most widely used, but buprenorphine- and heroin-assisted treatment are available. Through the treatment system exact numbers describing the persons in treatment for addiction are available, but one third to half of IDUs are not known by the drug abuse treatment system. From 1996 to 2006 a total of 24,840 persons have been in contact with the treatment system and in 2005 a total of 13,316 persons were treated for addiction.²⁶ Though treatment of drug addiction has shown to decrease mortality among addicts,^{27, 28} the number of deaths is still high. MST is shown to increase receipt of HAART²⁹ and IDUs in MST have better treatment responses than IDUs not in MST.^{30, 31}

Injecting drug use and HIV as markers of a certain risk taking behaviour

Individuals with certain personality traits are overrepresented among HIV infected individuals.³² From Hippocrates’ doctrine of the four temperaments this would apply to the choleric individual. In one theory of modern behavioural psychology the human personality can be described as extroverts (individuals who are present orientated, feeling directed and reward seeking) and introverts (individuals who are future and past orientated, cognition directed and consequence avoidant) and the personality can be stable or unstable referring to the degree of emotional liability.³³ Using these terms the choleric type would be an unstable extrovert. Extroverts are willing to take risks and thrive in changing and creative environments. Successful extroverts can be found in arts, sales and politics. Unstable individuals often have intense emotions and respond impulsively to them. Unstable extroverts are not likely to plan ahead. They are unlikely to carry condoms for the night out. They do not think of the risk of sexually transmitted diseases, but more on the present pleasure that they can achieve.³⁴ Unstable extroverts are more prone to alcohol and drug abuse and are more likely to inject drugs and use non-sterile needles.³⁵ These high-risk taking behaviours put them at high risk of HIV. With regards to treatment, the present/pleasure orientation makes it difficult for

the physician at the HIV clinic to argue that they have to take medication every day (maybe with side effects) for a future benefit, when they are only thinking of their next fix. The result is a high risk taking behaviour among IDUs, and HIV infection can maybe be seen as a marker of the highest risk taking behaviour in this group.³²

Therapeutic regimens

HAART has since its introduction in mid 1996 shown its efficiency in controlling the HIV disease.³⁶⁻³⁸ The first line regimen consists of a backbone of 2 nucleos(t)ide analogue reverse transcriptase inhibitors (NRTI) and either a (boosted) protease inhibitor (PI) or a non-nucleoside analogue reverse transcriptase inhibitor (NNRTI).⁹ In choosing a regimen for an individual with HIV, several factors have to be taken into consideration: Possible interaction with other medications, side effects, resistance, co-morbidity, the number of pills and the number of daily administrations. Previously the triple-NRTI regimen Trizivir® (abacavir/lamivudine/zidovudine) was often used in individuals with suspected low adherence, as the one-pill twice a day regimen was attractive. Later studies have shown this regimen to be inferior to the present first line treatments.³⁹

Mortality

IDUs have a much higher mortality compared to the age matched general population.^{40, 41} The mortality among heroin addicts in Denmark is approximately 2% per year or 2.0/100 PYO.²⁶ This is roughly 15 times higher compared to the general Danish population matched on sex and age.⁴² IDUs die more frequently of accidents, overdoses, infections, liver related diseases and less frequently of cancer, heart disease, diabetes.^{43, 44} By law all suspected drug related deaths in Denmark are referred to autopsy and toxicology testing, which are carried out to determine the cause of death. Due to a high proportion of IDUs in MST opioids will often be present in the toxicology screening, and the cause of death will be registered as overdose and thereby drug related. Denmark thus has a known high incidence of drug related deaths, compared to other countries.¹⁸ It is estimated that deaths directly related to addiction accounted for approximately 50% of deaths among addicts in 1996-2002.⁴³ Deaths indirectly related to addiction, such as AIDS and hepatitis, also comprise a large proportion of deaths compared to the non-addicted population (10.7% vs. 0.1%).⁴³ Accidents, suicide and violence are causes of death more related to the social aspects of addiction. Deaths from causes indirectly related to addictive behaviour accounted in 2000 for 32.1% of deaths compared to only 5.3% in the non-addicted population.⁴³

Invasive Staphylococcal disease

Worldwide *Staphylococcus aureus* (*S. aureus*) bacteraemia (SAB) is an important cause of morbidity and mortality.⁴⁵ Individuals infected with HIV are at increased risk of opportunistic and common bacterial infections and *S. aureus* ranks as one of the most common causes of bacterial infection.⁴⁶⁻⁴⁹ Risk factors for invasive *S. aureus* infection include advanced HIV disease,^{46, 47, 50, 51} prior hospitalisation, injecting drug use and the presence of intravascular devices.^{47, 48, 52-54} Further, HIV infection is associated with a higher risk of repetitive SAB.⁵⁵ HAART is known to reduce the prevalence of blood stream infections (BSI)⁵⁶ and strongly reduces morbidity and mortality among HIV-infected individuals in general.⁵⁷ A single study has reported the incidence, clinical characteristics and outcomes of HIV-associated SAB in the early-HAART period.⁴⁸ Antimicrobials with activity against *Pneumocystis jirovecii* and mycobacteria have also been shown to reduce rates of invasive bacterial disease.⁵⁸⁻⁶⁰ In Denmark, there have recently been reported an increasing incidence but decreasing in-hospital mortality of adult SAB in the general population.⁶¹ IDUs are at increased risk of community acquired (CA) SAB, especially right-sided endocarditis, but generally have a better prognosis.^{62, 63}

Study objectives

The overall aim of this PhD study was to describe relations of HIV and IDUs in Denmark with particular focus on mortality and disease burden.

The specific aims were:

- Study I: To compare mortality in HIV infected IDUs and HIV infected non-IDUs.
- Study II: To compare mortality, effect of HAART and differences in initial ART regiment in HIV infected IDUs and HIV infected non-IDUs who have initiated HAART.
- Study III: To compare incidence of and risk factors for *Staphylococcus aureus* bacteraemia in a nation-wide HIV infected and uninfected matched cohort.
- Study IV: To compare mortality in HIV infected and HIV uninfected IDUs in substance abuse treatment.

Data sources

The Danish HIV Cohort Study (DHCS) (Study I-IV)

DHCS is a prospective, observational, nationwide, multi-centre, population-based cohort study of all HIV infected individuals seen in the Danish HIV clinics since 1 January 1995. The cohort has been described in details elsewhere.^{8, 64} In brief the study is ongoing, with continuous enrolment of both newly diagnosed individuals and immigrants with HIV infection. At inclusion in DHCS, baseline characteristics are registered. Of special interest for the present studies HIV transmission group is registered: IDU, MSM, HSX and other/unknown. Study data are updated annually with information on antiretroviral therapy (ART), development of opportunistic infections and other AIDS-defining illnesses and laboratory values including HIV-RNA and CD4+ cell count. Of all individuals registered in DHCS, 10-11% has injecting drug use as transmission route.

The Danish Staphylococcal Database (Study III)

A continuous, nationwide registration of SAB in Denmark has been carried out at the Staphylococcal Laboratory at the Statens Serum Institut, Copenhagen, since 1956 and the database has previously been described in detail.^{61, 65, 66} In brief, the Staphylococcal Laboratory receives isolates of blood cultures positive for *S. aureus* from 14 out of the 15 Danish departments of clinical microbiology and clinical data are extracted from discharge records annually by a qualified clinician. Data used in this study included: date for episodes of SAB during the study period, age, gender, mode of bacteraemia (CA or hospital acquired/associated (HA)) and antibiotic susceptibility testing.

The Danish Civil Registration System (CRS) (Study I-IV)

The CRS is a national register established in 1967 that contains demographic data and vital status of all Danish citizens.⁶⁷ A unique 10-digit civil registration number is assigned to all individuals in Denmark. This prevents multiple registrations and easy tracking of individuals across various databases and registers. The CRS is near complete,⁶⁷ and selection bias due to loss to follow-up is minimal.

The Registry of Drug Abusers Undergoing Treatment (RDT) (Study IV)

RDT contains information on individuals in Denmark who since 1996 has received therapy for drug addiction. Treatment of drug addiction in Denmark occurs mainly in referral centres, which provide

data to the RDT. The register contains information on main drug of abuse and additional drug use, and if it is the first time of drug abuse treatment. RDT also contains data on socio-economic factors and type of treatment (e.g. substitution treatment or drug free treatment), but data in this field is infrequently reported. Drugs may be consumed in various ways, but data on route of administration is limited and infrequently reported. Data from drug treatment programmes in jails are not included in this study.⁶⁸

The Danish registry of causes of death (DRDC) (Study IV)

DRDC contains information extracted from all Danish death certificates since 1943.⁶⁹ Registration is currently complete through 2008 and thus the study has no information on causes of deaths for the year 2009 and further. For each deceased, the attending physician must report the primary (immediate cause of death) and the underlying cause of death. Causes of death occurring during the study period were coded according to International Classification of Diseases (ICD)-10. From this register we extracted the recorded underlying cause of death.

