



PhD thesis

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Consequences of social inequality among HIV-infected individuals in Denmark.

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This thesis was carried out at Copenhagen University Hospital, Rigshospitalet 2012-2015, and was handed in April 22 2015 for evaluation at the University of Copenhagen.

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Legarth R, Omland LH, Kronborg G, Larsen CS, Pedersen C, Gerstoft J, Obel N. Educational attainment and risk of HIV infection, response to antiretroviral treatment, and mortality in HIV-infected patients. *AIDS*, 2014 Jan 28;28(3):387-96.

Legarth R, Omland LH, Susanne O. Dalton, Gitte Kronborg, Carsten S. Larsen, Court Pedersen, Gitte Pedersen C, Gerstoft J, Obel N. Association between educational level and risk of cancer in HIV-infected individuals and the background population: Population-based cohort study 1995-2011. *J Infect Dis*. 2015 Apr 22. [Epub ahead of print].

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1. Preface

This PhD thesis was carried out in the period 2012-2015 during my stay at the Department of Infectious Diseases at Rigshospitalet.

I would like to thank my supervisors, Niels Obel and Jan Gerstoft. Niels has a tremendous capability of structuring and transforming clinical problems into a meaningful research and Jan has an amazing clinical insight and ability to point out the essential. I like to thank Niels for giving me the unique opportunity to be introduced to clinical epidemiology, and to work with the Danish HIV Cohort Study. I would also like to thank all the co-authors for contributing and commenting on my articles.

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Finally, I like to thank Johan, Dan, Bente and Niels for their exceptional support and care.

Dyssegård, April 2015

Rebecca Legarth

2. Abbreviations

AIDS: Acquired Immune Dificiency Syndrome
CRS: Civil Registration System
DAR: The Danish Attainment Register
DCR: The Danish Cancer Registry
DHCS: Danish HIV Cohort Study
DNRCD: Danish National Registry of Causes of Death
HAART; Highly Active Antiretroviral Therapy
HCV: Hepatitis C-virus
HIV: Human Immunodeficiency virus
ICD: International Classifications of Diseases
IDA: Integrated database for labour market research
IDU: Intravenous Drug Abuse
IR: Incidence Rate
IRR: Incidence Rate Ratio
MR: Mortality Rate
MRR: Mortality Rate Ratio
MSM: Men who have sex with men

3. Background

In early 1980 the first case reports on opportunistic infections in otherwise healthy homosexual men emerged [1–3], revealing the outlines of a communicable disease carrying with it severe immunosuppression and high mortality. HIV virus was identified in the wake of these first case reports on opportunistic infection in homosexual men from the US and western Europe [4,5]. HIV infection quickly spread to subpopulations with intravenous drug abuse (IDU), individuals who had received blood transfusions or blood products, and children through transmission from their mother [6].

The introduction of Highly Active Antiretroviral Therapy (HAART) around 1996-1997 led to a tremendous decline in AIDS-related mortality and morbidity, and HIV-infection transformed from a fatal disease with an expected life-span of less than 10 years into a chronic disease [7]. Life-expectancy among HIV-infected individuals increased substantially, and among well-treated individuals life-expectancy is now approaching that of the background population [8].

Implementation of HIV-treatment and preventive strategies have resulted in declining incidence of HIV-infections transmitted through blood transfusion, through use of blood products, and transmission from mother to child. However, mortality differs among HIV-infected individuals in regards to epidemiological characteristics, geographical region and resource-setting [9]. In high-income countries highest HIV prevalence is observed among men who have sex with men (MSM) and IDUs, but HIV prevalence among heterosexually transmitted individuals is raising due to increased immigration from endemic regions such as south-east Asia, sub-Saharan Africa and former eastern European countries [6,10].

Despite free and universal access to HIV-treatment in certain high-income countries HIV-infected individuals are still subject to a markedly increased mortality. Some of this excess mortality is related to the clinical course of HIV-infection such as advanced infection at time of diagnosis, exposure to long intervals with severe immunosuppression and an excess risk of some types of cancer [11]. In addition, some excess mortality has been attributed to risk factors unrelated to the clinical course of HIV-infection such as IDU [12,13], high risk-taking behaviour and a high proportion of smokers among HIV-infected individuals [14,15].

In the pre-HAART era individuals with low socioeconomic position had a slightly increased mortality following AIDS compared to individuals with a higher socioeconomic position. The difference in mortality between individuals with low and high socioeconomic position increased in the years following the introduction of HAART. Social inequity in mortality in the pre- and early-HAART periods have been attributed to differences in access to treatment [25–27]. Whether in low- and high income settings HIV-infection affects individuals of working age and thereby affects employment status [28–32], and maintaining socioeconomic position following an HIV diagnosis is crucial. Further, even in countries with comprehensive welfare systems like the Danish employment status has been shown to be an independent prognostic risk factor [33,34].

4. Socioeconomic position among HIV-infected individuals

Socioeconomic position is an arbitrary definition for grouping individuals within a community according to resources [35]. Classical indicators for personal resources are educational level, income or employment status, which are often used as proxies for socioeconomic position. Educational level reflects the “knowledge” capacity of an individual, and has been shown to be strongly associated with health behavior [36]. Further, educational level is a useful proxy for socioeconomic position among relative young individuals, and often also reflects resources within family structures [18]. Income and employment status are strongly interrelated, and reflects material resources in combination with individual physical and mental capacities [36].

Differences in health and mortality associated with socioeconomic position have been observed in several chronic diseases independent of health-care settings [16,17] and educational level has been found to explain substantially differences in incidence and prognosis in cardiovascular, psychiatric and cancer disease [19–24].

In high-income countries HIV prevalence is highest among MSM, IDU and immigrants from different endemic countries [6]. As the HIV-infected populations are diverse and multiform in respect to ethnicity, culture, religion and lifestyle, socioeconomic position will reflect these differences, and will reflect the underlying socioeconomic disparities normally observed within these populations.

