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Non-AIDS defining diseases before and after HIV diagnosis: Characteristics of risk, prognosis, and their usefulness in HIV screening

PhD dissertation

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Forord

Det er ingen hemmelighed at forskning er min store passion, og gennem de sidste 4 år har forskningen både været min hobby og mit arbejde. Årene som klinisk assistent og ph.d.-studerende ved infektionsmedicin har været fyldt med mange sjove, spændende, lærerige og udfordrende oplevelser - og ikke mindst af mødet med utallige fantastiske kolleger indenfor såvel som udenfor kælderen's mure. Mange af Jer betragter jeg i dag som mine venner, og tusind tak til Jer for den faglige sparring og for at være med til at holde humøret højt.

At det endte med at blive en ph.d.-afhandling bygget på data fra den danske HIV kohorte(DDHK) skyldes udelukkende én person, Nicolai Lohse. Nicolai's evne til at begå sig fagligt på allerhøjeste internationale niveau har uden tvivl været stærkt medvirkende til at manuskripterne, som denne afhandling er baseret på, alle er blevet godt modtaget af såvel kolleger som tidsskrifter. Nicolai har fungeret som en altid motiveret og engageret indpisker, der også har sørget for at kurere mine "børnesygdomme" indenfor epidemiologien og statistik. Vores nære venskab er den direkte årsag, at det tredje studie overhovedet blev søsat, idet Nicolai under en sommerhustur overdrog studieudkast såvel som de indledende analyser til mig hen over et par flasker rødvin. Mange, mange tak for din hjælpsomhed og tålmodighed.

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Preface

This thesis is based on three original papers and a review of the supporting literature. Originally, the thesis was only supposed to include two studies on the Danish HIV cohort study but along the way came the idea to do the "indicator" study which ended up adding an extra dimension to the first two papers.

The thesis is meant as a supplement to the three papers and I have tried not to repeat too many details from these papers.

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LIST OF ABBREVIATIONS

AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral treatment
CCI	Charlson Comorbidity Index
CD4	Cluster of differentiation 4
CDC	Center for disease control and prevention
CRS	The civil registration system
DHCS	The Danish HIV cohort study
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
ICD	International classification of diseases
IDU	Injection drug use
IQR	Interquartile range
IR	Incidence rate
IRR	Incidence rate ratio
MR	Mortality rate
MRR	Mortality rate ratio
MSM	Men who have sex with men
NHR	The national hospital registry of patients
OR	Odds ratio
PCP	<i>Pneumocystis Carinii</i> (now <i>Jiroveci</i>) pneumonia
PPV	Positive predictive value
RNA	Ribonucleic acid
VL	Viral load
TB	Tuberculosis

This thesis is based on the following papers:

- I. Hospitalization for Pneumonia among Individuals with and without HIV in Denmark 1995-2007: A Population Based Nationwide Cohort study. Søgaard OS, Lohse N, Gerstoft J, Kronborg G, Østergaard L, Pedersen C, Pedersen G, Sørensen HT, Obel N; Clin Infect Dis; 2008 Nov 15;47(10):1345-53.
- II. Mortality after hospitalization for pneumonia among individuals with HIV, 1995-2008: a Danish cohort study. Søgaard OS, Lohse N, Gerstoft J, Kronborg G, Østergaard L, Pedersen C, Pedersen G, Sørensen HT, Obel N. PLoS One. 2009 Sep 14;4(9):e7022.
- III. Morbidity and Risk of Subsequent Diagnosis of HIV Infection: A Population Based Case Control Study Identifying Indicator Diseases for HIV infection. Søgaard OS, Lohse N, Østergaard L, Kronborg G, Røge B, Gerstoft J, Sørensen HT, Obel N. *submitted 2011*

1. BACKGROUND

1.1 THE BEGINNING OF THE HIV EPIDEMIC

In June 1981, the US Center for Disease Control and Prevention (CDC) published a report about *Pneumocystis carinii* pneumonia in five homosexual men in Los Angeles.¹ *Pneumocystis* pneumonia is almost exclusively limited to severely immunosuppressed patients. The occurrence of pneumocystis pneumonia in five previously healthy individuals without a clinically apparent underlying immunodeficiency was unusual and demanded special attention. This was the first published report of what, a year later, became known as acquired immunodeficiency syndrome (AIDS). In 1983, French researchers led by Francoise Barré-Sinoussi and Luc Montagnier found that AIDS was caused by a novel human retrovirus, which was later named human immunodeficiency virus (HIV).²

HIV originates from African non-human primates. It is currently believed that humans acquired chimpanzee simian immunodeficiency virus (SIV_{cpz}) by cross-species contamination, probably predation, around 1910 in what is now known as the Democratic Republic of Congo (former Belgian Congo).³ Although the spread of the virus in humans was initially slow, this ancestor of HIV-1 group M would subsequently fuel one of the most devastating epidemics in modern human history. In 2010, UNAIDS estimated that almost 60 million people have been infected with HIV and more than 25 million people have died of HIV-related causes since the beginning of the epidemic.⁴ Some 33.3 million people are currently living with HIV. Further, 2.6 million new infections and 1.8 million AIDS-related deaths occur annually.

1.2 AIDS BEFORE AND AFTER THE INTRODUCTION OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

Within 10 years after infection with HIV, most individuals develop symptoms. The CD4⁺ T lymphocyte counts have usually dropped below 200 cells/ μ L, HIV viral loads are high, and both the humoral and cellular immunity are severely dysfunctional.⁵ The immune system becomes susceptible to opportunistic infections and infection-related cancers, which under normal circumstances rarely cause disease in immunocompetent individuals. These conditions are known as AIDS-defining and mark the end-state of HIV infection.⁶ The median survival following AIDS diagnosis in the absence of antiretroviral treatment is 3.7 years if the CD4⁺ cell count is less than 200 cells/ μ L.⁷ Hence, without treatment for HIV more than 95% of infected individuals will die within 12-14 years from the day of infection.

Recognizing the causative agent of HIV as a retrovirus led to an immediate emphasis on arresting the replicative cycle of the virus. A compound that had been previously synthesized for potential use against cancer, 3'-azido-3'-deoxythymidine (AZT or zidovudine), substantially inhibited viral reverse transcriptase and HIV replication in vitro. Early reports of AZT therapy for HIV infection yielded promising results.⁸ However, the clinical effect of the drug was short-term and appeared to be greatest in the late course of disease. Other compounds were subsequently tested as monotherapy, but all gave rise to treatment resistant HIV strains which abrogated the antiretroviral effect.⁹ In 1996, researchers discovered that combining three different antiretroviral drugs dramatically decreased viral replication and led to undetectable HIV levels in peripheral blood.¹⁰ This treatment strategy, known as highly active antiretroviral therapy (HAART) almost instantly became widely used in the Western world. Not only did combination treatment block viral replication, CD4+ cell counts increased greatly and immune function recovered in HIV patients on HAART.⁵

1.3 NON-AIDS DEFINING COMORBIDITIES

With the introduction of HAART, AIDS became increasingly less common in well-controlled HIV patients.¹¹ Treatment with the early antiretroviral drugs was associated with numerous side effects including renal, hepato, and mitochondrial toxicities, as well as metabolic changes and bone marrow depression.¹²⁻¹⁴ As more and less toxic compounds were developed, these major side effects from HAART were significantly reduced. However, during the past years it has become apparent that typical AIDS-defining illnesses have been substituted by new comorbid conditions (often referred to as non-AIDS defining conditions) that threaten even those patients who maintain virologic suppression.¹⁵

The most intensely studied of these conditions are: atherosclerotic cardiovascular disease, non-AIDS defining malignancies, liver disease and renal disease.¹⁶ There appears to be a clear association between increasing risk of non-AIDS defining conditions and decreasing CD4+ count counts (e.g., fatal liver disease and fatal non-AIDS malignancies are more common in people with lower CD4 counts).^{13,17} However, even people with high CD4 cell counts remain at risk of serious non-AIDS events.