Definitions

IDUs

In study I-III, individuals were considered as IDUs if they reported injection drug use as the most likely transmission route for HIV infection. In study IV the term IDUs is also used as an approximation for all individuals in the study, though all individuals might not actually administer drugs via injection. A limitation in DHCS is the registration of transmission route (injecting drug use versus other routes of infection). The transmission route is self-reported at the patient's first visit to the HIV clinic and it is not registered whether IDUs are current users, users in MST or former users. Some patients might fail to report injecting drug use to reduce social stigma. Further, no follow up data on injecting status (current, MST or former) are available.

HIV infection

In all four studies the definition of an HIV infected individual was the same. If an individual was identified in DHCS they were considered to be infected with HIV. If an individual was not present in DHCS, they were considered to be HIV uninfected. This is an approximation, as it is estimated that 1000 individuals are infected but yet undiagnosed with HIV and thus unaware of their infection. This number has through 1995 been reached from back calculations, and from 1996 the

number is based on the assumption of a constant HIV incidence.⁷ All individuals in DHCS diagnosed after 1 January 1995 are followed from date of HIV diagnosis. No information on time of infection is available, though CD4+ cell count at time of diagnosis gives a rough estimate, for how long an individual has been infected. In study IV it is reported that three HIV uninfected individuals died of HIV. This could emphasise the fact that individuals with a positive HIV antibody test is not always seen in an HIV clinic. Only individuals with HIV-1 infection were included in the studies.

SAB

The Staphylococcal Laboratory receives isolates from most cases of SAB from the departments of clinical microbiology in Denmark for typing and national surveillance. An episode of SAB was counted if registered in The Danish Staphylococcal Database. HA SAB was defined as SAB diagnosed more than 48 hours after hospital admission, a catheter related infection or otherwise health care associated infection. CA SAB was defined as SAB diagnosed <48 hours after hospital admission and none of the above. Repetitive SAB was present if the new case was diagnosed more than 12 weeks after the previous one. We registered all episodes of SAB including repetitive SAB during the study period, and this was used for calculating incidence rates (IR) in three calendar time periods. Only the first recorded episode of SAB was used in the analysis of risk factors.

Study subjects

All study participants had to be Danish residents (i.e. excluding tourists and individuals living in Greenland) and above the age of 16 at HIV diagnose or study entry for HIV negative individuals. Immigrants with known HIV infection at time of immigration entered the analyses at time for immigration

General methodological and statistical considerations

Cohort studies

All the studies for this thesis were conducted as cohort studies (study I, II, IV) or as a matched cohort study (study III). In a cohort study a defined group is followed over a period of time and the number of events of interest (outcomes) are registered.⁷⁰ The DHCS is a nationwide prospective observational cohort study. The study is open and population based. The primary outcomes of interest in the studies are death (study I, II, IV) and SAB (study III). Some outcomes are surrogate markers e.g. for HIV infected individuals on HAART, a high VL is as surrogate for non-adherence or treatment failure. Surrogate markers are often used, as they are cheaper and easier to measure than the actual event of interest. VL is a well-established surrogate marker in HIV science.⁷¹

Bias and confounding

Observational studies are prone to random error and/or systematic error (bias). Random error is due to chance and is estimated by confidence intervals (CI) and p-values in the statistical methods. Systematic error can occur in the way individuals are selected into a study (selection bias), the way variables are registered or measured (information bias) or from confounding. A confounder is an independent risk factor related both to the event of interest and to the exposure.⁷⁰ I.e. IDU is a confounder in study III where IDU is both associated with HIV infection and the outcome SAB.

In the studies we have tried to reduce selection bias in various ways. In all the studies we have used incident cases only, the geographical area is restricted to Denmark and the number lost to follow-up is minimized. In study I, II and IV the event of interest is death. Due to national registries it is possible to track deaths even if we have lost contact with the individual at the HIV clinic. Individuals lost to follow-up are mainly due to emigration. Information bias is minimized by the standard procedures for DHCS and the Danish staphylococcal database, where trained personal register data for all included individuals. Also objective and well-defined criteria are used for defining disease and exposure.

To account for confounding we have used several approaches. In study III we have used the approach of a matched cohort study, where each HIV infected individual is matched to presumably HIV negative population individual on the confounders age and gender and followed to the event of interest – in this case SAB. Exclusion is used in study IV to define a group of IDUs with the highest

risk for HIV. In the statistical analysis we have where appropriate used restricted, stratified and multivariate analyses.

Time up-dated variables

In study III CD4+ cell count, VL, HAART and age was treated as time-updated variables. In study IV HIV infection and age was treated as a time-updated variables. Infection with hepatitis C virus (HCV), however, is not treated as a time-updated variable (study I and II), as this information is not available in DHCS.

Competing risks

In studies on specific causes of death one have to consider competing risks. For example if an HIV infected individual dies in a car accident, the same individual cannot die from an HIV related event. When fitting the Cox regression analysis for HIV related and non-HIV related death (study I) the causes of death were treated as competing risks. From study entry all patients were at risk for both types of death. When death occurred, the cause of death was registered and the observation period stopped. In the analysis of HIV related death, a patient dying from an HIV related death was registered as an event. A patient dying from a non-HIV related or unknown cause was censored at time of death. The opposite was applied to the analysis of non-HIV related death.⁷⁰

Statistical methods

Intergroup baseline characteristics were compared using the χ^2 - test for dichotomous variables and Kruskal-Wallis test for continuous variables. Median and interquartile ranges (IQR) were determined for continuous variables like age, duration of HIV infection, time to HAART and CD4+ cell counts. For class variables, frequencies and percentages were computed. Significance level was set at $p < 0.05$.

Non-parametric analysis of time to event (mortality) was studied with Kaplan-Meier survival plots (study I, II and IV). This statistical approach was also used in the additional analysis of time to HAART from first eligible (see discussion and perspective section).

Cox regression analysis (study I and II) and Poisson regression analysis (study III and IV) were used for parametric analysis of time to event and to explore risk factors for events among groups. Hazard ratios, IR, incidence rate ratios (IRR), mortality rates (MR) and mortality rate ratios (MMR)

were calculated where appropriate. To split person years of observation (PYO) for calculation of IR (study III and IV), we used the Stratify macro for SAS.⁷²

Proportional hazards is a prerequisite for regression analysis.⁷³ The proportional hazards were tested by Schoenfeld plots (study I and II) and Kaplan-Meier plot (study IV), and the non-proportional hazard in study IV was handled by stratification.⁷³

SAS statistical software 9.1 (SAS Institute Inc, Cary, NC, USA) was used for data analysis.

Ethical considerations

The studies in this thesis have been approved by the Danish Data Protection Agency under the following journal numbers. Study I and II (record no. 2008-41-1781), study III (record no. 2007-41-1196) and study IV (record no. 2007-41-0885). The DHCS has been presented to the local ethical committee.

Study I

Aim

To estimate the impact of injecting drug use as transmission group on mortality in HIV infected individuals in the HAART era.

Background

Mortality in IDUs is substantially higher than in the general population,⁷⁴⁻⁷⁶ due to well-known risks such as overdoses, accidents, bacterial and viral infections and HIV-related causes of death.^{77, 78} Also among HIV infected individuals, individuals with injecting drug use as transmission route have higher mortality.^{10, 11, 79, 80} However, differences in national health care systems and the course of the HIV epidemic make it difficult to compare these results to Danish conditions.

Methods

Study population

From DHCS we included HIV infected patients who were diagnosed with HIV before 1 January 2008 and who were alive on 1 January 1997. Deaths were categorized according to DHCS as HIV related if the patient died from an AIDS defining disease (opportunistic infection, Kaposi sarcoma, HIV associated lymphoma, AIDS dementia or HIV wasting), and non-HIV related if the patient died from other causes. Outcomes were: 1) death from any cause, and 2) HIV related death versus non-HIV related death.

Statistical analyses

The Kaplan-Meier analysis was used to construct the survival curve for overall mortality. Cox proportional hazard regression analyses were used to estimate MRR for HIV infected IDUs and non-IDUs. When fitting the Cox regression analysis for HIV related and non-HIV related deaths, the causes of death were treated as competing risks.

Main results

Overall mortality

During 30,403 PYO 753 (16.5%) patients died. Among IDUs 206 (42.3%) individuals died during 3,187 PYO (MR: 65/1000 PYO, 95% CI: 56-74/1000 PYO) and among non-IDUs 547 (13.4%) deaths occurred during 27,216 PYO (MR: 20/1000 PYO, 95% CI: 18-22/1000 PYO). Among IDUs

63 (30.6%) deaths occurred before the individual initiated HAART and 143(69.4%) after HAART initiation. The estimated 1 and 10 years probabilities of survival were 92.9% (95% CI: 90.6–95.3) and 53.2% (95% CI: 48.1-58.3) among IDUs and 96.8% (95% CI: 96.3-97.4) and 82.1% (95% CI: 80.7-83.6) among non-IDUs (figure 3).