In Denmark MSM still constitute a major part of the HIV-infected population infected through unprotected sexual exposure [37,38]. Educational level within this population tend to be higher than in the general population [38–40]. However, within the MSM-population educational level has not been found to affect risk taking behaviour in regard to unprotected sexual exposure [38,41]. Further, high levels of specific knowledge about HIV among MSM does not seem to affect risk taking behaviour related to unprotected sexual exposure [38]. On the contrary, increased risk taking behaviour has been detected among immigrants and heterosexually infected HIV-infected individuals with low socioeconomic position [38,42].

Socioeconomic position among HIV-infected individuals who are IDUs varies according to different regions of Europe and US, but in general the proportion of HIV-infected IDUs with low educational level is higher than in the general population [43,44]. Further, independently of different geographical region mortality and morbidity is substantially increased among HIV-infected IDUs, and delayed initiation of HAART, reduced response and adherence to HAART has been observed [12,44–46].

HIV-infected immigrants from low- or middle income countries constitute an increasing subpopulation among HIV-infected individuals in Denmark. Measuring socioeconomic position among immigrants is challenging, as immigrants constitute a heterogeneous group in respect to ethnic features, religion, culture and history of migration. Further, immigrants in a high-income country may be better off than individuals residing in country of origin often referred to “the healthy immigrant effect” [35]. Immigrants from low and middle income countries display increased mortality and morbidity and differ in respect to clinical indicators at time of access into healthcare [47]. In addition, risk of advanced infection at time of diagnosis is higher among immigrants from non-western countries [48].

5. Objectives

As HIV infection often affects individuals of working age, and HIV-treatment is life-long, minimizing socioeconomic consequences of HIV-infection is therefore not only of crucial importance for the infected individual but also on a community-level, since public health and macroeconomic gains from eliminating these inequities could be considerable.

This PhD-thesis aims at contributing to the understanding of relations between socioeconomic position and HIV infection, and to add knowledge to how social and treatment interventions can be targeted to further reduce social inequalities in HIV treatment, maintaining socioeconomic position, risk of cancer, morbidity and mortality among HIV-infected individuals.

Studies carried out in connection with this Ph.D. thesis, where based on the following hypotheses:

- Increased life-expectancy following the introduction of HAART has increased the possibility for self-sufficiency and decreased the need for early retirement among HIV-infected individuals. (Paper I)
- Educational attainments achieved prior to HIV infection might affect the time to start of HAART, adherence and response to HAART and the clinical outcomes following HIV diagnosis. (Paper II)
- Educational level influence risk and prognosis of different types of cancers among HIV-infected individuals differently compared to the background population. (Paper III)

6. Methodology

Study designs

The studies included in this thesis were all performed as cohort studies on the basis of data collected in the Danish HIV Cohort Study (DHCS). DHCS was established 1 January 1995, and is a population-based nationwide cohort study including all HIV-infected individuals seen at one of the eight Danish HIV centres. Data on individuals infected with HIV prior to and still alive at 1 January 1995 were collected retrospectively, and HIV-infected individuals diagnosed prior to 1 January 1995 constitute a subpopulation of “prevalent” cases. HIV-infected individual included after 1 January 1995 are enrolled in the cohort at time of first contact to a HIV centre.

Data includes demographics, date of HIV diagnosis, AIDS-defining events, antiretroviral therapy, and route of transmission. Clinical data on CD4 count and HIV RNA are collected from electronic laboratory databases.

To generate a comparison cohort from the background population 19 age- and gender-matched population controls per HIV-infected individual were randomly extracted from the Danish Civil Registration System (CRS). All population controls were living in Denmark at the time of inclusion of their corresponding HIV-infected individual. Including a comparison cohort allows for evaluation of differences in distribution of risk factors and outcomes among HIV-infected individuals and the background population.

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Study populations

DHCS includes data on more than 6,000 HIV-infected individuals, of which around 2,000 HIV-infected individuals were included at 1 January 1995 and therefore constitutes a cohort of prevalent cases.

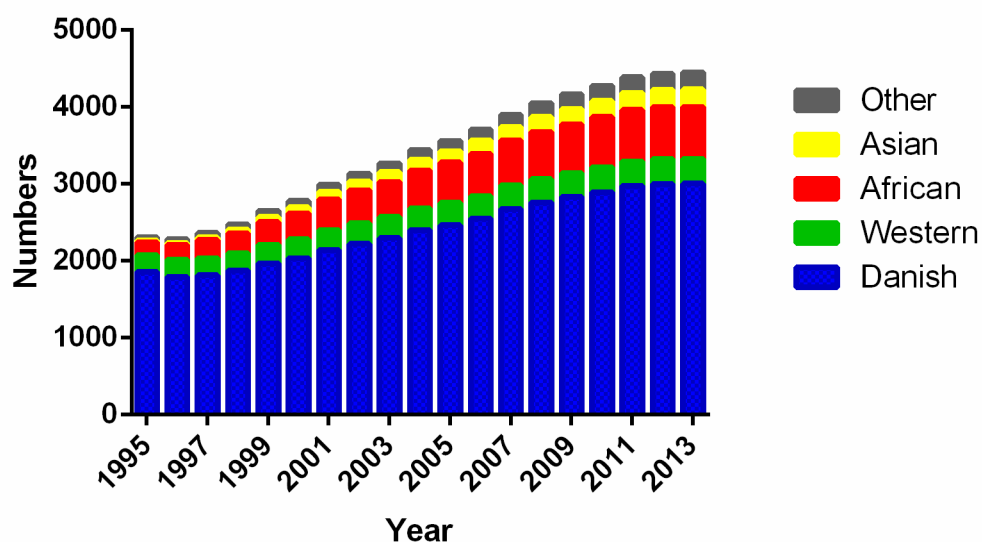


Figure 2. HIV-infected individuals in DHCS by country of birth and calendar year.