The exact mechanisms underlying the increased risk of serious non-AIDS conditions associated with HIV-induced immunodeficiency remain to be defined. Immune activation, a marker of HIV disease progression and a key determinant of CD4 depletion has been shown to persist in HAART-treated persons with undetectable virus, albeit at a lower level.¹⁸ People who cease antiretroviral therapy have elevated risk of developing serious non-AIDS events and also of experiencing elevated levels of immune activation.^{19,20} Thus, immune activation has been suggested to be one of the driving mechanisms in the pathogenesis of these conditions, but other factors such as lifestyle (smoking, drug use, and alcohol) and drug toxicity are also likely to play a role.¹⁵

1.4 LOWER RESPIRATORY TRACT INFECTIONS IN HIV

As mentioned, an unexpected accumulation of *Pneumocystis Jiroveci* (formerly *Carinii*) pneumonia episodes led to the discovery of the HIV/AIDS epidemic, and its association with severe immunodepression led to the inclusion of the infection as an AIDS-defining disease. While this was one of the most commonly encountered infections in the early phases of the epidemic, pneumocystis pneumonia is now primarily observed in people who are first diagnosed at a late stage of HIV infection.^{21,22} It is rarely observed in well-controlled HIV patients²² and hence, other lower respiratory tract infections are now dominating the clinical picture in infectious diseases departments in developed countries.²³

Globally, *mycobacterium tuberculosis* (TB) is a major cause of pulmonary infections among HIV patients.²⁴ Like pneumocystis pneumonia, pulmonary TB is closely associated with severe immunodepression and pulmonary TB in a person with HIV infection is also categorized as an AIDS-defining disease.⁶ However, active TB infection can also be observed in HIV patients with low CD4⁺ cell counts after initiation of HAART - probably due to immune reconstitution.^{25,26} The greatest burden of HIV-associated tuberculosis is found in sub-Saharan Africa, but a regional epidemic of HIV-associated tuberculosis is also raging in parts of Eastern Europe.^{24,27} In Denmark, HIV-associated tuberculosis is primarily observed in immigrants from Eastern Europe and sub-Saharan Africa. Due to the difference in aetiology, pathogenesis, and their status as AIDS-defining diseases, pneumocystis pneumonia and tuberculosis were not included in our studies of pneumonia (paper I+II).

Early in the HIV epidemic it was recognized that morbidity and mortality due to bacterial pneumonia were higher in HIV-infected persons than in the general population.²⁸ In 1993 the US CDC categorized two or more episodes of bacterial pneumonia within a 1-year period as an AIDS-defining event.⁶ The introduction of HAART also led to fewer pneumonia-related hospitalizations, but a study by Kohli et al. suggested that the risk of bacterial pneumonia in the HAART era remained higher among persons with HIV than those without HIV.²⁹ Infection with *Streptococcus pneumoniae* is the most common cause of bacterial pneumonia among people with human immunodeficiency virus (HIV) and a major cause of morbidity and mortality.³⁰ Whether the incidence of invasive pneumococcal disease (IPD) has declined after the introduction of HAART is uncertain, and IPD may be up to 100 times more frequent among HIV-infected persons than non-HIV-infected persons.^{31,32}

A number of risk factors for pneumonia and pneumococcal disease have been identified over the past twenty years. Low CD4⁺ cell count is an example of a well-known risk factor for pneumonia and pneumococcal disease.³³⁻³⁹ Other risk factors related to progression of HIV-infection are viral load (HIV RNA)^{34,38,40,41} and clinical disease stage.^{33,36,37} Increased risk of pneumonia has also been associated with certain comorbidities and abnormal paraclinical findings including: Pulmonary tuberculosis,⁴² chronic obstructive pulmonary disease,⁴⁰

cirrhosis,^{39,40} hepatitis C,³⁴ low albumin,^{34,37} and anaemia.^{34,37} Previous pneumonia is also a risk factor^{29-31,33} whereas use of HAART has been shown to be protective.^{35,36,38,40,42} Prophylactic antibiotic use with azithromycin or trimethoprim-sulfamethoxazole,^{36,38,40,43} pneumococcal,^{32,44} and influenza vaccination⁴³ have a protective effect in some studies.

Other factors such as sex and race may also play a role, as black people appear to have an increased risk of both all-cause pneumonia as well as pneumococcal disease^{37,38} and women may have an increased risk of pneumonia.³⁸ Lifestyle and socio-economic risk factors for pneumococcal disease in HIV-infected people include: Smoking,^{35,39,41,42} cannabis use,⁴¹ injecting drug use,^{34,36,38-43} alcohol abuse,^{35,36,38,40} having close contact with children,⁴² level of education,^{36,42} and poor housing.⁴²

Despite their commonness, acute lower respiratory infections have received relatively little attention in studies of non-AIDS defining conditions. A range of studies which have estimated pneumonia incidences in HIV-infected and uninfected populations is listed below (Table 1). Collectively, these studies suggest that in spite of widespread use of HAART, HIV-infected individuals remain at high risk of non-AIDS defining infections and lower respiratory tract infections in particular.

Table 1. Effect of HIV infection on the incidence and outcome of all-cause pneumonia in adults in population-based studies.

References	Time period	HIV status	Incidence (events / person-years)	Case-fatality
Hirschtick ⁴⁵	Pre-HAART	Positive	55/1000	≈6%
		Negative	9/1000	
Floris-Moore ⁴⁶	Pre-HAART	Positive (male)	104/1000	-
		Positive (female)	120/1000	-
Sullivan ⁴⁷	Pre-HAART	Positive	227/1000	-
Tumbarello ⁴⁸	Pre-HAART	Positive	125/1000	-
Kohli ²⁹	Pre- and post HAART	Positive	85/1000	≈7.7%
		Negative	7/1000	-
Floris-Moore ⁴⁶	Post-HAART	Positive (male)	82/1000	-
		Positive (female)	180/1000	-
Sullivan ⁴⁷	Post-HAART	Positive	91/1000	
Gordin ⁴⁹	Post-HAART	Positive (DC)	20/1000	-
		Positive (VS)	13/1000	-
Tumbarello ⁴⁸	Post-HAART	Positive	88/1000	-
Lopez-Palomo ⁵⁰	Post-HAART	Positive	≈44/1000	-
Curran ⁵¹	Post-HAART	Positive	≈20-32/1000	≈9.1%

1.5 IDENTIFICATION OF INDIVIDUALS WITH UNDIAGNOSED HIV INFECTION

Despite three decades of efforts, controlling the HIV epidemic remains a tremendous public health challenge.⁵²⁻⁵⁴ Many individuals newly diagnosed with HIV present at a late stage of the disease with severe immune depletion, resulting in delayed initiation of HAART which undermines their prognosis.^{55,56} Further, HIV viral load is predictive of transmission risk.⁵⁷ The highest levels of viremia are seen during acute infection and advanced HIV-1 disease.⁵⁸ If persons with undiagnosed HIV infection can be identified early in the course of the infection or before they progress to AIDS, this may reduce onward transmission of HIV.⁵⁹⁻⁶¹ Thus, in the light of the significant benefits associated with early identification of people with undiagnosed HIV infection (Table 2) intensified HIV testing and treatment has been advocated to control the HIV epidemic.^{62,63}