In the unadjusted analysis, injecting drug use as transmission group more than tripled the mortality in HIV infected patients (MRR: 3.2; 95% CI: 2.7-3.8). After adjusting for age, sex, race and year of diagnose the mortality among IDUs was still more than three times higher than among non-IDUs. Sub analysis on patients diagnosed after 1997 did not change the results substantially, neither did sub analysis on ethnically Danish patients only.

Causes of death

Cause of death was registered as HIV related or non-HIV related in 685 (91.0%) cases. A total of 21 deaths among IDUs were categorised as HIV related whereas 168 of deaths among non-IDUs were HIV related. We observed no increased risk of HIV-related mortality in IDUs (adjusted MRR: 1.1; 95% CI: 0.7-1.7). However, injecting drug use was associated with a substantial increase in non-HIV related mortality (adjusted MRR: 4.6; 95% CI: 3.8-5.6).

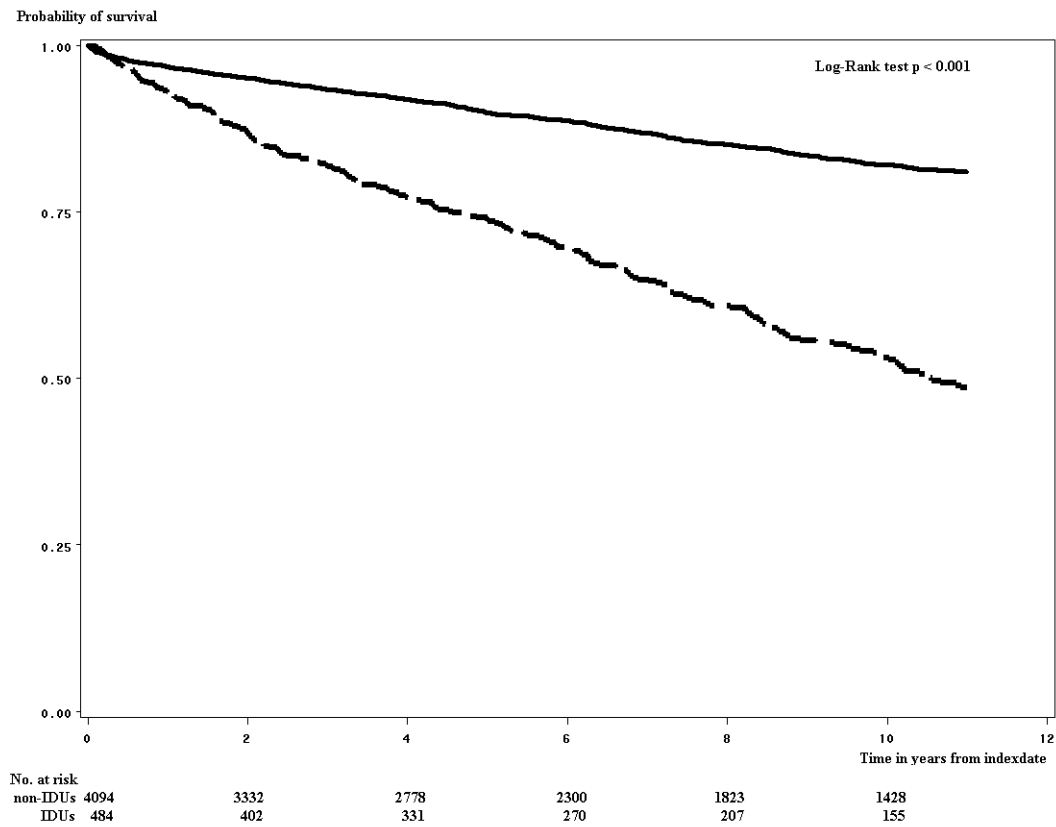


Figure 3: Kaplan-Meier plot displaying survival for HIV infected non-IDUs (solid line) and HIV infected IDUs (broken line).

Study II

Aim

To compare mortality, response to HAART and differences in initial ART regimen in HIV infected IDUs and non-IDUs, who have initiated HAART.

Background

Since HAART was introduced, it has shown its efficiency in controlling the HIV disease and in lowering morbidity and mortality in HIV infected individuals including IDUs.³⁶⁻³⁸ Several studies have compared the effect of HAART on mortality among various HIV transmission groups, and most studies find that IDUs compared to e.g. MSM and HSX have less benefit of HAART, mainly due to lower adherence.^{10-12, 81-83} Generally the question of adherence is difficult to account for.⁸⁴ When administered correctly, HAART has the same efficacy in IDUs as in other HIV-infected patients.^{12, 83} The optimal timing of HAART initiation is still controversial. However, delay in HAART initiation until CD4+ cell counts are low results in higher rates of death,⁸⁵ and it is shown, that IDUs initiate HAART at later stages of HIV disease.^{10, 86, 87}

Methods

Study population

We included all HIV infected patients registered in the DHCS who initiated HAART before 31 December 2007. Main outcomes were suppressed VL and death.

CD4+ cell counts, viral loads and mortality

To evaluate the response to HAART we assessed the proportion of patients who achieved an undetectable VL during follow-up (defined as plasma HIV-RNA <500 copies/mL) and absolute CD4+ cell counts. Unadjusted values for 12-week intervals were computed for IDUs and non-IDUs as described elsewhere.⁸⁸ MRs were computed for IDUs and non-IDUs.

Time from eligible for therapy until HAART initiation

A patient was found eligible for therapy when at least one of the national criteria for start of HAART was first met (in practice CD4+ cell count and HIV-RNA). Since HAART was not fully

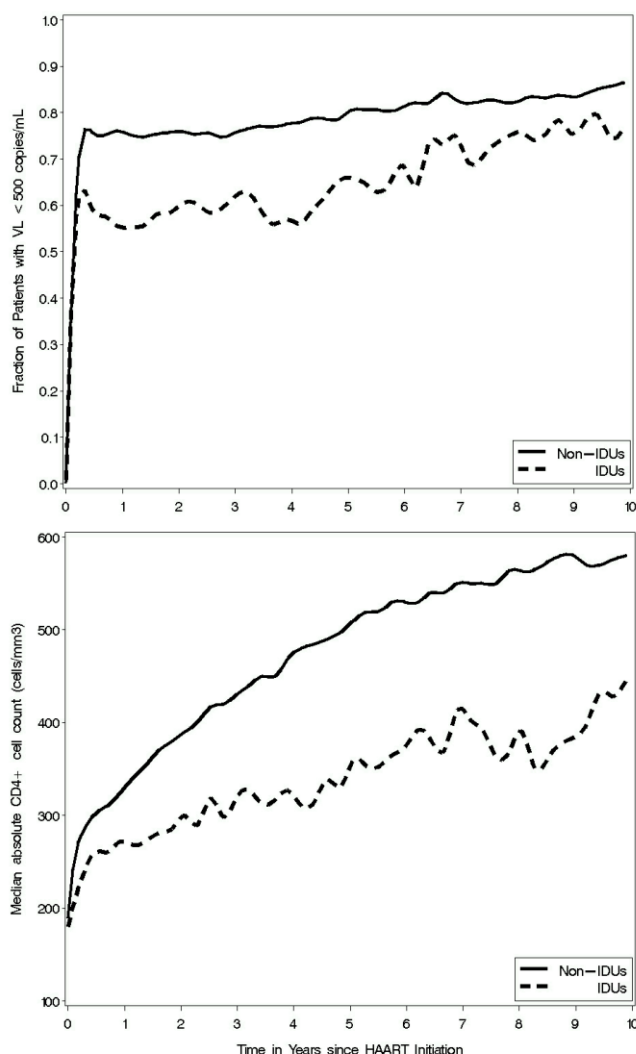
implemented as standard of care before 1 January 1997, patients who met HAART initiation criteria before 1 January 1997 was set as eligible for therapy at 1 January 1997.

Statistical analyses

The Kaplan-Meier analysis was used to construct the survival curve for overall mortality. Cox proportional hazards regression analyses were used to estimate MRRs for IDUs and non-IDUs.

Main results

A total of 3615 patients, who represent 22,804 PYO, initiated HAART and were used in the analysis. 346 patients (9.6%) were categorized as IDUs with 1861 PYO and 3269 patients (90.4%) were categorized as non-IDUs with 20,943 PYO. IDUs had a higher CD4+ cell count at time of HIV diagnosis, but CD4+ cell count at HAART initiation and nadir CD4+ cell count did not differ significantly, though there was a tendency for lower nadir CD4+ cell count in IDUs.



Impact of HAART on viral load and CD4+ cell count

One year after HAART initiation 55% (95% CI: 50-61; n=296) of IDUs had reached viral control, but this was substantially less ($p=0.0002$) than for non-IDUs 76% (95% CI: 75-78; n=2873). (Figure 4; top). Also, after 5 and 10 years of follow-up fewer IDUs than non-IDUs had gained full viral control. IDUs also attained lower absolute CD4+ cell count after start of HAART, than did non-IDUs. (Figure 4; bottom)

Figure 4: Fraction of individuals with suppressed VL (top) and absolute CD4+ cell counts years after HAART initiation (bottom).