Figure 2. illustrates that the distribution of HIV-infected individuals by country of birth has been subject to changes during 1995-2013. The proportion of immigrants in DHCS has increased, and

especially numbers of immigrants from endemic regions has increased. Among non-Danish immigrants recordings of educational attainments rely on self-reporting at time of immigration. In addition, the number of missing data on educational attainment is higher among immigrants in the Danish registries. This thesis is based on studies which only include HIV-infected individuals and population controls that were born in Denmark to limit problems arising due to these differences in registration methods. Moreover, the exclusion of HIV-infected individuals of non-Danish origin was based on a wish to minimize confounding from cultural or ethnical origin.

Further, HIV-infected individuals who reported Intravenous Drug Use (IDU) as route of transmission or were co-infected with Hepatitis C-virus (HCV) were excluded. These subpopulations has been shown in several studies to suffer from increased mortality and morbidity compared to HIV-infected individuals without IDU or co-infection with HCV [12]. Further, associations between socioeconomic position and mortality has been shown to exhibit different patterns among IDU or HCV co-infected individuals [43].

In paper I we only included HIV-infected individuals who were alive one year following HIV-diagnosis, to minimize any initial effect of morbidity and mortality on employment status. In paper II we split follow-up time in the first year following HIV-diagnosis and in the subsequent years, as mortality was increased in the first year following HIV-diagnosis. Lead-in mortality following HIV-diagnosis has been described in other studies [9,49].

Data sources

Civil Registration System (CRS)

CRS was established 2 April 1968 and contains information on all persons born alive of a mother already registered in CRS, who have been registered in church register or resides legally in Denmark for more than 3 months. CRS contains information on migration, vital status, kinship and civil status. All information is linked to the unique 10-digit Civil Personal Register number, and data is updated daily [50].

Danish National Registry of Causes of Death (DNRCD)

DNRCD was established 1875, and since 1970 all deaths among Danish residents have been registered electronically on individual level. The registry contains information on date of death, causes of death e.g. underlying disease, cause of immediate events that lead to the death and contributing causes. Causes of death according to International Classifications of Diseases (ICD)-codes are supplied by the medical doctor who verifies death, and could be general practitioner, attending physician during hospital admission or attending physician from emergency services. Data is updated annually [51,52].

The Danish Cancer Registry (DCR)

DCR was established 1943, and contains information on all malignant neoplasm and certain precancerous and benign tumours. Data collected includes topography, morphology extent of tumour at time of diagnosis and date of diagnosis. All recordings during 1943-1978 are registered using ICD-7 classification and during 1974- classified by ICD-10 codes. Reporting to the registry is mandatory, and reminders based on data from cancer Registry in Danish National Registry of

Patients, the Danish Pathology Register and DNRCDD are regularly sent to hospitals and physicians. As the registry extract data directly from the Danish Pathology Register the proportion of morphologically verified tumours based on histological examination by a pathologist is 89 % [53].

The Danish Attainment Register (DAR)

DAR is generated by collaboration between Danish educational institutions records (Student Register, Academic Achievement Register, Population's Educational Register and Adult Education and Continuing Training Register) and Statistics Denmark. Individual-level data is collected from compulsory-schooling to university-level education and training, and includes enrolment status, highest completed levels of education and exams. Coverage for the Danish-born population born 1945-1990 is 97%, and 85-90% for the immigrant population born 1945-1990. Information on educational achievements obtained outside Denmark rely on self-reported data at time of immigration [54].

Integrated database for labour market research (IDA)

IDA has been provided by Statistics Denmark since 1980 and collects data from the Danish tax authorities, educational institutions and employment services. Data includes information on labour market affiliation (employed, unemployed or outside the labour market), welfare services, social benefits and primary source of income. Data is updated annually [55].

Statistical methods

Different statistical methods were used in the papers.

Logistic regression

Multivariate logistic regression models were used in nested case-control studies to estimate the association between educational attainment and risk of HIV diagnosis and stage of HIV infection at time of diagnosis. Logistic regression estimate odds ratio (OR) in the cross-sectional design of the nested case-control study, and age (time updated variable), sex and year of HIV infection were included as covariate in the adjusted analyses. In a Danish setting the prevalence of HIV infection is low, and in line with the Rare Diseases assumption Odd ratio will be the approximately the same as risk ratio in the underlying study base [56].

Kaplan-Meier survival analysis

As data was censored Kaplan-Meier was used in the survival analyses and to construct survival curves. Kaplan-Meier estimates probability of survival at any point in time as the product of conditional probabilities of surviving prior time intervals accounting for censoring. Kaplan-Meier methods rely on the following three assumptions: Individuals who are censored have the same expected survival as the individuals who continued to be followed, survival probabilities are unrelated to time of entry in to follow-up, and that outcome happens at a specified time point [57].

Competing risk

Cumulative incidence function including competing risk were used in settings with multiple failures possibilities. This was the case when evaluating cause-specific mortality and cause-specific cancer incidence (paper II and paper III), where the one-to-one relation between risk (absolute) and rate (relative) were lost. In these analyses we used competing risk to asses absolute risk estimates for the multiple failures. Adjustment for covariate in the cumulative incidence function was not possible [58].

Regression model

Poisson Regression Models were used to estimate relative risk estimates of Incidence Rate Ratios (IRR) and Mortality Rate Ratios (MRR). Poisson Regression models rely on the assumption that rates are constant with time, and thereby not allowing for interaction with time. This assumption can be relaxed by splitting follow-up in time-bands, and letting the assumption of constant rate hold within each time-band. In the analyses Poisson Regression Models were adjusted by including covariates such age as a time-updated variable, gender, year of HIV diagnosis [56].