The U.S. CDC recommend routine HIV testing for all persons under age 65 who come into contact with the US health care system.⁶⁴ While this approach might be beneficial in terms of prolonging life expectancy⁵⁶ and cost-effective in areas with high HIV prevalence,^{65,66} alternative approaches such as targeted HIV testing may be more appropriate in low prevalence areas such as Denmark.⁵⁴ In addition, although access to care is free at the point of delivery in most European countries, limited availability of HIV care and stigma associated with the disease remain widespread.⁶⁷ Consequently, targeted HIV testing rather than universal HIV testing may be the most acceptable strategy for individuals as well as authorities at the present time.⁶⁸

Targeted HIV testing requires knowledge of special characteristics (behavior, signs, symptoms, and diseases), which may indicate undiagnosed HIV infection in the general population. CDC's revised classification of AIDS-defining illnesses contains a list of 21 conditions,⁶⁹ which are well known to be strongly associated with HIV infection. Targeted HIV testing based on the presence of diseases associated with HIV, so-called indicator diseases,⁶⁸ has been put forward as a way to identify persons with undiagnosed HIV. During recent years, the concept of indicator-disease based HIV testing has received a great deal of attention in the European AIDS Clinical Society. In 2008, Brian Gazzard and colleagues published an important paper in which they reviewed the current literature on HIV indicator diseases and recommended a broader implementation of this HIV screening strategy.⁶⁸ However, as the authors acknowledged, guidance is based mainly on expert opinion in the absence of data⁶⁸ and a comprehensive study of HIV indicator diseases using appropriate HIV negative controls has not been conducted to date.

Table 2. Potential benefits and drawbacks from earlier presentation of people with undiagnosed HIV infection.

Potential benefits from earlier presentation	Mechanism
Lower HIV transmission	Reduced sexual risk behavior ⁷⁰ Prevention of mother-to-child transmission ⁷¹⁻⁷³ Viral suppression following HAART initiation reduce risk of onward HIV transmission ^{57,60,62}
Lower morbidity / mortality	Fewer AIDS events before diagnosis ⁷⁴ Lower risk of immune reconstitution syndrome (IRIS) after HAART initiation ^{75,76} Improved CD4+ cell recovery ^{77,78} Reduced loss of immunological memory ^{79,80} Improved prognosis on HAART ^{74,81} Lower risk of non-AIDS defining morbidity (e.g., cancer, neuropathy, cardiovascular, liver, and renal disease) ^{19,81}
Cost reduction of HIV care	Lower costs associated with treatment of AIDS and non-AIDS defining conditions ⁸² Fewer new HIV cases ^{66,83} Lower demand on health care resources related to treatment and monitoring of HIV infection. ^{65,78}
Potential drawbacks from earlier presentation	
Increased drug expenses	Short term increases in drug expenses due to more people on HAART
Adverse events from HAART	Increased exposure to antiretrovirals may increase the risk of adverse events ¹⁵
Resistance development	Due to longer HAART exposure ¹⁴
Increased discrimination	Due to known HIV seropositivity ⁵⁴

2. AIMS

This thesis has the following aims:

1. To compare population-based incidence rates (IRs) of first-time hospitalizations for pneumonia among persons with and without HIV infection in Denmark, to estimate changes in IRs and IR ratios (IRRs) over time and according to age in the 2 populations, to estimate the influence of immunocompetence defined by CD4+ cell count, and to explore potential risk factors for non–AIDS-defining pneumonia among HIV-infected individuals.
2. To estimate the impact of a first hospitalization for pneumonia on mortality among Danish HIV patients, to examine changes over calendar time in mortality following hospitalization for pneumonia, and to identify prognostic factors for death following pneumonia.
3. To delineate medical conditions which identify individuals at increased risk of later HIV diagnosis and their associated occurrence.

3 METHODOLOGICAL CONSIDERATIONS

3.1 DATA SOURCES

3.1.1 AN INTRODUCTION TO DANISH MEDICAL DATABASES

The Danish Civil Registration System, established in 1968, allows for personal identification and the possibility of collecting information about the same person in several registries through a 10-digit personal registration number (CPR number), assigned at birth, which uniquely identifies each person. This CPR number is the key to linking data from different medical databases. Apart from the Danish HIV cohort study, data used for studies in this thesis were obtained from medical databases under administration of the Danish National Board of Health (Figure 1). These primary data sources offers great advantages due to the fact that they already exist, which effectively eliminates the need for additional data collection, sparring time, effort, and money.

3.1.2 DANISH HIV COHORT STUDY (DHCS)

The DHCS is an open, prospective cohort study initiated in 1998 as the HIV cohort study in Western Denmark.⁸⁴ This population-based study was expanded in 2004 to cover all Danish HIV clinics and became a nationwide cohort. Data reaching back to 1 January 1995 were retrieved from medical files and entered into the database.

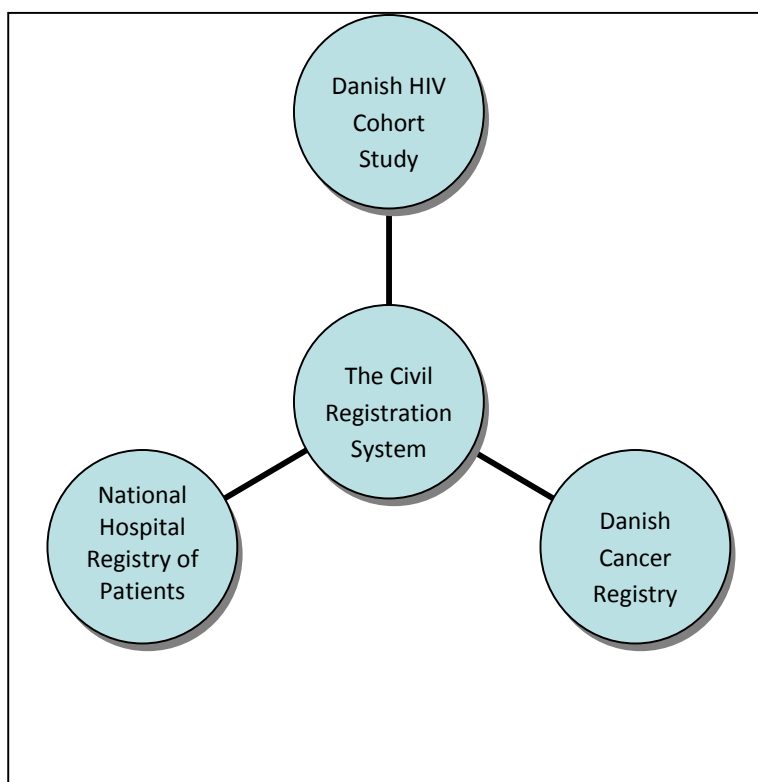


Figure 1. Sampling of population controls matched to patients in DHCS is done in the Civil Registration System by data managers at the Danish Board of Health. This subsequently allows for linkage of both DHCS patients and controls to other medical databases using the unique personal registration numbers.

DHCS thus covers all prevalent HIV cases as of 1 January 1995 and all incident HIV cases since then. Study data are updated annually with individual information on antiretroviral treatment, development of opportunistic infections and other AIDS-defining illnesses, and laboratory data including plasma HIV RNA (viral load) and CD4⁺ cell count.⁸⁵ Cross-checking and validation algorithms are incorporated in the database management in order to catch data retrieval and typing errors. DHCS is based at Rigshospitalet, Copenhagen, and headed by Professor Niels Obel.