Initial HAART regimens

Non-IDUs were more likely to have a NNRTI included in their initial HAART regimen and IDUs were more likely to start a regimen exclusively containing NRTIs, including Trizivir® or a PI containing regimen (not statistically significant). In this cohort of patients who had all started HAART, time from HAART eligibility to HAART initiation was substantially longer in IDUs compared to non-IDUs (approximately four vs. one month), and IDUs had a higher number of different HAART regimens per PYO than non-IDUs.

Mortality

During 22,804 PYO 576 (15.9%) patients died. Among IDUs 138 (39.9%) patients died during 1861 PYO (MR: 74/1000 PYO, 95% CI: 62-87/1000 PYO) and among non-IDUs 438 (13.4%) deaths occurred during 20,943 PYO (MR: 21/1000 PYO, 95% CI: 19-23/1000 PYO). The adjusted MRR was 3.6 (95% CI: 2.9-4.3) for IDUs compared to non-IDUs. Figure 5 shows the Kaplan-Meier survival curves for the two groups. We found that HIV infected IDUs had a higher mortality after start of HAART than other HIV infected patients. The estimated 1, 5 and 10 years probability of survival was 96.4% (95% CI: 95.8–97.1), 89.9% (95% CI: 88.8-91.0) and 81.6% (95% CI: 80.0-83.3) among non-IDUs and 91.2% (95% CI: 88.1-94.2), 68.5% (95% CI: 63.2-73.9) and 46.0% (95% CI: 38.9-53.1) among IDUs.

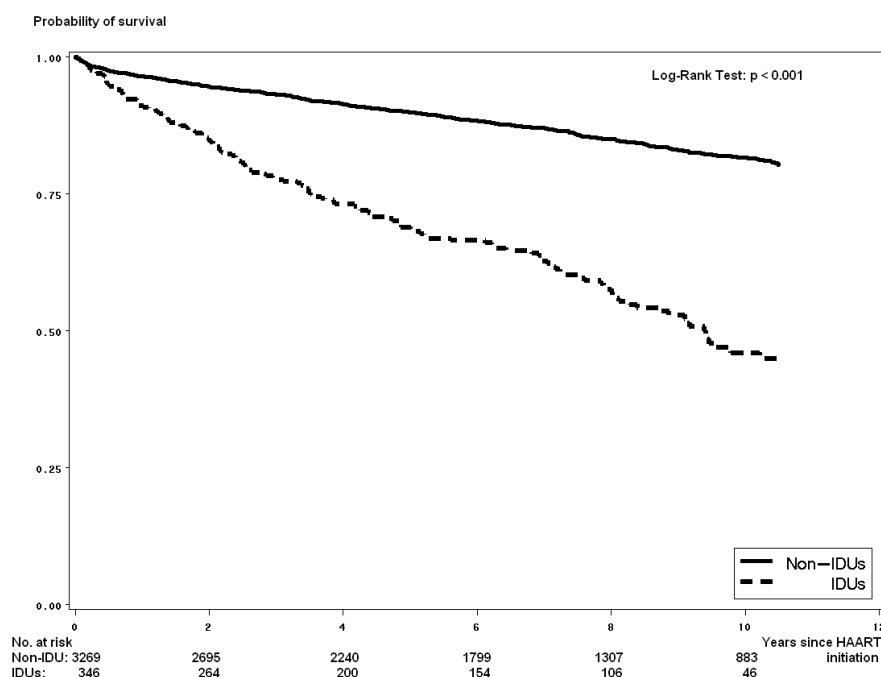


Figure 5: Kaplan-Meier plot displaying the proportion of survival after HAART initiation in IDUs and non-IDUs.

Study III

Aims

To compare incidence of and risk factors for SAB in a nation-wide HIV infected and uninfected matched cohort.

Background

SAB is an important cause of morbidity and mortality.⁴⁵ HIV infected individuals are at increased risk of opportunistic and common bacterial infections and *S. aureus* ranks as one of the most common causes of bacterial infection.⁴⁶⁻⁴⁹ Risk factors for invasive *S. aureus* infection are advanced HIV disease,^{46, 47, 50} prior hospitalisation, injecting drug use and the presence of intravascular devices.^{47, 48, 52-54} Further, HIV infection is associated with a higher risk of repetitive SAB.⁵⁵ HAART is known to reduce the prevalence of BSIs⁵⁶ and strongly reduces morbidity and mortality among HIV-infected individuals in general.⁵⁷

Methods

Study population

Individuals living in Denmark with a diagnosis of HIV at time of study initiation or individuals who were diagnosed with HIV in the study period were eligible for the study. We aimed to identify up to 19 HIV uninfected population individuals, who were matched on sex and age to the corresponding HIV infected individual, on the day of this persons' HIV diagnosis. We identified an average of 18.9 population individuals per HIV infected individual. No information on risk factors was available for population individuals.

PYO were counted from 1 January 1995, date of HIV diagnose or immigration (whichever was last) until emigration, death or 31 December 2007 (whichever came first). In the analysis of risk factors, observation time was stopped after the first episode of SAB identified in The Danish Staphylococcal Database.

IRs for three calendar time periods were computed, and sub-analyses were carried out on HIV transmission groups. Poisson regression analysis was used to estimate the overall IRR for SAB among HIV infected individuals vs. HIV uninfected individuals. Poisson regression analysis was

also used in a sub-study to identify risk factors for first episode of SAB among HIV infected individuals only, and in HIV infected individuals divided on HIV transmission group.

Main results

In this study a total of 4871 HIV infected and 92,116 HIV uninfected individuals were included. A total of 329 SABs were observed, of which 45 were repetitive cases. 169 cases occurred in HIV infected individuals, of which 37 were repetitive cases. In HIV uninfected individuals we observed 160 cases of SAB, of which 8 were repetitive cases. The frequency of methicillin-resistant *S. aureus* (MRSA) was low in both HIV infected and non-HIV infected, and no difference in 30-day mortality was observed.

Among HIV infected individuals, 50% of first-time SAB occurred in individuals reporting injecting drug use as HIV transmission route. IDUs tended to be younger at SAB, had higher CD4+ cell count (at HIV diagnosis, nadir and latest prior to SAB) and were less likely to have an AIDS diagnosis prior to SAB, compared to other HIV transmission groups. Fewer IDUs received HAART and were less likely to be virally suppressed at time of SAB, but none of these results reached statistical significance.

Incidence of Staphylococcus aureus bacteraemia over calendar period

One hundred and sixty nine cases of HIV associated SAB occurred during 34,208 PYO (IR: 494/100,000 PYO) and 160 SABs occurred among HIV uninfected individuals during 783,724 PYO (IR: 20.4/100,000 PYO). Compared to HIV uninfected individuals, the overall crude IRR for HIV associated SAB was 24.2 (95% CI: 19.5-30.0). The crude IRR for HIV infected vs. HIV uninfected declined over time from 42.2 (95% CI: 28.1-63.3) in 1995-98, to 27.4 (95% CI: 17.6-42.7) in 1999-2002 and 15.0 (95% CI: 10.7-20.9) in 2003-07. Overall, the incidence of SAB declined considerably over calendar time in HIV infected individuals, but was stable in HIV uninfected individuals (figure 6, left). IR in the different HIV transmission groups varied. IDUs had the highest incidence of SAB in all three time periods, and experienced the smallest proportional decrease in SAB IR (figure 6, right). IDUs had the highest number of repetitive SAB among HIV infected individuals; 25 of 37 (67.6%).

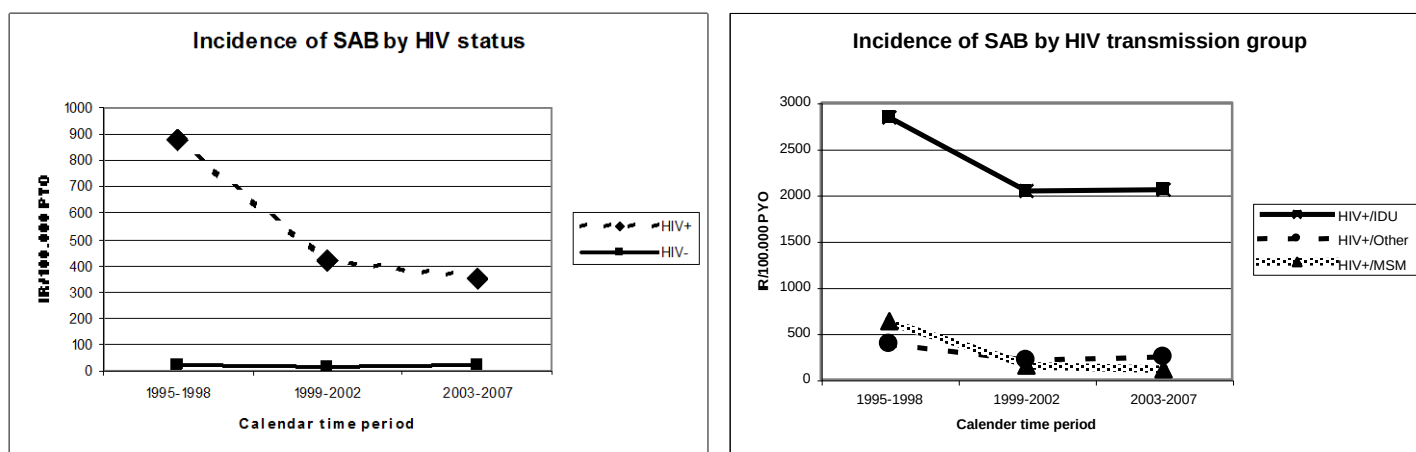


Figure 6: Incidence of SAB in three calendar time periods divided by HIV status (left) and by HIV transmission group (right).