7. Study I: Employment status in persons with and without HIV-infection in Denmark: 1996-2011.

Study outline

To evaluate how well the prolonged median survival time among HIV-infected individuals have transformed in to improved self-sustainability, we aimed at estimating annual employment and disability retirement rates in the years following HIV-diagnosis compared to an individually matched cohort from the background population.

We included 2,799 HIV-infected individuals who fulfilled the inclusion criteria, and 22,369 population controls individually matched at baseline by age, gender and country of birth. We evaluated annual employment and disability retirement rates as numbers registered as employment or receiving disability retirement for at least 6 months divided by the number under observation within a specific calendar-year.

Results

Employment rates at study inclusion increased during the study period among HIV-infected individuals from 54.8 (95% CI 50.5–59.6) in the pre-1996 period to 77.4 (95% CI 72.8–82.2) in 2000-2011, but remained lower than in the background population during all study periods.

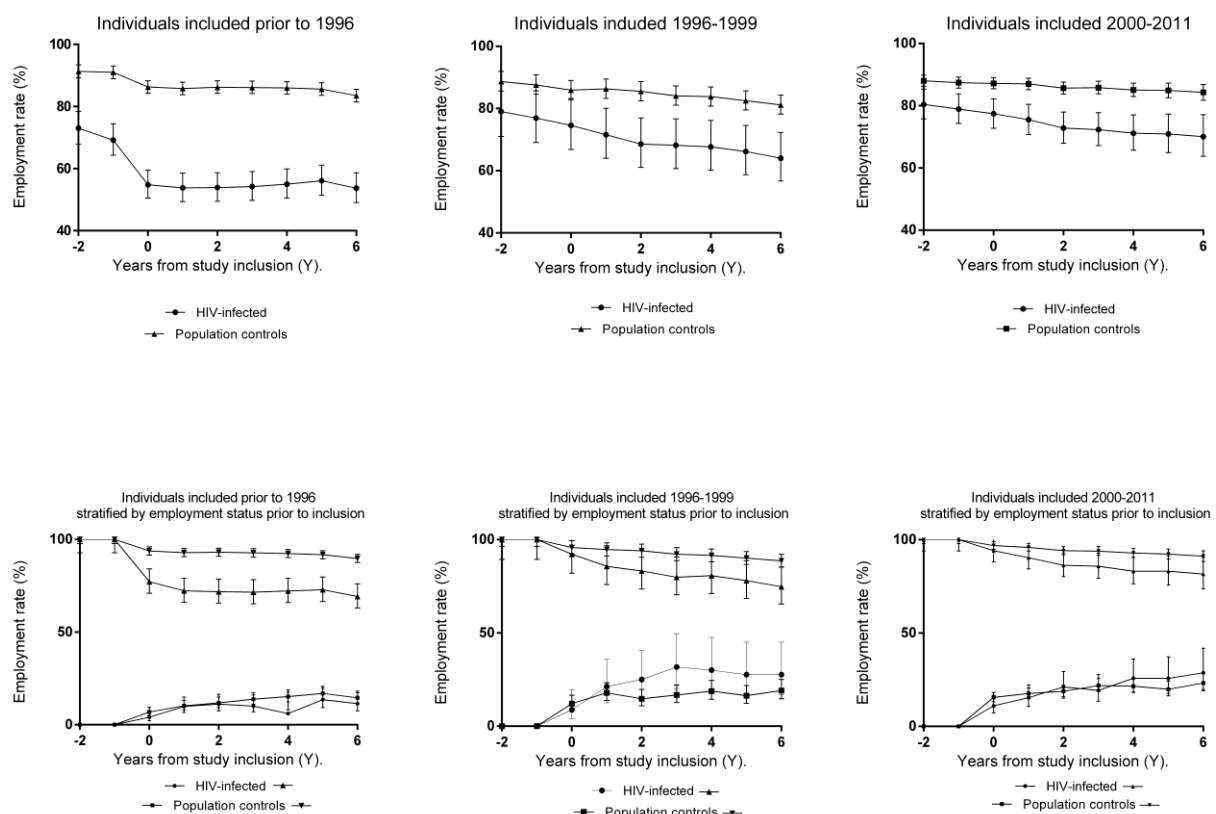


Figure 3 Employment rates among HIV-infected individuals and population controls stratified by year of study inclusion and pre-inclusion employment (%).

Employment rates declined by 8.0 % (95 % CI; -11.0 to -4.0) during the first 5 years after study inclusion among HIV-infected individuals and by 4.0 % (95% CI; -5.0 to -3.0) among population controls. Decline in employment rates were most pronounced among HIV-infected individuals of male sex, with late or very late presentation of HIV infection or who had medium educational attainment.

5 years after study inclusion HIV-infected individuals, who were employed prior to inclusion, had an employment decline of 12.0 % (95% CI; -15.0-9.0) compared to a decline of 6.0% (95% CI; -6.0 to -5.0) among population controls.

Proportion of HIV-infected individuals receiving disability retirement 5 years from study inclusion decreased from 32.3 % (95% CI; 29.0-36.3) in the pre-1996 cohort to 11.6 % (95% CI; 9.4-14.4) in the 2000-2011 cohort. Risk factors for receiving disability retirement were low educational attainment, very late presentation of HIV infection and unemployment at study inclusion.

Considerations

Our findings on lower employment rates among HIV-infected individuals than in the general population are in line with previous studies [34]. We found employment rates were lower at study inclusion, and decreased especially in the first years following study inclusion among HIV-infected individuals, which is in line with the findings of Dray-Spira et al. that estimated a cumulative risk of employment loss of 14 % within 2 years of HIV-care enrolment and of 34% within 5 years of HIV-care enrolment. Estimating the risk of employment loss is challenged by the fact that employment loss can be a transitory state, and individuals may shift in and out of employment. In our study we detected a higher frequency of employment shift among HIV-infected individuals compared to what was observed in the background population.