3.1.3 DANISH CIVIL REGISTRATION SYSTEM (CRS)

CRS is a national registry of all Danish residents, which contains information on date of birth, sex, date of migration, and date of death.⁸⁶ The CPR number, assigned at birth, uniquely identifies each person since 1968. Further, those who live or work in Denmark legally for a certain amount of time must register with the CRS. The purpose of the CRS is to administrate the personal identification number system and general personal data forwarded by the municipal registration offices to the CRS. The CRS is updated within a week of a person's birth, death, or emigration. Use of the CPR number enables Danish HIV clinics to avoid multiple registrations of the same patient and allows tracking of deaths and persons lost to follow-up due to emigration.⁸⁷

3.1.4 THE DANISH NATIONAL HOSPITAL REGISTRY (NHR)

NHR contains information on all patients discharged from Danish hospitals since 1977. Records for each hospitalization include CPR number, hospital department, inpatient and outpatient discharge diagnoses, and dates of admission and discharge. Diagnoses are coded by the treating physician according to the International Classification of Diseases, 8th revision (ICD-8) until the end of 1993 and 10th revision (ICD-10) thereafter.

3.1.5 THE DANISH CANCER REGISTRY

Since 1943, the registry has recorded all incident cases of carcinoma, sarcoma, leukaemia, lymphoma, multiple myeloma, and mycosis fungoides in Denmark. In addition, a number of tumour-like and benign lesions have also been recorded. During the period 1943-2003, tumours were classified according to a modified Danish version of the International Classification of Diseases, 7th revision (ICD-7) as well as International Classification of Diseases for Oncology (ICD-O) from 1 January 1978 and onwards. From 1 January 2004, tumours were classified according to ICD-10. In addition, tumours diagnosed in the period 1978-2003 were reclassified according to ICD-10 by conversion of the ICD-O codes.

3.2 METHODS

3.2.1 LITERATURE SEARCH

A versatile approach was used to keep track of the quickly evolving field of HIV research.

- Regular searches on Pubmed using combinations of keywords such as “HIV”, “pneumonia”, “epidemiology”, “pneumococcal infections”, “mortality”, “HIV screening”, “comorbidity”, and “HIV transmission”.
- Table of contents (TOC) email alerts from major medical journals (New England Journal of Medicine, JAMA, Lancet, BMJ, and PLoS Medicine), basic science journals (Nature, Nature Medicine, and Nature Immunology) and infectious diseases-related journals (Lancet Infectious Diseases, Clinical Infectious Diseases, Journal of Infectious Diseases, AIDS, JAIDS, Current Opinion in HIV research).
- Literature updates from professional websites such as Medscape and UNAIDS.
- Subscription to HIV mailing list from Greg Folkers at NIH/NIAID.
- Frequent communication with supervisors and colleagues in the field of HIV research and epidemiology.
- Participation in international scientific HIV and infectious disease conferences.

3.2.2 SAMPLING OF GENERAL POPULATION CONTROLS

Up to 99 population controls for each HIV patient were sampled from CRS, matched on age and gender at HIV diagnosis (and registration in the same municipality in paper I). The control cohort was used to compare risk of hospitalization for pneumonia (paper I) and specific hospital discharge diagnoses (paper III) in persons with HIV compared to the general population.

3.3 DEFINITION OF MAIN EXPOSURES AND OUTCOMES

3.3.1 HIV

HIV infection was the main exposure of interest in paper I and the primary outcome in paper III. HIV patients in DHCS were identified from hospital records and electronic laboratory reports of CD4+ cell counts and HIV-RNA viral loads. As these tests were conducted on all HIV patients in the HIV clinics as part of initial screening, the risk that a patient is missed in DHCS is negligible. The date of HIV diagnosis was defined as the date of first contact to an HIV clinic, first HIV-RNA measurement, or first CD4+ cell count (whichever came first).

3.3.2 PNEUMONIA

Pneumonia was used as the primary outcome in paper I and as exposure in papers II+III. We used the NHR to identify all hospital contacts with a discharge diagnosis of pneumonia using ICD-8 codes 480.XX-486.XX,

073.XX and 471.XX, and ICD-10 codes J11.0 (influenza with pneumonia), J12.x–J18.x (pneumonia), A481.x, (ornithosis), or A709.x (legionellosis). Thus, both community-acquired and hospital-acquired pneumonias were included. We defined the onset of pneumonia as the date of hospital admission. AIDS-defining *Pneumocystis jiroveci* pneumonia (PCP, ICD-10 codes B.20.6 and B.59.x) was not counted as an episode of pneumonia.

For a sample of 77 HIV-infected patients with a discharge diagnosis of pneumonia, reviewing medical records validated the diagnoses identified in the NHR. We confined the review to Aarhus County, since data quality in the NHR is considered uniform throughout the country.⁸⁸ Pneumonia diagnoses recorded in the NHR for patients without HIV had been validated previously,⁸⁹ and we used the same criteria for the HIV patients. A discharge diagnosis of pneumonia was considered confirmed when an infiltrate was documented in a chest X-ray and at least one of the following clinical or laboratory findings was present: body temperature $\geq 37.5^{\circ}\text{C}$; cough; dyspnoea; chest pain or rales coincident with the area of infiltrate; increased sputum; purulent sputum; microorganism isolated from blood culture, leukocyte count $\geq 12 \times 10^9 \text{ L}^{-1}$ or C-reactive protein concentration $> 100 \text{ mg} \times \text{dL}^{-1}$. We computed the percentage of episodes recorded in the NHR fulfilling the above criteria.

73 of 77 HIV patients, corresponding to 95% (95% confidence interval [CI]: 87%-98%), registered with pneumonia in the NHR, had their diagnosis confirmed by data in their medical records. In an earlier validation of pneumonia diagnoses among 100 non-HIV patients, the diagnosis was confirmed for 90 patients (90%, 95% CI: 82-95%) on the basis of their medical records.⁸⁹

As noted in the discussion section of paper I, data on the etiology of pneumonia would have strengthened the study. Most of the pneumonia episodes in were registered by the treating physician as unspecified bacterial pneumonia. Although information on the etiology of pneumonia was included in the ICD-8 and ICD-10 diagnosis in some instances this information presumably is incomplete and (to my knowledge) has not been validated. In paper I, a thorough investigation of causative agents would have required a complete review of medical records for all HIV patients [n=582] and controls [n=7,042] who were hospitalized for pneumonia. This was beyond the scope of the paper and we were also worried that the diagnostic testing would be more extensive in HIV patients than among persons with HIV which would bias the comparison of causative agents between the two groups.

3.3.3 DEATH

The primary outcome in paper II was all-cause mortality following the hospital admission date for pneumonia. Causes of death, extracted from patient files and available in the DHCS database, were divided into HIV-related causes (AIDS-defining illnesses and bacterial infections, serious non-AIDS causes (cardiovascular disease [i.e. myocardial infarction or stroke], end stage renal and liver disease, COPD, and non-AIDS-defining malignancies), unnatural causes (i.e. drug overdose, suicide, accident), and other/unknown causes. We were unable to

classified deaths as “directly related to pneumonia” due to insufficient information in the medical records and the DHCS database.

3.3.4 HAART

HAART was defined as either a 3-drug regimen that included a non-nucleoside reverse transcriptase inhibitor, a protease inhibitor, and/or abacavir; or a 2-drug regimen with a combination of a non-nucleoside reverse transcriptase inhibitor and a boosted protease inhibitor.