Risk of Staphylococcus aureus bacteraemia among HIV infected individuals

In a univariate analysis, latest CD4+ cell count, ethnicity, HIV transmission group, HAART, suppression of HIV-RNA and calendar time period were associated with risk of SAB. In the multivariate analysis, with adjustment for CD4+ cell count alone, the effect of the time period were strongly affected, as were the effects of HIV transmission group, HAART and HIV-RNA level. In the second multivariate analysis, including all variables except for plasma HIV-RNA, the latest CD4+ cell count prior to SAB remained the single strongest predictor of SAB.

In a stratified multivariate analysis on HIV transmission group, latest CD4+ cell count <100 cells/ μ L remained the strongest predictor for SAB in all groups, though much more pronounced in the MSM group with an IRR of 31.1 compared to 3.8 for IDUs. (Table 1)

Table 1: Adjusted incidence rate ratios of first *Staphylococcus aureus* bacteraemia in HIV infected patients divided on HIV transmission group by latest CD4+ cell count.

Variable	Incidence rate ratio (95% CI) ^b		
	IDU	MSM	HXS
Latest CD4+ cell count, cells/ μ L ^a			
≥350	1 (ref)	1 (ref)	1 (ref)
100-349	2.1(1.1-3.9)	3.2(1.0-10.0)	1.4(0.4-4.2)
0-99	3.8(1.5-9.2)	31.1(10.3-94.0)	10.1(3.3-30.7)

^aTime up-dated variable; ^bAdjusted for latest CD4+ cell count, age, ethnicity, sex, HAART and time period. Not adjusted for plasma HIV-RNA due to low numbers.

Study IV

Aim

To compare mortality in HIV infected and HIV uninfected IDUs in drug abuse treatment.

Background

In study I we showed that among HIV infected individuals IDUs had a higher mortality than non-IDUs. The differences in mortality was not related to HIV infection but to other causes of death.⁸⁹ Compared to the general population IDUs have higher mortality.^{40, 42, 74, 90} Comparing mortality in HIV infected IDUs to HIV infected non-IDUs might overestimate the MRR in IDUs, due to higher baseline risk in this group. The most appropriate control group to evaluate the effect of HIV infection on mortality in IDUs, would be HIV uninfected IDUs. Only few studies have compared these two groups and with conflicting results.^{44, 91-94} One study showed no excess mortality for HIV infected IDUs in drug abuse treatment compared to HIV uninfected IDUs in the HAART era.⁹¹ In other studies HIV infection was associated with increased risk of death among IDUs.^{44, 92-94}

Methods

Study population

All individuals in RDT who initiated drug abuse treatment from 1 January 1997 until 31 December 2009 were eligible for the study. The study was limited to individuals who reported use of amphetamine, heroin, cocaine, methadone, opioids or buprenorphine, either as main drug or side-drug.

Individuals were divided in two main groups – patients who entered drug abuse treatment for the first time and patients who previously had been in drug abuse treatment. Further, the individuals were categorized in three sub-groups according to HIV status in DHCS: 1) IDUs that were already diagnosed with HIV at baseline, 2) IDUs that were diagnosed with HIV during the study period (seroconverters), and 3) IDUs that could not be identified in DHCS and therefore were considered HIV uninfected. Outcomes were overall death and cause specific death.

Specific causes of death registered by ICD-10 codes were obtained from DRDC, and were divided into 9 categories.

Statistical analyses

PYO were counted from day of admission to drug abuse treatment (earliest 1 January 1997) until death, emigration or 31 December 2009 (whichever came first). Individuals were kept in the analysis even if they dropped out of drug abuse treatment or had treatment interruptions.

A Kaplan-Meier plot was constructed for overall mortality in HIV infected and HIV uninfected individuals, with HIV as a time varying covariate and allowing for delayed entries in the HIV strata for individuals tested positive for HIV during the study period. Poisson regression analysis was used to estimate MRR for death in HIV infected IDUs vs. HIV uninfected IDUs.

Main results

A number of 26,036 individuals with a total of 176,417 PYO were included in this study.

13,844 individuals initiated drug abuse treatment for the first time. 44 (0.3%) were diagnosed with HIV at baseline, 55 were diagnosed with HIV during the study period and 13,745 were not diagnosed with HIV throughout the study period. For individuals diagnosed with HIV at baseline, median time from HIV diagnose to drug abuse treatment was 8.1 years (IQR: 2.3-13.3 years) and for seroconverters, time to HIV diagnose after drug abuse treatment initiation was 4.2 years (IQR: 2.0-7.4 years). For individuals diagnosed with HIV at baseline, CD4⁺ cell count at HIV diagnosis was 320 cells/ μ L (IQR: 204-515 cells/ μ L), and for seroconverters, CD4⁺ cell count at diagnosis was 476 cells/ μ L (IQR: 268-645 cells/ μ L). A high proportion of HIV infected IDUs reported another HIV transmission group than injecting drug use.

Mortality

Among individuals in first time drug abuse treatment, 1026 deaths were observed during 82,848 PYO, 25 among HIV infected and 1001 among HIV uninfected individuals. A Kaplan-Meier survival plot is shown in figure 7. HIV infected IDUs had a higher mortality through out the study period, but in the first half-year after drug abuse treatment initiation the difference was higher. During the first 6 months, HIV infected IDUs had a MR of 250.0/1000 PYO compared to HIV uninfected individuals MR of 10.7/1000 PYO, giving an adjusted MMR of 13.8 (95% CI: 5.5-35.1). In the period following the first 6 months, the adjusted MMR were 2.5 (95% CI: 1.6-3.9).

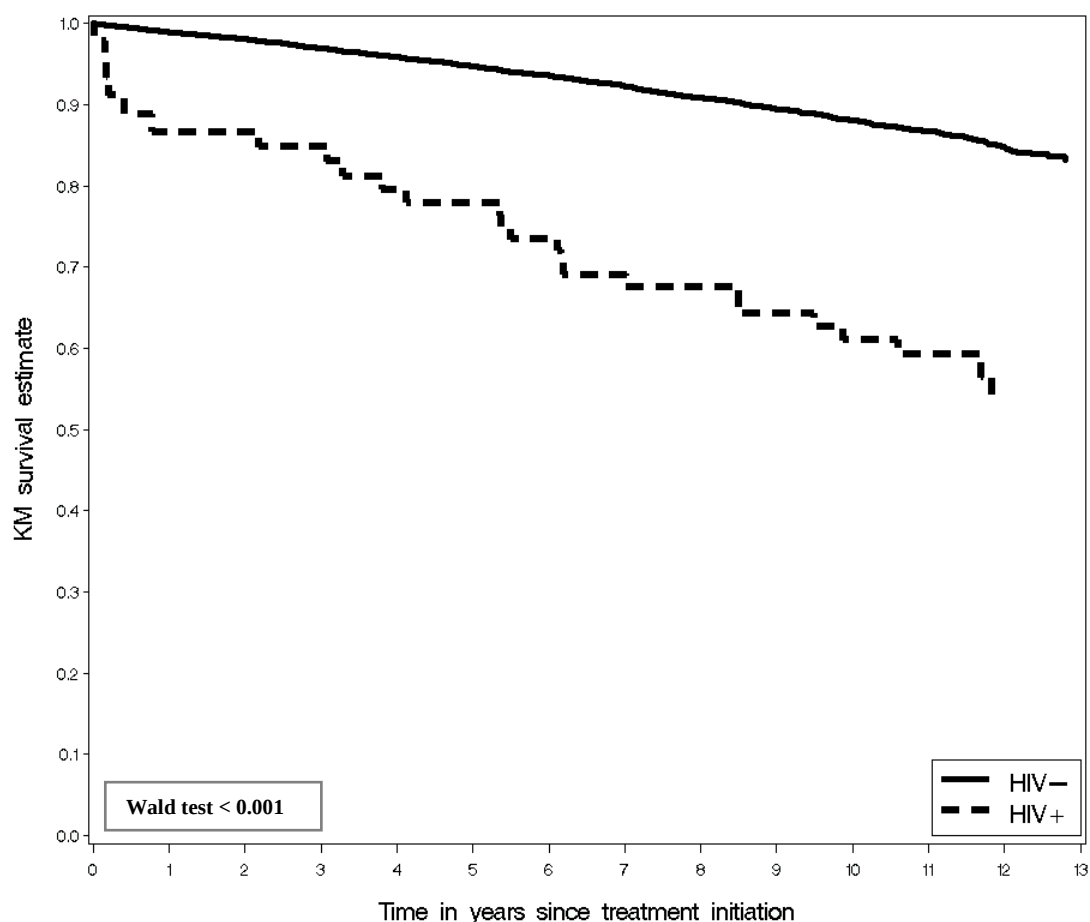


Figure 7: Kaplan-Meier survival plot for IDUs in first time drug abuse treatment. HIV infection was treated as time varying co-variate with the possibility for delayed entry in the HIV strata.