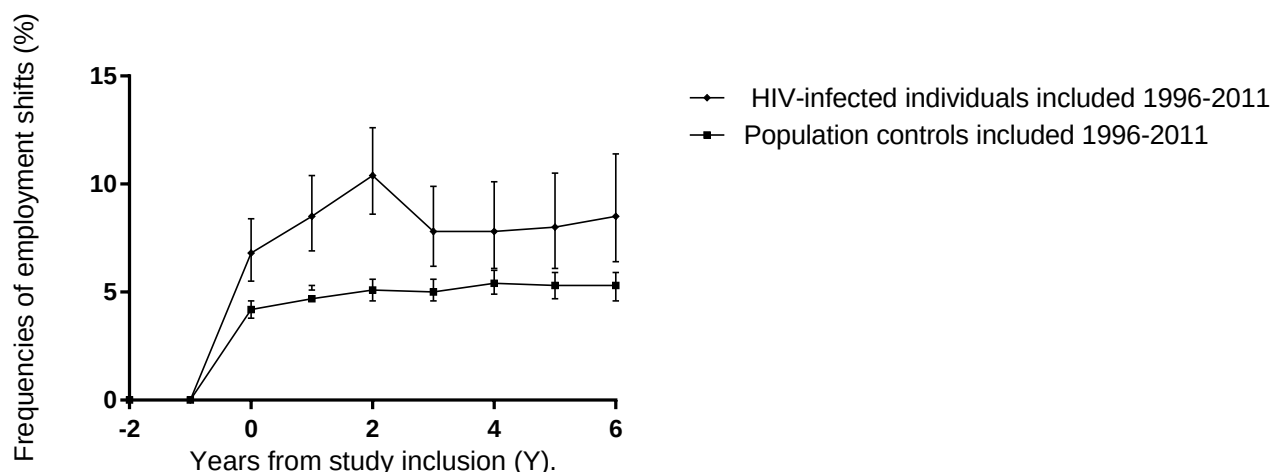


Figure 4 Frequencies in employment shift among HIV-infected individuals and population controls (%).

Our study includes a cohort from the background population, which is individually-matched on age, sex and country of birth at time of study inclusion. Including a cohort from the background population allows us to relate our results within the HIV-infected population with overall trends observed in the background population for example the financial crisis during 2008-2012. We used stratified analyses in our study, to identify specific subpopulations, that because of HIV infection deviates from what is observed in the background population. Stratification by educational

attainment and pre-inclusion employment status was performed both for the HIV-infected individuals and population controls.

Perspective

Employment status has been shown to be associated with mortality regardless of socioeconomic status [59,60] though the causality is not clear. Excess risk associated with unemployment has been attributed mainly to external factors such as suicide; diseases of the circulation system; alcohol- and tobacco-related causes [60].

Furthermore, studies have found that factors such as HIV-related stigma, social and psychological distress following an HIV diagnosis can influence employment status among HIV-infected individuals [61–63]. However, there might exist reverse causality between ill-health and risk factors like high alcohol-consumption which lead to unemployment, and will therefore be a potential confounder.

Employment status among HIV-infected individuals has been influenced by the transition of HIV infection from terminal disease to a chronic disease following the introduction of HAART. The median age of newly enrolled HIV-infected individuals are still below 50 years of age, and the age distribution among HIV-infected individuals is younger than in other groups of patients with chronic diseases [64]. The fact that a majority of the HIV-infected population is within the working ages which normally has the highest employment rates, stresses the socioeconomic effects of HAART on employment [28,29].

8. Study II: Educational attainment and risk of HIV infection, response to antiretroviral treatment, and mortality in HIV-infected patients.

Study outline

Excess mortality has been identified among HIV-infected individuals, and that educational attainment might be associated with delayed HIV diagnosis and delayed initiation of HIV-treatment [65]. This study aimed to evaluate how educational attainment was associated with presentation, clinical outcome and mortality among Danish-born individuals diagnosed with HIV-infection during 1998-2011

We included 1,277 HIV-infected individuals who fulfilled the inclusion criteria, and 5,738 population controls individually matched at baseline by age, gender and country of birth.

Results

Risk of HIV-diagnosis decreased with increasing educational attainments among individuals with heterosexual route of transmission, but we did not detect any association in the whole HIV population (adjusted-OR 1.3(95% CI 0.97-1.6)/ 1.1 (95% CI; 0.9-1.3)).

Adjusted-OR for late presentation of HIV-infection among HIV-infected individuals with medium or low educational attainment was 1.2 (95% CI; 0.9-1.6) compared to high educational attainments. Adjusted-OR did not change substantially for very late HIV presentation. Of a total of 947 HIV-infected individuals who fulfilled the criteria for start of HAART 86.0 % (95% CI; 80.6-90.0) with high educational attainment, 86.6% (95% CI; 83.2-89.4) with medium educational attainment and 83.5 % (95% CI; 78.3-87.6) with low educational attainment were started in HAART one year from criteria fulfilment.

Mortality-analyses were split in the first year following HIV-diagnosis and long-term mortality ≥ 1 year from HIV-diagnosis. No association between educational attainment and all-cause mortality was detected during the first year following HIV-diagnosis, but long-term mortality was increased 1.8-fold for individuals with low educational attainment compared to HIV-infected individuals with high educational level which paralleled the gradient for population controls. HIV-infected individuals with low educational attainment had a 3.6-fold increased tobacco- and alcohol-related mortality compared to HIV-infected individuals with medium or high educational attainment, compared to a 2-fold increased tobacco- and alcohol-related mortality among population controls.