3.3.5 CD4+ CELL COUNT AND HIV VIRAL LOAD (VL) AS TIME-UPDATED VARIABLES

Measurements of CD4+ cell count and VL are unevenly distributed over time. In papers I+II we used the principle of “last observation carried forward” to determine CD4+ cell count and VL between measurements. *Nadir CD4⁺ cell count* was defined as the lowest CD4⁺ cell count ever measured at a previous point in time.

3.4 CHANCE, BIAS, AND CONFOUNDING FACTORS

3.4.1 CHANCE

The observations on which this thesis is based were made on a sample of HIV patients (those included in DHCS). This sample, even though it was selected without bias, may misrepresent the situation in the global HIV population because of chance. However, results of an unbiased sample tend to approximate the true value. The divergence of an observation on a sample from the true population value, due to chance alone, is called random variation. Random variation can never be eliminated totally, so chance has to be considered when assessing the results of clinical observations.

3.4.2 BIAS

Selection bias, which occurs when comparisons are made between groups of persons that differ in the determinants of outcome other than the ones under study, are likely to have occurred in papers I+III. *Berkson's selection bias* results from the greater probability of hospital admission for people with two or more conditions than for people with one condition. In paper I, clinicians may have had a lower threshold for hospital admission of an HIV-infected person presenting with signs and symptoms of pneumonia than for a person without HIV. If so, pneumonia would be diagnosed in hospitals more frequently in HIV-infected persons than in the general population and the relative risks in our study would tend to overestimate the effect of HIV infection. In paper III, HIV diagnosis is the outcome of interest, but in-patient or out-patient hospital visits may have increased the risk of being HIV tested as part of the diagnostic work-up and thus, hospital contact may by itself be a risk factor for subsequent HIV diagnosis.

Bias in estimating an effect can be caused by measurement errors in the needed information. Such bias is often referred to as *information bias*. Different types of information bias may have occurred in all three papers. In paper I, the admitting clinician's awareness of a person's HIV status may have increased the subsequent diagnostic procedures and thus the validity of the pneumonia diagnosis. If so, this would be an example of differential misclassification, because underdiagnosis of pneumonia (failure to detect pneumonia), would occur more frequently among non-HIV-infected compared to HIV-infected individuals. In paper II, causes of death were in many cases uncertain and, in some cases, multifactorial. Causes of death registered in DHCS were based on information extracted from medical records. Although misclassification of causes of death is likely, this bias is unlikely to be associated with the exposure (pneumonia) and can be considered as an example of non-differential misclassification. Misclassification is also likely to have occurred in coding of hospital discharge diagnosis in paper III. The positive predictive value (PPV) of NHR discharge diagnoses for numerous diseases compared to medical chart reviews have been assessed. Though the PPV varies from one diagnosis to another, the predictive value of registry diagnoses compared to medical records is generally high (70%-99%).⁸⁸

3.4.3 CONFOUNDING FACTORS

A variable that is associated with both the exposure (e.g., HIV) and the outcome (e.g., pneumonia) is a potential confounding variable. We controlled for various confounding variables in the studies. Age is a well established risk factor for many diseases including pneumonia, for which the highest risk of disease is observed at the extremities of age. The median age of the DHCS population at study entry was 37 years in paper I. To control for the effect of age on the risk of pneumonia, we matched HIV patients to the general population controls by age at the time of study entry. Also in paper I, we used stratification to control for the effect of age. In papers I+III we also controlled for *gender* by matching HIV patients to population controls in the study design.

Comorbidity was assessed with the Charlson Comorbidity Index (CCI). The index, which includes 19 major disease categories, has been adapted and validated for use with hospital discharge data in ICD databases for predicting short- and long-term mortality.⁹⁰ In paper II, a CCI score was computed for each patient based on all available foregoing NHR discharge diagnoses. A previous AIDS diagnosis (conferring 6 CCI points) was not included in our computations.⁹¹ Hence, adjustment for CCI score takes multiple comorbidities into account but limited, of course to the comorbidities that we know of (*i.e.*, those registered in the NHR).

Some potential confounding variables could not be adjusted for. For example, we did not have data on smoking, a well-known risk factor for pneumonia that may be more common in HIV-infected individuals, particularly among injection drug users. A recent cohort study found that 40% of HIV-infected individuals were smokers,⁹² compared to a smoking rate of 27% in the Danish population as a whole in 2006.⁹³ In this example, smoking may cause us to overestimate the relative risk of pneumonia among HIV patients compared to the background population.

3.4.4 HANDLING OF BIAS AND CONFOUNDING

Except for randomization, all methods for dealing with extraneous differences between groups share a common limitation: They are effective against only those variables that are singled out for consideration. They do not account for risk or prognostic factors that are not known at the time of the study, or for those that are known but for one reason or another not taken into consideration. For the same reasons, we have not relied on only one method of controlling for bias. Rather, we have used several methods together, layered on one and another. Table 3 shows different strategies for handling of controlling bias in study design and analysis.

A number of the methods listed in table 3 were employed in the three papers. *Restriction* was used in the design of paper I-III, and in the analyses of paper I+III. *Exclusion* was used in the design in paper III. *Matching* was used in the design of all three papers and in the analysis of paper III. *Stratification* was used in the analysis in paper I-III. *Multivariate analyses* were used to control for confounding in all three papers. Tracking of individuals via CRS was used to minimize loss to follow-up for all study subjects. The same *objective diagnostic criteria* for pneumonia were used to validate pneumonia cases both among persons with HIV and population controls in paper I.

Arguably, ninety-five population controls per HIV patient added little extra statistical power compared to ten population controls in studying a common event such as hospitalization for pneumonia in Paper I. The high number of population controls per HIV patient reflected that this dataset was obtained from the Danish National Board of Health for multiple purposes - some of which involved studying rare events such as anal cancer. However, it is unlikely that the large number of controls introduced more bias than would be the case in an identical study with a smaller number of controls since the proportion of persons with certain risk factors would approximately be the same in the two studies.

The rationale for matching on municipality was that living in larger cities has been associated with increased risk of certain disease (such as respiratory infections) and shorter life expectancy. Most people with HIV infection live in Copenhagen, Aarhus, Odense - the three largest cities in Denmark. Thus, matching on municipality was used to reduce this potential bias in the study.

Table 3. Methods to minimize bias in the study design and analysis phases.

Type of bias	Method	Description	Design	Analysis
<i>Confounding / Selection bias</i>				
	Randomization	A way to give each patient an equal chance of falling into one or the other group	√	
	Restriction	Limit the range of characteristics of persons in the study	√	√
	Exclusion	Excluding persons with unwanted characteristics in the study	√	√
	Matching	For each patient in one group, select one or more patients with the same characteristics (except the one under study) for a comparison group	√	√
	Stratification	Compare rates within subgroups		√
	Multivariate adjustment and mathematical modelling	Adjust for differences in a large number of factors related to the outcome		√
	Minimizing "lost to follow-up"	Implementing procedures to track those who drop out	√	
<i>Information bias</i>				
	Blinding	Assessing outcomes without knowledge of individual group allocation	√	
	Standardization	Standardizing the measurement process	√	
	Using objective criteria	Using predefined, validated criteria for defining exposure and outcome	√	

adapted from "Clinical epidemiology: the essentials" 3rd edition by Fletcher and Fletcher⁹⁴

4 STUDY DESIGN AND STATISTICAL ANALYSIS

All three studies were population-based cohort studies. In paper I and III, population controls without HIV were sampled from the CRS and used for comparative analyses. We had to use different approaches to analyze the effect of HIV on risk of pneumonia and the effect of pneumonia on mortality, and to identify diseases associated with subsequent HIV infection.