Cause of death

For HIV infected individuals, HIV related death was the main cause of death for both IDUs in first time drug abuse treatment, and for IDUs in experienced drug abuse treatment with MR ranging from 15.7 to 18.7/1000 PYO. MR related to drug use was second highest to HIV in HIV infected individuals and the highest among HIV uninfected individuals.

For 23 of 25 deceased HIV infected individuals in first time drug abuse treatment CD4+ cell count was available. 10 (43%) died with latest CD4+ cell count before death ≥ 350 cells/ μ L, 11 (48%) with a CD4+ cell count of 100-349 cells/ μ L and only 2 (9%) with a CD4+ cell count < 100 cells/ μ L. At time of death 17 of 25 individuals were in HAART and of those 11 had fully suppressed HIV-RNA. The three HIV related deaths among HIV uninfected individuals is either due to mistakes in registration of cause of death ($n=1$) or has occurred in individuals tested positive for HIV, but not seen in one of the HIV treatment centres for follow up and care ($n=2$).

General conclusions

In conclusion the studies for this thesis have demonstrated that HIV infected IDUs have a higher non-HIV related mortality than HIV infected non-IDUs. That a smaller fraction of IDUs in HAART are virally suppressed compared to non-IDUs in HAART and that also HIV infected IDUs in HAART have a higher mortality than HIV infected non-IDUs in HAART. Further, the studies showed that HIV infected individuals were more likely to experience SAB, but that this risk was unevenly distributed among HIV transmission groups and calendar time periods. Last the studies showed that among IDUs in drug abuse therapy HIV infected individuals had a higher mortality compared to HIV uninfected individuals, although only 10% of deceased HIV infected individuals had a CD4+ cell count below 100 cells/ μ L at time of death.

Discussion and perspectives

Reducing death among HIV infected IDUs (Study I, II and IV)

Study I demonstrated a substantially increased non-HIV related mortality in HIV infected IDUs, compared to HIV infected non-IDUs.⁸⁹ This result is in accordance with findings from other cohorts of HIV infected individuals,⁷⁹ where pre-AIDS mortality in HIV infected IDUs, compared to HIV infected non-IDUs, is caused by concurrent risk factors in this population, such as bacterial infections, overdoses, accidents, suicides and violence.^{77, 95} This is well in accordance with the findings from our study (Study IV). Results from study IV also showed, that though HIV infected IDUs had higher mortality than HIV uninfected IDUs, the latest CD4+ cell count before death in HIV infected IDUs was generally high and it can be questioned if the higher mortality is related to HIV infection per se.

Study II showed that also IDUs receiving HAART had a higher mortality.⁸¹ One study on mortality reported no increased mortality in HIV infected IDUs compared to non-IDUs.⁹⁶ Another study reported that IDUs initiating HAART at CD4+ cell counts >300 CD4+ cells/ μ L had the same mortality as non-IDUs,⁹⁷ and Wood et al. reported that compliant IDUs in HAART had the same mortality than non-IDUs.⁹⁸

We found that IDUs in Denmark had a high CD4+ cell count at time of diagnosis, this compared to findings from other studies, where IDUs generally are diagnosed late.⁹⁹ This could be attributed to

the fact that IDUs are a well-known risk group, and that they are more likely to get tested for HIV infection, whenever in contact with the health care system or drug abuse treatment facilities. IDUs probably have suboptimal health care seeking behaviour¹⁰⁰ and compliance issues,¹⁰¹⁻¹⁰³ which are also indicated in study II, where IDUs were found to have a lower nadir CD4+ cell count and were less likely ever to be exposed to HAART during the study period.

Optimizing HAART for HIV infected IDUs (Study II)

For more than a decade HAART has shown its efficacy in controlling the HIV-disease.³⁶⁻³⁸ New studies emphasise the benefit of early treatment of the HIV infected patient, in preventing depletion of the patient's immune system and increasing long-term survival.⁸⁵ A study from Wood E et al. focused on treatment to increase viral suppression, in order to reduce contagiousness and transmission of the disease.¹⁰⁴ Therefore early diagnosis becomes increasingly important. As shown in study II and III, IDUs are generally diagnosed at an earlier stage of disease than non-IDUs, which gives the opportunity of carefully monitoring the disease progression, and to initiate HAART when required. In contrast to the higher CD4+ cell count at time of HIV diagnosis, IDUs had a tendency towards lower nadir CD4+ cell count prior to initiation of HAART. IDUs were also shown to have a delay in HAART initiation, which is consistent with findings from other studies.^{10, 87, 105-107}

However, the results from study II have to be interpreted carefully as they are only descriptive and as the study was not designed for this purpose. In other studies IDUs are shown to initiate HAART less frequently^{10, 30, 87, 105, 106} and since we only included patients who actually initiated HAART in the analysis, we are likely to underestimate the time to treatment

Below a Kaplan-Meier plot of time to HAART from first eligible day is displayed (figure 8). This plot also includes individuals who never initiated HAART and therefore gives a more realistic picture of time to HAART in IDUs and non-IDUs. In this analysis, median time to HAART for IDUs is 303 days and 35 days for non-IDUs.

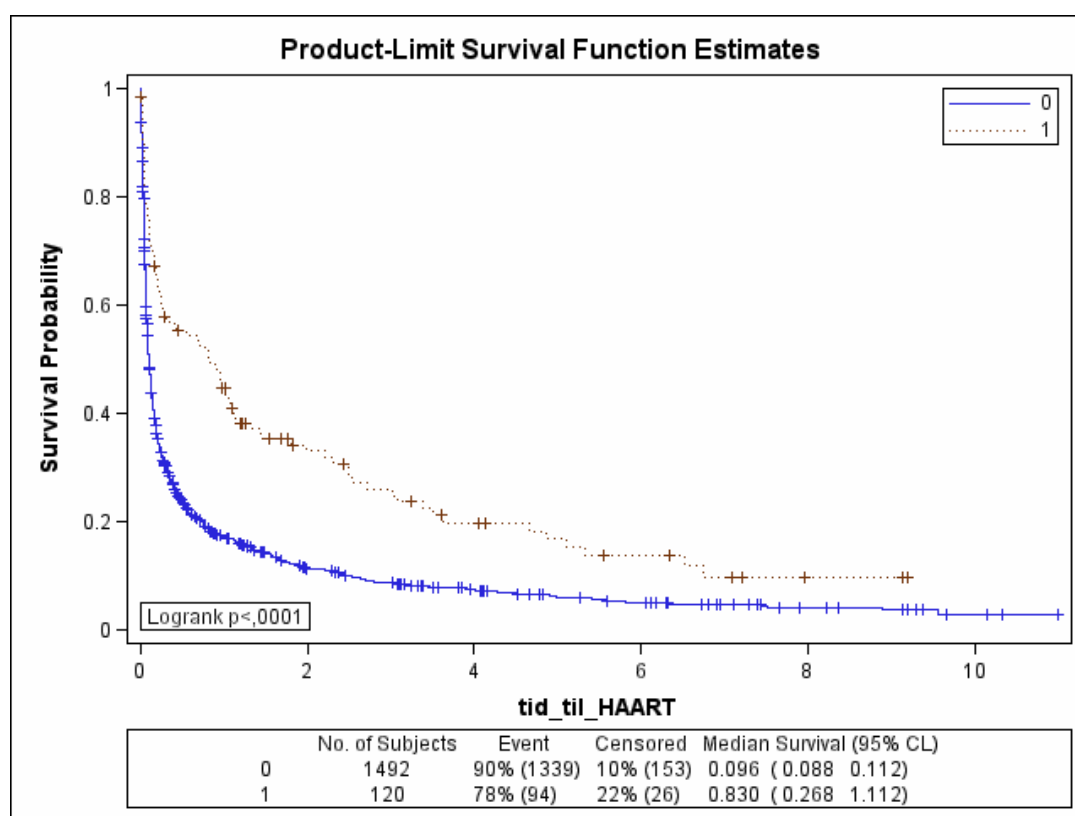


Figure 8: Kaplan Meier plot displaying time (in years) to HAART from first eligible for individuals in DHCS diagnosed from 1 January 1997 – 31 December 2007. Strata 0 / blue = non-IDUs. Strata 1 / red = IDUs.