Considerations

Educational attainment was included as an exposure variable in the cross sectional study and as a variable for stratification in the longitudinal cohort study. Data on education was identified in the Danish attainment registry, and was categorized by the length of schooling. Low educational attainment covered mandatory education of ≤ 9 years, medium educational attainment covered mandatory and vocational education of 9-12 years, and high educational attainment covering formal education of ≥ 12 years. Highest education achieved was assessed in the calendar year of study inclusion. Individuals were included from 25 years of age to allow for time to achieve educational attainment.

Individuals in the prevalent cohort in DHCS have been subject to varying length of time with pronounced immunosuppression, and display different patterns of morbidity and mortality than individuals included prospectively from 1 January 1995 [66]. Individuals diagnosed in the first years following the introduction of HAART also display increased mortality compared to individuals diagnosed from 1999 and onwards. The higher portion of late or very late presentation of HIV infection among these individuals could be due to suspended HIV testing. To minimize confounding individuals diagnosed with HIV prior to 1. January 1998 were excluded.

Substantial lead-in mortality was present among HIV-infected individuals in the first year following HIV diagnosis [9,49]. To address the assumptions for regression models on proportional hazard or constant risk over time we split follow-up in two periods; < 1 year following HIV diagnosis and ≥ 1 year following HIV diagnosis.

Perspective

Advanced HIV-infection at time of diagnosis is associated with increased long-term morbidity and mortality, and IDU, co-infection with HCV and immigration have been identified as risk factors for late or very late presentation of HIV-infection [12,45,48]. Educational attainment and socioeconomic position have also been associated with increased risk of late or very late presentation of HIV in other geographically regions [43,67–69]. However, we only detected an increased risk of late and very late presentation among Danish-born HIV-infected individuals with low educational attainment who were infected heterosexually but not among Danish-born MSM with low educational attainment.

We detected an increased educational inequality in smoking- and alcohol-related mortality among HIV-infected individuals compared to population controls. In Europe as a whole, educational inequalities in mortality are seen within nearly all categories of death causes, though substantial variability between regions/countries and gender exist [17]. Further, studies have detected increasing social inequity during 1987-2011, even when adjusting for trends in the general educational level of the general population, which is increasing [70].

9. Study III: Association between educational level and risk of cancer in HIV-infected individuals and the background population: Population-based cohort study 1995-2011.

Study outline

HAART has led to declining incidence of AIDS-related mortality and AIDS-defining cancers, and HIV-infected individuals now live longer and the incidence of non-AIDS-related mortality and non-AIDS-defining cancers has increased. Our aim in this study was to evaluate education-related inequity in risk and prognosis of cancer among HIV-infected individuals and an individually-matched cohort from the background population.

Educational level was grouped into two categories: Low educational level (≤ 9 years, mandatory) and high educational level (> 9 years, mandatory, vocational or formal).

Cancers were categorized according to ICD-10 codes in infection-related, tobacco- and alcohol-related, ill-defined and other cancers. Cancers were categorized according to the carcinogens considered to contribute most to the risk of cancer in a high- income setting [71,72].

Results

We included 3,205 HIV-infected individuals who fulfilled the inclusion criteria, and 22,435 population controls individually matched at baseline by age, gender and country of birth. IRR of cancer among HIV-infected individuals with low vs. high educational attainment was 1.4 (95% CI; 1.1-1.7) compared to 1.1 (95% CI; 0.9-1.2) among population controls with low vs. high educational attainment. IRR for tobacco- and alcohol-related cancer among HIV-infected individuals with low vs. high educational attainment was 2.1 (95% CI; 1.3-3.3) compared to 1.3 (95% CI; 1.1-1.6) among population controls with low vs. high educational attainment.

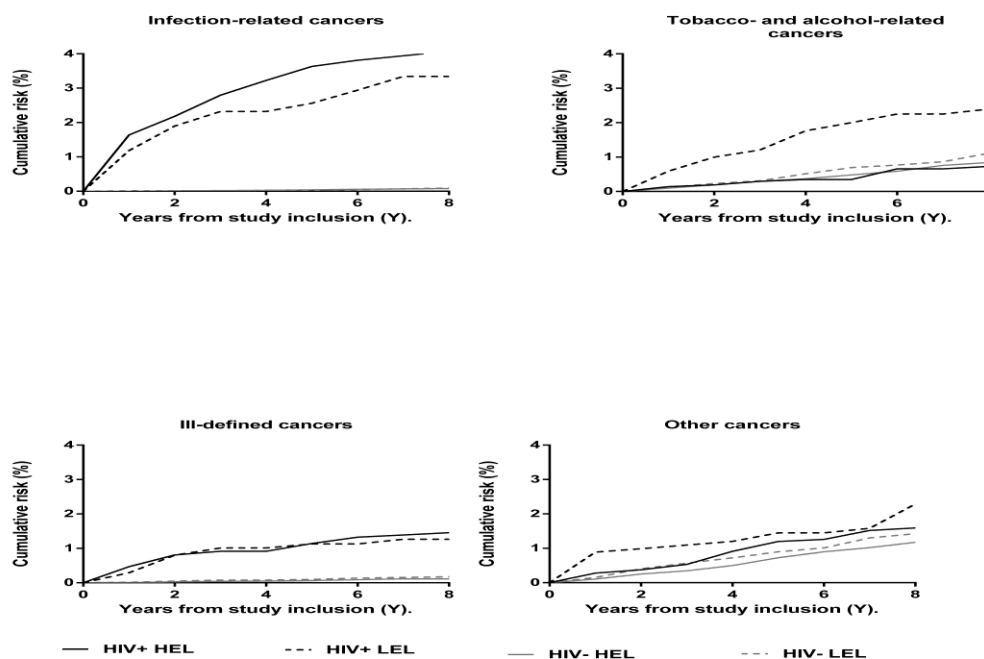


Figure 5 Cumulative incidence of Infection-related, Tobacco- and alcohol-related, Ill-defined and Other cancers, with death and remaining cancers as competing risk, stratified by educational level among HIV-infected individuals and population controls.