4.1 COHORT ANALYSIS OF THE RISK OF HOSPITALIZATION FOR PNEUMONIA

In paper I, subjects were followed from 1 January 1995 or date of HIV diagnosis, whichever came last. Population controls entered the study on the same day as their matched HIV-infected person. We computed time at risk from date of first observation until the date of first hospitalization for pneumonia, death, emigration, or 1 May 2007, whichever came first (Figure 2).

Incidence rates (IR) of pneumonia hospitalization were computed for HIV-infected patients and controls as the number of events per 1000 person-observation years. In an analysis restricted to HIV-infected patients with current CD4⁺ counts >500 cells/μL and their respective HIV-uninfected controls, we compared IRs in the last time period. We computed incidence rate ratios ([IRR]=IR_{HIV}/IR_{controls}) and 5- and 10-year cumulative risk of pneumonia after 1 January 1997. We used a Poisson regression model to explore risk factors for first-time hospitalization for pneumonia for all individuals with HIV. Variables entered into the model included both constant covariates such as race and sex, and time-dependent covariates such as HAART use and current CD4⁺ cell count.

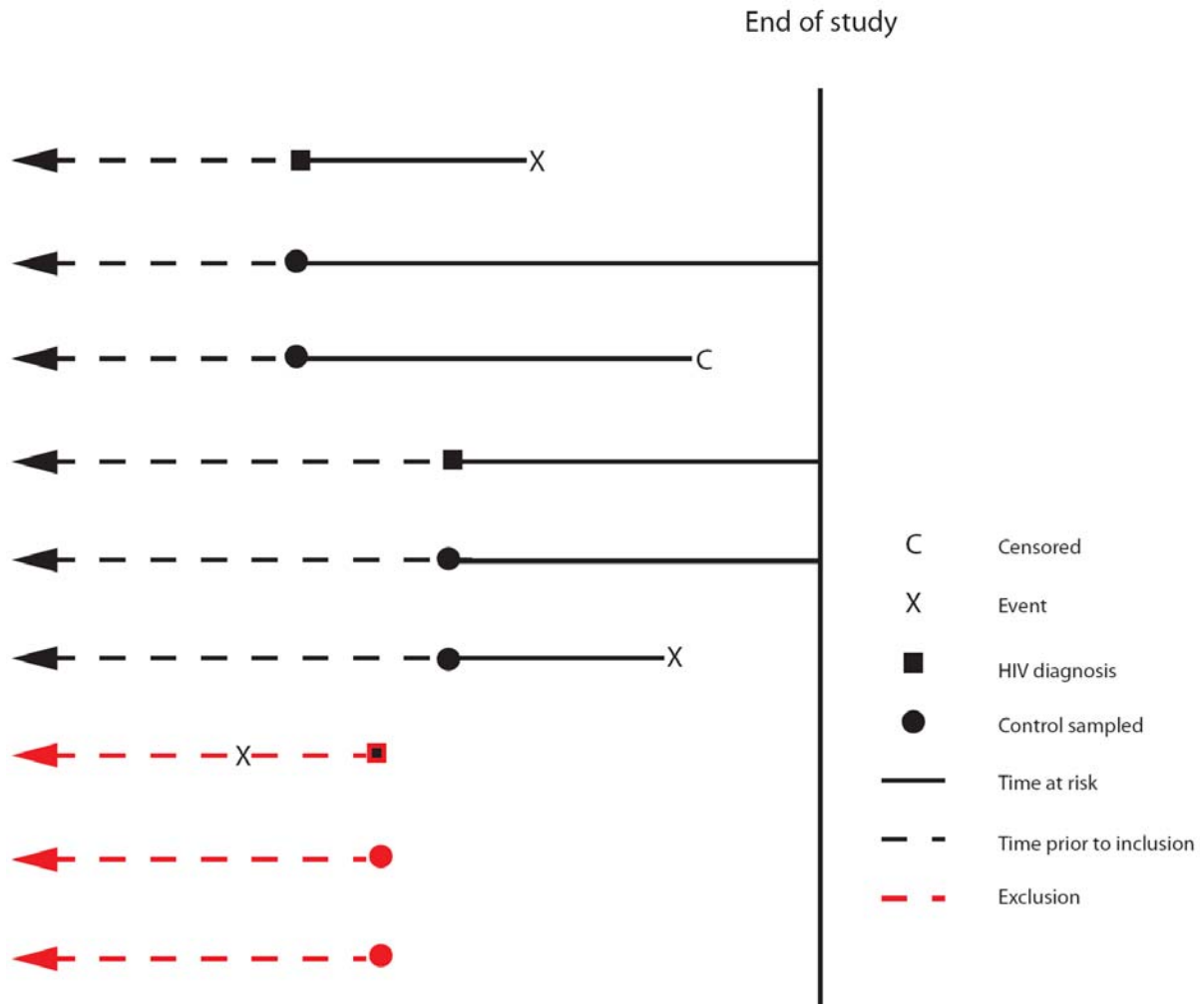


Figure 2. Schematic illustration of the study design used in paper I. Persons in DHCS are followed from the date of HIV diagnosis (squares). Matched population controls were sampled and followed from the date of HIV diagnosis of their corresponding HIV case (circles). The incidence rate (IR) for persons in one group is defined as the number of new events (X) per time unit. The incidence rate ratio (IRR or relative risk) is defined as: $IRR = IR_{HIV} / IR_{CONTROLS}$. In order to limit the study to first-time pneumonia hospitalizations, individuals with a recorded episode of pneumonia between 1977 and 1 January 1995 were excluded. Exclusion of persons with HIV subsequently led to exclusion of their matched control persons (illustrated at the bottom of the figure).

4.2 COHORT ANALYSIS OF MORTALITY FOLLOWING HOSPITALIZATION FOR PNEUMONIA

This study was also restricted to persons in DHCS who were at least 16 years old on the date of HIV diagnosis and who had no recorded hospitalization for pneumonia before entering DHCS. Study subjects were followed from their registration in DHCS to death, loss to follow-up, or 1 July 2008, whichever came first.

We first computed 30-day and 90-day cumulative mortality following the first hospitalization for pneumonia and constructed Kaplan-Meier survival curves, stratified into 3 calendar periods. We then assessed the effect of a first hospitalization for pneumonia on mortality. We compared the mortality rate in persons who had no previous history of pneumonia (reference group) with that of persons with a first hospitalization for pneumonia within the last 0-90 days, within the last 91-365 days, and more than 365 days ago. Poisson regression analysis was used to adjust for potential confounders. In this regression model, pneumonia was entered as a time-dependent covariate and "death" as the outcome. Finally, we used logistic regression to identify prognostic factors for 30-day and 90-day mortality following hospitalization for pneumonia.