Some studies have shown that IDUs are more likely to initiate inappropriate antiretroviral therapy, including dual therapy and triple-NRTI regimens.¹⁰⁸ In contrast, we found that IDUs were mainly started on appropriate HAART regimens, although a higher fraction initiated triple-NRTI regimens. The problem with suboptimal initial HAART regimens shown for IDUs are likely to diminish, as triple-NRTI regimens are no longer part of the national treatment guidelines. Methadone is widely accepted in Denmark as treatment of opioid abuse, and may play an important role in the clinicians' choice of antiviral drugs, since pronounced interaction between NNRTIs and methadone exists.¹⁰⁹ IDUs were more likely to initiate a PI containing regimen. IDUs had a higher number of different HAART regimens per observation year. Discontinuation and change of HAART is more likely to occur when the patient experiences adverse effects.¹¹⁰ PI containing HAART regimens are known to cause a high degree of discontinuation of HAART,¹¹¹ mainly due to gastro-intestinal adverse effects. Less resistance towards PI containing regimens compared to NNRTI regimens¹¹² could also explain the reluctance of prescribing NNRTI for patients presumed to have low adherence. The higher number of HAART regimens among IDUs could also be attributed to non-structured treatment discontinuations and physicians re-initiating HAART.¹¹³

We found that 55% of HIV infected IDUs obtained viral control after one year of HAART. In other cohorts the following has been observed: Wood et al. reported from Vancouver that 51% of IDUs had undetectable VL after one year compared to 71% among non-IDUs.¹² The Swiss cohort study reported that current IDUs had an OR of 0.81 compared to non-IDUs for viral suppression³⁰ and in Spain IDUs had a hazard ratio of viral suppression of 0.86 compared to MSM.¹⁰

Resistance could potentially also affect the poorer viral response in IDUs, but resistance is generally low in Denmark.¹¹⁴ Only one of 84 cases of transmitted resistance during the years 2001-09 was observed among IDUs (personal communication). Another study has also shown no increased risk of resistance in IDUs compared to non-IDUs.¹¹²

Reducing incidence of SAB (Study III)

Study III focussed on morbidity in HIV infected individuals – more specifically SAB. Other studies have reported HIV as an important risk factor for SAB.^{46, 47, 49, 50} Our study showed a declining incidence over time for HIV infected individuals, but a constant incidence for age matched non-HIV infected individuals. The study also emphasized that the disease burden was unevenly distributed, so that IDUs had a much higher IR than other HIV transmission groups. When studying the risk factors for SAB it quickly became obvious that risk of SAB was very much influenced by HIV transmission group. MSM were likely to have HA SAB acquired at a low CD4+ cell count, probably related to hospitalizations for AIDS associated diseases in the early calendar period.⁴⁷ IDUs predominantly had CA SAB, acquired at a higher CD4+ cell count, which presumably is related to lifestyle and injecting practises.⁶³ However, IDUs risk of SAB increased with lower CD4+ cell counts indicating that immunodeficiency per se increased the risk of SAB. Senthilkumar et al.⁴⁸ reported an IRR of 16.5 for HIV associated SAB, with a majority of cases related to intravascular devices, which again was related to manifestations of severe immunodeficiency, requiring intravenous treatments.

Several studies have reported an increased risk of MRSA colonisation and infection in HIV infected individuals.¹¹⁵⁻¹¹⁹ The prevalence of MRSA in Denmark is low⁶¹ and we found that rates among HIV infected individuals were low and comparable to the general population.

Further reductions in SAB IRs can be expected by reducing immunodeficiency via increased HAART coverage, by reducing the proportion of late presenters and by encouraging sterile injecting methods among IDUs.

Psycho-socio-economic factors related to IDUs in drug abuse treatment (Study IV)

RDT contains information on socio-demographic characteristics, e.g. level of education, marital status, number of children, housing and employment vs. social benefits etc. However, data are fragmented and missing for many enrolments and not suitable for further analysis. On the other hand the data gives important information on the marginalisation of IDUs and even further marginalisation of IDUs diagnosed with HIV during the study period. (Table 2)

Characteristic	Previous drug abuse treatment			First time drug abuse treatment		
	HIV+ at baseline	HIV- at baseline		HIV+ at baseline	HIV- at baseline	
		HIV sero-converters	HIV-		HIV sero-converters	HIV-
	(n=220) n (%)	(n=113) n (%)	(n=11859) n (%)	(n=44) n (%)	(n=55) n (%)	(n=13745) n (%)
Habitation:						
Single	138(62.7)	73(64.6)	7176(60.5)	35(76.6)	44(80.0)	10480(76.3)
Co-habiting	49(22.3)	27(23.9)	2226(18.8)	8(18.2)	10(18.2)	2838(20.7)
Unknown	33(15.0)	13(11.5)	2457(20.7)	1(2.3)	1(1.8)	427(3.11)
Educational level	n=93	n=64	n=5788	n=26	n=36	n=8479
<= Primary school	50(53.8)	53(83.8)	3457(59.7)	10(38.5)	20(55.6)	4960(58.5)
Apprentice	10(10.8)	3(4.7)	1113(19.2)	8(30.8)	5(13.9)	2072(24.4)
High school	4(4.3)	3(4.7)	326(5.6)	1(3.8)	2(5.6)	583(6.9)
Higher education	29(31.2)	5(7.8)	892(15.4)	7(26.9)	9(25.0)	864(10.2)
Income	n=24	n=1	n=1281	n=13	n=0	n=3301
Job / salary	0(...)	0	222(17.3)	2(15.4)	...	947(28.7)
Cash benefit	3(12.5)	0	469(36.6)	6(46.2)	...	1143(34.6)
Disability pension	20(83.3)	1(100.0)	298(23.3)	3(23.1)	...	251(7.6)
Other	1(4.2)	0	292(22.8)	2(15.4)	...	960(29.1)
Housing	n=192	n=98	n=9735	n=41	n=52	n=13156
Own	132(68.8)	45(45.9)	5741(59.0)	26(60.5)	17(30.9)	6556(47.9)
Street/shelter	25(13.0)	21(21.4)	1049(10.8)	5(12.2)	14(26.9)	928(7.1)
Other	35(18.2)	32(32.7)	2946(30.3)	10(24.4)	21(40.4)	5672(43.1)
Type of treatment						
MST	88(40.0)	18(15.9)	2669(22.5)	15(34.1)	12(21.8)	1872(13.6)
Other replacement	2(0.9)	3(2.7)	345(2.9)	3(6.8)	2(3.6)	699(5.1)
Drug free	11(5.0)	6(5.3)	3738(31.5)	8(18.2)	5(9.1)	7899(57.5)
Other/unknown	119(54.1)	86(76.1)	5107(43.1)	18(40.9)	36(65.5)	3275(23.8)

Table 2: Demographic characteristics of 26,036 Danish drug users in treatment stratified on drug abuse treatment history at baseline and HIV status.

The socio-demographic data of the study population reveals an overall marginalised group in the Danish society. IDUs have generally a very short education and no job. They often live alone, only few have housing of their own and they often have a side abuse of alcohol. A higher percentage of IDUs have non-Danish origin than in the general population.²⁰ Numbers in table two could indicate that the individuals acquiring HIV during the study period are more marginalised than HIV uninfected IDUs (habitation, housing, type of main drug), which again may put them in greater risk for HIV. The older age at time for first attending the drug abuse treatment for HIV infected compared to HIV uninfected could be a result of strong marginalisation of the group of HIV infected IDUs within the injecting drug use community. This makes HIV infection a marker of a group that is hard to reach with health care facilities and health care information / prevention campaigns. On the other hand HIV infected individuals entering drug abuse treatment seem to have more controlled housing, an income and less side abuse, which could indicate that when IDUs get a diagnosis of HIV social measures will be established.

Studies based on DHCS have previously suggested that socio-economic factors may partly explain the high mortality observed in HCV/HIV co-infected patients.^{120, 121} In these studies it was shown that siblings of HCV/HIV co-infected patients had a higher overall mortality (familial excess risk of death) compared to siblings of HIV mono-infected patients. This is suspected to be a result of shared susceptibility to high-risk behaviours, resulting in excess mortality caused from substance-abuse related deaths and other unnatural deaths, and not by HCV infection or increased susceptibility to other infectious diseases. It was also hypothesized that this patient group may have a suboptimal health seeking behaviour, poor adherence to medical treatment and may face inappropriate or lacking attention of health care. An equivalent phenomenon may also account for a part of the excess mortality seen in our studies, as the two groups studied are likely to be very similar. 90% of IDUs are registered to be antibody HCV positive and less than 10% of non-IDUs are antibody HCV positive.

Generalization

Denmark with its free and tax paid health care system, combined with a liberal attitude to harm reduction methods towards IDUs, probably represent a best scenario for care and treatment of HIV infected IDUs. It is unrealistic to believe that the same results are achievable in other settings where either drug abuse is seen as a crime, or in settings where the health care system is based on

individual health care insurance. Results from study IV can only be applied to IDUs in drug abuse treatment.