No education-related inequity was detected for the risk infection-related or ill-defined cancers. IRR for other cancers was 1.7 (95% CI; 1.1-2.8) among HIV-infected individuals with low vs. high educational attainment compared to 0.9 (95% CI; 0.7-1.0) among population controls with low vs. high educational attainment.

Overall 1-year survival following cancers did not differ among HIV-infected individuals with low vs. high educational level, but HIV-infected individuals with high educational level had increased survival compared to HIV-infected individual with low educational level (50.3 % vs. 30.3%, difference 20.0 % (95% CI; 9.4-30.6). The opposite pattern was observed among population controls. The difference in long-term survival observed among HIV-infected individuals was mainly explained by a markedly higher long-term survival following Infection-related cancers among HIV-infected individuals with high educational level (66.6 % vs. 39.8 %; difference 26.8 % (95% CI; 11-44 %).

Considerations

Educational attainment was included as an exposure variable, but in contrast to study II medium and high educational level was collapsed into one group due to limited numbers of events. Cancers were categorized according to ICD-10 codes and most prominent of known carcinogens [71,72]. Though etiologies to cancers are often multifactorial, we categorized cancers according to the carcinogens rated as the most contributing factors for specific cancers in high-income countries [73].

The exclusion of IDUs and individuals co-infected with HCV was based on the previously stated reasons such as increased all-cause mortality and increased cause-specific mortality due to intoxication and non-natural deaths. The HIV-infected individuals excluded due to IDU or co-infection with HCV had a lower median age (38.0 years (IQR; 33.5-43.6) for high educational level and 36.1 years (IQR; 30.8-40.9) for low educational level) compared to the remaining HIV-infected individuals. Further, the proportion of women was higher (19.1 % for high educational level and 35.5% for low educational level) within this subpopulation. IRR for all cancer was 1.2 (95% CI; 0.99-1.5) when adjusted for age (time-updated in 5-year intervals) and gender.

These differences in characteristics within IDU or HCV co-infected HIV-infected individuals raised concern that cancers might be underreported due to inadequate health care seeking and that including this subpopulation might contribute with confounding related to the vulnerable and fragile life-situation these individuals are exposed to.

Perspective

This study was conducted in a Danish setting and HIV-infected individuals differ among others in respect to ethnicity, life-style and route of transmission cross different geographical regions. The population of IDUs in Denmark differ substantially from IDUs living in other countries e.g. southern Europe [74,75], these differences has to be included in interpretation of the results.

As the study is based on register-based data the proportion of MSM in comparison cohort from the background population was not known. The proportion of MSM among HIV-infected individuals was 64 %, and therefore much higher than what would be expected in the background population. Further, the proportion of individuals with high educational level seems to be higher among MSM

than in the general population [38], and our estimates may be influenced by unmeasured and residual confounding.

Oncogenic exposure might be different among HIV-infected individuals, and there might be synergistic effects of different carcinogenic factors combined with the immunodeficiency derived by HIV-infection which differ from HIV-uninfected individuals. HIV-infected individuals have been found to have higher prevalence of HPV [76,77], and HPV-infection combined with exposure to smoking might attribute with excess risk of head- and neck cancers, oral cancers and lung cancers [78] different from HIV-uninfected.

Incidence of cancer was high in the first months following HIV-diagnosis, which might be explained by the fact that HIV-infection often is detected during contact with the healthcare-system caused by other health-related problems e.g. cancer [79,80]. Some of these cancers were infection-related cancers including AIDS-defining cancers, and would be expected to be detected at a higher rate around the time of HIV diagnosis. This phenomenon is parallel to the lead-in mortality observed within the first year following HIV diagnosis, and identifies a subpopulation among HIV-infected individuals who are most vulnerable and who might benefit from early intervention.

10. Conclusion and perspective for future research.

This Ph.D. thesis demonstrates that:

- Following the introduction of HAART self-sustainability increased among HIV-infected individuals. Employment rates among HIV-infected individuals increased from 1996 to 2011, but remained lower than among population controls. Disability retirement rates declined during the study period, but remained higher than among population controls.
- Educational attainment, as a proxy of socioeconomic position, did not influence late or very late presentation of HIV-infection, start and response to HIV-treatment. Low educational attainment was associated with an increased risk of HIV-diagnosis. Low educational level was further associated with increased long-term all-cause mortality and with an increased tobacco- and alcohol-related mortality.
- Low educational level was associated with excess risk of some types of cancers (especially tobacco- and alcohol-related) among HIV-infected individuals. Educational inequity in overall cancer risk and tobacco- and alcohol-related cancer was higher among HIV-infected individuals than in population controls. Long-term survival following a cancer diagnosis was lower among HIV-infected individuals with low educational level than among HIV-infected individuals with high educational level.

A general finding in the papers included in this thesis is that HIV-infected individuals are particularly vulnerable the first year following HIV-diagnosis. This “lead-in” effect is observed in regard to both employment status, risk of cancer and mortality. Both from a clinical and a socioeconomic perspective this period therefore calls for particular attention. A common finding in Paper II and paper III is the excess risk, of cancer and cause-specific mortality respectively, related to tobacco- and alcohol-consumption among HIV-infected individuals with low educational level. These findings are in line with what is observed in the general population but the socioeconomic gradient seems to be reinforced among HIV-infected individuals.

The studies have underlined, that identifying the most vulnerable subpopulations among HIV-infected individuals is crucial to construct guidelines for optimal HIV-treatment, containing transmission and minimizing negative clinical outcomes. Further, as HIV-infection to a large extent affects relatively young individuals, who are still within working age, maintaining the socioeconomic position HIV-infected individuals enjoyed prior to HIV diagnosis has immense effect on individual level as well as on community-level.