4.3 COHORT ANALYSIS OF ASSOCIATIONS BETWEEN DISEASES DIAGNOSED IN HOSPITALS AND RISK OF SUBSEQUENT HIV DIAGNOSIS

In paper III, we extracted hospital diagnoses from all outpatient contacts and hospital stays from the NHR and the Danish Cancer Registry, up to the day prior to the index date. ICD-10 codes were the primary source for grouping diseases. We defined 22 disease categories of interest according to the type and anatomical location of the disease (paper III, Appendix Table 1). ICD-8 codes were matched to the corresponding ICD-10 disease categories and first-time diagnoses were assigned to the appropriate category. In addition, a total of 161 subcategories were created for the 22 disease categories. Except for tuberculosis, we excluded AIDS-defining diseases, as their association with HIV infection is well established.⁶

Analysis 1: For each of the 22 disease categories diagnosed in the 5-year period prior to the index date, conditional logistic regression analysis was used to estimate odds ratios (OR) as an unbiased estimate of the incidence rate ratio⁹⁵ for subsequent HIV diagnosis (unadjusted and adjusted for hospital contacts for the remaining 21 disease categories). The 161 subcategories were also analyzed in the 5-year period prior to the index date - however, adjustments were only made for other diseases within the same category (e.g., the OR for syphilis was adjusted for diagnosis of condyloma, anogenital herpes simplex, hepatitis A, non "A" viral hepatitis, and other sexually transmitted infections).

Analysis 2: Individual observation data was then stratified into three time periods prior to the index date (Figure 3) to explore changes in ORs leading up to the index date. For every time period, risk estimates were calculated for each disease category (adjusted for the remaining 21 disease categories). For each of these analyses, only the cases and their respective controls followed from the beginning of a given time period up to the index date were included.

Exploratory subanalysis: To identify specific HIV-indicator diseases, we explored risk estimates for the 161 specific subcategories within each of the 22 disease categories. In all analyses, only first-time diagnoses for a given disease/disease category were utilized.

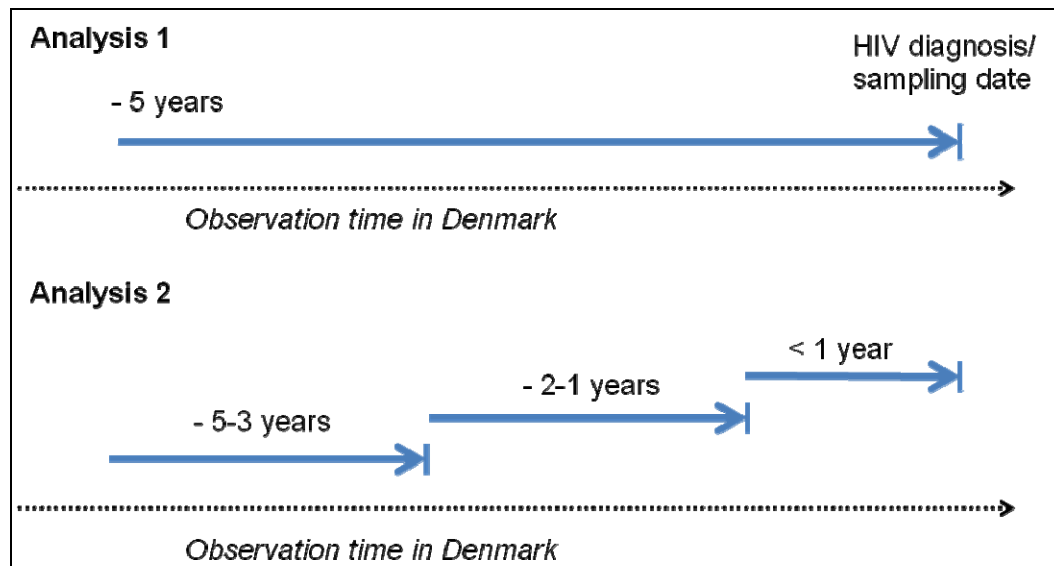


Figure 3. The outline of the two types of analysis used in paper III. Analysis 1 investigates medical events in 5 years prior to HIV diagnosis/sampling date. Analysis 2 investigates associations between time of hospital contact and time of HIV diagnosis / sampling date.

5 RESULTS

5.1 PAPER I

HOSPITALIZATION FOR PNEUMONIA AMONG INDIVIDUALS WITH AND WITHOUT HIV INFECTION, 1995-2007: A DANISH POPULATION-BASED NATIONWIDE COHORT STUDY

Background: Compared with the general population, persons with HIV infection have increased rates of non-AIDS-defining malignancies¹⁷ and cardiovascular,^{96,97} liver,⁹⁸ and renal diseases,⁹⁹ even among patients with full virological suppression and high CD4⁺ cell counts. Bacterial pneumonia (first-time or recurring) is a common hospital diagnosis in persons with HIV, including those receiving HAART,^{46,100} and respiratory failure is the leading cause of ICU admissions among HIV-infected patients.¹⁰¹ A number of studies have reported increased rates of pneumonia in persons with HIV compared to the general population, but the impact of HAART and CD4⁺ cell count on risk of pneumonia in HIV-infected patients is still controversial.

Methods: Individuals in the DHCS were matched with up to 99 persons from the CRS according to sex, date of birth, and municipality of residence at the time of HIV diagnosis. Data on hospital discharge diagnoses were obtained from the NHR; mortality and emigration data from the CRS. Subjects were observed from HIV diagnosis until first hospitalization for pneumonia (excluding *pneumocystis jiroveci*), death, emigration, or 1 May 2007. We computed incidence rates and ratios, and used Poisson regression to identify risk factors for pneumonia in the HIV population.

Main results: We found that the risk of first-time hospitalization for pneumonia remained 6-fold higher in HIV-infected individuals than in the general population until 2007, despite a decrease in incidence after the introduction of HAART (Figure 4a). The increased risk was observed even in persons with near-normal CD4⁺ cell counts. The strongest risk factors for pneumonia were low current CD4⁺ cell count, IDU as the mode of HIV transmission, and, among HAART-naïve patients, a high current viral load. Interestingly, use of HAART was associated with a decreased risk of pneumonia. The CD4⁺ cell count independent effect of HAART on crude and adjusted IRR was investigated for the five levels of current CD4⁺ cell counts, comparing HAART-naïve to HAART-experienced individuals. However, the protective effect of HAART was only observed at CD4⁺ counts ≤ 200 cells/ μ L.

As shown in Figure 4b, all transmission groups except IDU experienced a decline in the risk of hospitalization for pneumonia during the time of the study. On the contrary, the risk of pneumonia remained largely unchanged throughout the study in the group with IDU as mode of transmission (IR \approx 60/1000

PYFU).