Future challenges

Though the proportion of individuals diagnosed with HIV with injecting drug use as transmission route has diminished over the last decade, we continuously have to focus on spreading information on how to avoid getting infected. The IDU community is traditionally difficult to reach with normal campaigns and all professionals involved with these individuals must continuously educate this marginalized group. The falling incidence of new HIV cases transmitted via injecting drug use might be a result of effective harm reduction campaigns e.g. needle exchange programmes. But as the last paper (paper IV) emphasize, a high proportion of IDUs report sexually transmitted HIV, so safe sex messages and condom distribution is equally important in this group.

The thesis also showed (paper II) that IDUs initiated HAART later than other HIV transmission groups after they were first found eligible, though IDUs were generally diagnosed with a high CD4+ cell count (paper II and III). Action has to be taken to reduce the time span until HAART initiation from the time where the patients are first found eligible for treatment. This effort has many challenges as more IDUs have unstable housing, active ongoing drug abuse and psychiatric disease, which all will make it difficult for the HIV clinic to get in contact with the individual and persuade them to life long HAART. The physicians at the HIV treatment centres are not likely to be able to lift this task by themselves, and cooperation with physicians and other staff members at the drug abuse treatment clinics is mandatory, as they are likely to have a closer contact with the IDUs. This cooperation is also of vital importance if we want to improve HAART outcomes and increase adherence. It is unlikely that major reductions in HIV related mortality is possible as emphasized by this thesis. HIV infected IDUs do not have an HIV excess mortality compared to HIV infected non-IDUs and HIV infected IDUs have a high CD4+ cell count at time of death. The reductions in mortality for HIV infected IDUs has to be achieved via harm reduction and by reducing mortality from other causes (overdose, accident, violence, infections etc.)

English summary

HIV/AIDS is a common cause of morbidity and mortality among injecting drug users (IDUs) worldwide. Also in Denmark IDUs contribute to the HIV epidemic, though the proportion of IDUs seems to be declining over time.

The aim of this PhD thesis was to explore the impact of injecting drug use on morbidity and mortality among HIV infected individuals, and the impact of HIV infection on mortality in IDUs. The thesis consists of four studies and a review. All four studies are based on data retrieved from the Danish nationwide register on HIV infected individuals seen at the HIV treatment centres (The Danish HIV Cohort Study). The register contains data from 1 January 1995 and is continually updated. Information from other nationwide registries: The Danish Civil Registration system, The Danish Staphylococcal Database, The Registry of Drug Abusers Undergoing Treatment and Registry of Specific Cause of Death, were also used in the studies.

In the first study mortality in HIV infected IDUs and non-IDUs was studied over a 12-year period in the highly active anti retroviral treatment (HAART) era. The second study compared response to HAART, mortality and differences in initial ART regimen between HIV infected IDUs and non-IDUs. In the third study the incidence of and risk factors for *Staphylococcus aureus* bacteraemia (SAB) in HIV infected and uninfected individuals were studied. Furthermore the effect of HIV transmission route was explored. The fourth study aimed to analyze potential differences in mortality in HIV infected and HIV uninfected IDUs in drug abuse treatment.

Remarkable differences in mortality among Danish HIV infected IDUs and non-IDUs were shown, with IDUs having a more than 3-fold increased risk of death compared to non-IDUs. The increased risk of death seemed to be non-HIV related and is likely due to well-known risk factors associated with intravenous drug abuse.

In the second study we explored the effect of HAART on HIV infected IDUs and non-IDUs. The study showed that IDUs had a lesser degree of viral suppression, a poorer response in absolute CD4⁺ cell count and a substantially higher mortality compared to HIV infected non-IDUs. Still more than half of HIV infected Danish IDUs obtained viral suppression after initiating HAART. Although diagnosed at an early stage of disease, initiation of HAART was delayed for IDUs.

Blood stream infections are more prevalent in HIV infected individuals as well as in IDUs. The third study focussed on SAB in different HIV transmission groups. The study demonstrated a declining but high incidence of SAB among HIV infected individuals compared to HIV uninfected individuals. The burden of SAB was disparately distributed among groups of HIV infected individuals so that IDUs had an almost 20-fold higher incidence rate of SAB compared to men who have sex with men in the years 2003-7. Immunodeficiency was the strongest predictor of SAB among HIV infected individuals, but injecting drug use as HIV transmission group, non-suppressed HIV-RNA and lack of HAART also predicted SAB.

The last study demonstrated that mortality among IDUs in Denmark who have initiated drug abuse treatment is about 3-fold higher in HIV infected individuals compared to HIV uninfected individuals. Whether or not the higher mortality is caused by HIV infection in itself can still be questioned, since CD4+ cell count at time of death was relatively high.

Thus, new insights into the epidemiology of HIV in Danish IDUs were analysed and presented in this thesis. Hopefully, the results of these studies will emphasize the possibility and need for timely and appropriate HIV treatment and care for IDUs. But also and not least emphasise that the life of IDUs face many challenges, where HIV infection is only one.

Danish summary – dansk resume

HIV/AIDS er på verdensplan en velkendt årsag til sygelighed og dødelighed blandt injicerende stofmisbrugere (IDUs). I Danmark bidrager IDUs også til HIV-epidemien, skønt andelen af IDUs blandt nykonstaterede HIV-smittede ser ud til at falde over tid.

Formålet med det aktuelle ph.d.-studie var at beskrive effekten af injicerende stofmisbrug på sygelighed og dødelighed blandt danske HIV-smittede og effekten af HIV på dødelighed blandt danske IDUs. Afhandlingen består af 4 studier og en oversigt. Alle fire studier er baseret på data hentet fra det danske landsdækkende register over HIV smittede personer (Den danske HIV kohorte), der følges på et af de HIV behandlende centre. Registeret indeholder data fra 1. januar 1995 og bliver løbende opdateret. Data fra andre landsdækkende registre, herunder: CPR-registeret, den danske stafylokok database, register over stofmisbrugere i behandling og dødsårsagsregisteret, blev også anvendt i studierne.

I det første studie blev dødeligheden blandt IDUs og ikke-IDUs i tiden efter introduktionen af potent anti-retroviral behandling (HAART) undersøgt over en 12-års periode. Det andet studie sammenlignede effekten af HAART på dødelighed mellem HIV-smittede IDUs og ikke-IDUs. I det tredje studie undersøgte incidensen og risikofaktorerne for *Staphylococcus aureus* bakteriæmi (SAB) hos HIV-smittede og ikke HIV-smittede. Yderligere blev forskelle mellem HIV-smittegrupper undersøgt. Det fjerde studie undersøgte forskelle i dødelighed hos HIV-smittede og ikke HIV-smittede stofmisbrugere i stofmisbrugsbehandling.

Der blev påvist stor forskel i dødelighed blandt danske HIV-smittede IDUs og ikke-IDUs, og individer smittet gennem stofmisbrug havde en mere end tre gange øget risiko for død sammenlignet med ikke-IDUs. Den øgede dødelighed syntes ikke at være relateret til HIV infektion, men skyldes formentlig velkendte risikofaktorer forbundet med intravenøst stofmisbrug.

I det andet studie undersøgte vi effekten af HAART blandt HIV-smittede IDUs og ikke-IDUs. Studiet viste at stofmisbrugere havde et dårligere respons på behandling målt i antallet af HIV-RNA kopier/ml i blod, i absolut CD4+ celletal og havde en væsentlig højere dødelighed sammenlignet med andre HIV-smittede. Men mere end halvdelen af danske HIV-smittede IDUs opnåede viral

suppression efter at være opstartet HAART. IDUs blev diagnosticeret tidligere i deres sygdomsforløb, men opstarten af HAART var forsinket.

Invasive bakterielle infektioner er hyppigere blandt HIV-smittede og IDUs. Det tredje studie fokuserede på SAB blandt forskellige HIV-smittegrupper. Studiet viste en faldende men høj incidens af SAB blandt HIV-smittede sammenlignet med ikke HIV-smittede. Andelen af SAB var skævt fordelt mellem de forskellige HIV-smittegrupper, idet IDUs havde en næsten 20-gange højere incidens rate af SAB sammenlignet med homoseksuelle mænd i årene 2003-7. Lavt CD4+ celletal var den stærkeste markør for SAB blandt HIV-smittede, men injicerende stofmisbrug som HIV-smittegruppe, ikke-supprimeret HIV-RNA og manglende HAART var også markører for SAB.

Det sidste studie viste at dødeligheden blandt danske IDUs, der er påbegyndt stofmisbrugsbehandling, er cirka tre gange større blandt HIV-smittede sammenlignet med stofmisbrugere uden HIV. Det er usikkert, om den højere dødelighed skyldes selve HIV-infektionen, idet CD4+ celletallet var forholdsvis højt på død tidspunktet.

Afhandlingen præsenterer ny viden om og analyser af epidemiologien blandt danske HIV-smittede stofmisbrugere. Forhåbentlig vil resultaterne fra disse studier tydeliggøre muligheden for og nødvendigheden af rettidig og tidssvarende HIV-behandling og kontrol også for stofmisbrugere. Men studierne understreger også, at livet som stofmisbruger har mange udfordringer, hvoraf HIV-infektion kun er en.

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