A number of questions are left open. Further insight into the association between socioeconomic position, comorbidity and life-style related risk factors among HIV-infected individuals could be a stepping-stone to increase survival among HIV-infected individuals with low socioeconomic position. Moreover, identifying risk factors for loss of socioeconomic position and self-sustainability following an HIV diagnosis among immigrants and IDUs could identify areas for interventional strategies within these most vulnerable populations. Further, identifying risk factors for employment loss in the first period following HIV-diagnosis could contribute with preventive incentives that could lead to crucial benefit on a community-level as well as on individual level.

11. Dansk resume

Prognosen for HIV-infektion er markant forbedret siden indførelsen af HAART, men HIV patienter har fortsat højere dødelighed og morbiditet end baggrundsbefolkningen. HIV-populationen består i vid udstrækning af yngre personer, der vil skulle have livslang behandling, hvorfor opretholdelse af den socioøkonomiske status fra før HIV-diagnosen er af afgørende betydning ikke kun for den enkelte HIV-patient, men også ud fra samfundsøkonomisk betragtning. Identifikation af eventuel social ulighed i adgangen til HAART, i behandlingsrespons eller i det kliniske forløb af HIV-infektionen vil kunne bidrage til at sænke den øgede morbiditet og dødelighed blandt HIV patienter. Da HIV patienter er en heterogen gruppe med forskellig kulturel baggrund, religion, etnicitet og livsstil, kan kvantificering af socioøkonomisk status på en fælles meningsfuld målestok være udfordrende.

Denne Ph.d.-afhandling bygger på 3 studier, hvor den inkluderede studiepopulation bestod af dansk fødte HIV-patienter uden HCV Co-infektion eller intravenøs stofmisbrug. Studie 1 fandt, at efter indførelsen af HAART steg graden af selvforsørgelse blandt HIV patienter. I perioden 1996-2011 steg beskæftigelsen blandt HIV patienter, men forblev lavere end i baggrundsbefolkningen. Den lavere beskæftigelse blandt HIV-patienter var uafhængig af beskæftigelsesstatus præ-HIV diagnose. Andelen af HIV-patienter, der modtog førtidspension, faldt i periode 1996-2011, men forblev højere end i baggrundsbefolkningen.

Studie 2 fandt at uddannelsesniveau ikke var associeret med en sen eller meget sen HIV-diagnose, forsinket start på HIV-behandling eller nedsat behandlingsrespons. Uddannelsesniveau var derimod associeret med en øget risiko for HIV-infektion blandt heteroseksuelle personer. Studie 2 fandt yderligere at uddannelse var associeret med den langsigtede dødelighed, herunder særligt den tobaks- og alkoholrelaterede dødelighed.

Studie 3 fandt at uddannelsesniveau var associeret med øget risiko for visse typer af kræft, herunder især tobaks- og alkoholrelaterede kræftformer, blandt HIV-patienter. Uligheden i kræftisiko, herunder tobaks- og alkoholrelateret kræft, var større blandt HIV-patienter end i baggrundsbefolkningen. Den langsigtede overlevelse efter en kræftdiagnose var lavere blandt HIV-patienter med lavt uddannelsesniveau end blandt HIV patienter med højt uddannelsesniveau.

Dette Ph.d.-studie fandt tegn på social ulighed i prognosen for HIV-patienter, som ikke synes forklaret ved sociale forskelle i adgangen til HIV-behandling, i kvaliteten af HIV-behandlingen eller i respons på HIV-behandling. Studiet fandt social ulighed blandt HIV-patienter på trods af, at de mest sårbare grupper blandt HIV-patienter var ekskluderet fra studiepopulationen. Der synes især at være en udtalt social ulighed i forhold til cancer og dødelighed relateret til tobak og alkohol, og denne ulighed var større, end hvad der blev observeret i baggrundsbefolkningen.

12. English summary

Prognosis for HIV-infection has improved substantially since the introduction of HAART, but HIV-infected individuals are still subject to excess mortality and morbidity. The HIV-infected population consist of relatively young individuals requiring life-long treatment, and maintaining socioeconomic position achieved prior to HIV-infection is crucial not only for the infected individual but also on a community-level. Further, identification of social inequity in access to or response to HAART or in the clinical course of the HIV-infection could further contribute to lower the excess morbidity and mortality. As the HIV-infected population is multiform and heterogenic in regard to culture, religion, ethnicity and life-style, creating a common ground for measurement of socioeconomic position is challenging.

In this PhD thesis including a study population consisting of Danish-born HIV-infected individuals without HCV co-infection or intravenous drug abuse, we found that following the introduction of HAART self-sustainability increased among HIV-infected individuals. Employment rates increased during 1996-2011 among HIV-infected individuals, but remained lower than among population controls independently of pre-HIV infection employment status. Disability retirement rates declined during the study period, but remained higher than among population controls. Further, we found that educational attainment, as a proxy of socioeconomic position, did not influence late or very late presentation of HIV-infection, start and response to HIV-treatment. Educational attainment was associated with an increased risk of HIV-diagnosis among individuals with low educational level. Educational level was further associated with an increased long-term all-cause mortality and to an increased tobacco- and alcohol-related mortality. Educational level was associated with excess risk of some types of cancers (especially tobacco- and alcohol-related) among HIV-infected individuals. Educational inequity in overall cancer risk and tobacco- and alcohol-related cancer was higher among HIV-infected individuals than in population controls. Long-term survival following a cancer diagnosis was lower among HIV-infected individuals with low educational level than among HIV-infected individuals with high educational level.

In conclusion, we detected a social inequity in prognosis among HIV-infected individuals which seemed to be unrelated to differences in access, time to start or response to HIV-treatment. This social inequity was detected despite exclusion of the most vulnerable HIV-infected individuals from the study population. Especially cancer and mortality related to tobacco and alcohol exhibited a social gradient that differed from what was observed among population controls.

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Paper I