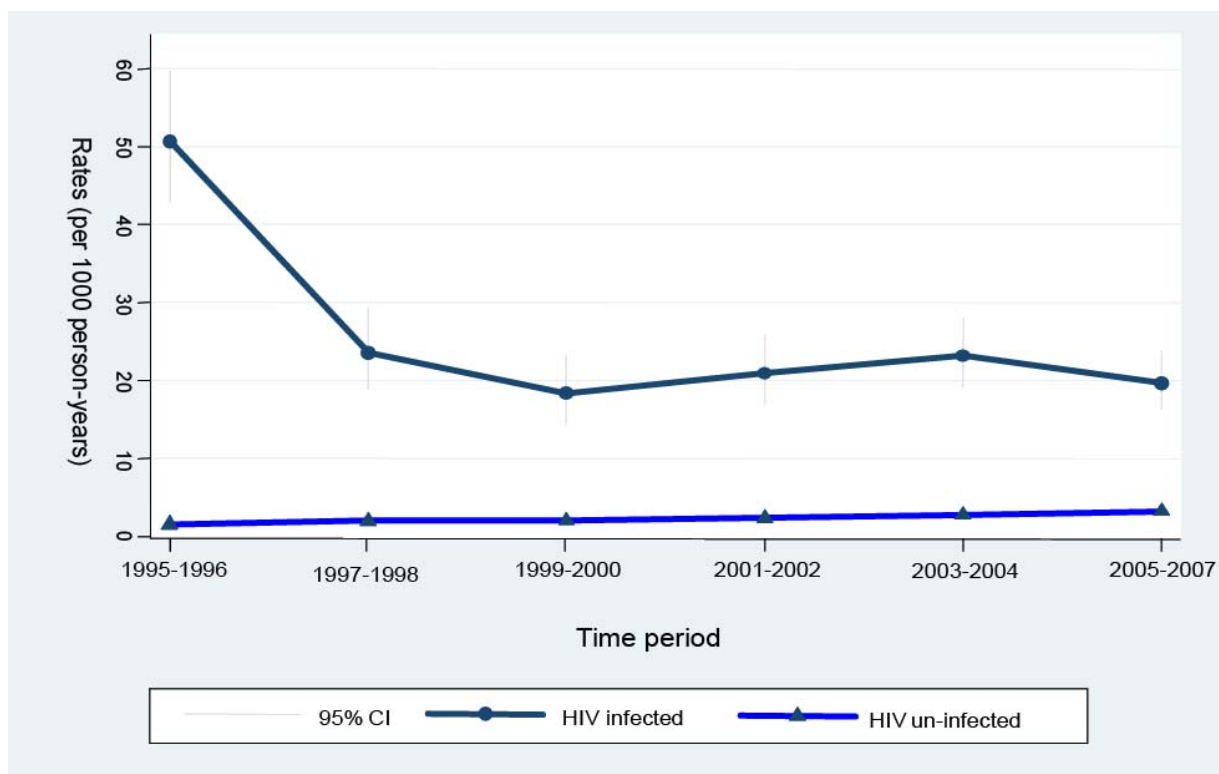


Figure 4a. Incidence of first-time hospitalization for pneumonia in Denmark among HIV and non-HIV-infected individuals, 1995-2007.

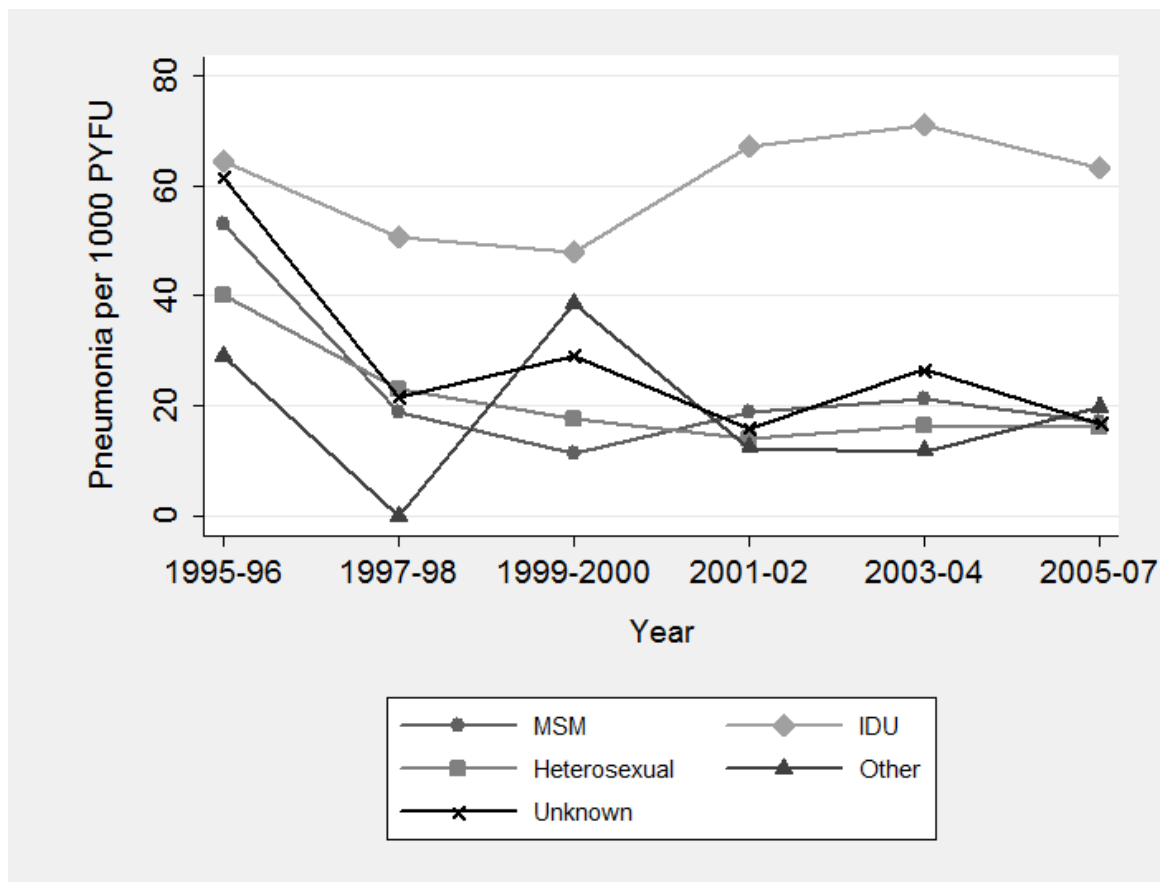


Figure 4b. Impact of mode of HIV transmission on temporal trends in IRs of pneumonia.

Comments: This study has some important implications:

- 1) Use of HAART is associated with significant decline in the risk of pneumonia among people with HIV infection. This lowered risk is primarily related to the reconstitution of the immune system as evidenced by increasing CD4+ cell counts, but HAART also has beneficial effects on the immune system that reaches beyond CD4+ cells.
- 2) Despite this positive effect of HAART, people with HIV remain at significantly higher risk of hospitalization for pneumonia than people without HIV infection. The question is why this excess risk persists despite near-normal immune status (using CD4+ as a surrogate marker). This difference in risk could either be a “real” phenomenon or be the result of residual confounding which will be discussed in detail later in this thesis.

3) Past or present injection drug users with HIV infection may be the group of individuals who would benefit most from prophylactic measures such as pneumococcal immunization.

5.2 PAPER II

MORTALITY AFTER HOSPITALIZATION FOR PNEUMONIA AMONG INDIVIDUALS WITH HIV, 1995-2008: A DANISH COHORT STUDY

Background: Early in the HIV epidemic it was recognized that morbidity and mortality due to pneumonia were higher in HIV-infected persons than in the general population.²⁸ However, more than a decade after the widespread introduction of HAART in high-income countries, the risk of pneumonia among HIV-infected persons remains high compared to persons without HIV.¹⁰² A better understanding of modifiable prognostic factors for death after pneumonia could potentially reduce mortality from this illness.

Methods: In a nationwide, population-based cohort of individuals with HIV, we included persons hospitalized with pneumonia from the Danish NHR and obtained mortality data from the CRS. Comparing individuals with and without pneumonia, we used Poisson regression to estimate relative mortality and logistic regression to examine prognostic factors for death following pneumonia.

Main results: We observed 699 episodes of first hospitalization for pneumonia among 4,352 HIV patients. Ninety-day mortality after pneumonia decreased from 22.4% in 1995-1996 to 8.4% in 2000-2008. Mortality remained elevated for more than a year after hospitalization for pneumonia with an adjusted mortality rate ratio of 5.38 (95% CI: 4.27-6.78), 1.80 (95% CI: 1.36-2.37), and 1.62 (95% CI: 1.32-2.00) for days 0-90, 91-365, and 366+, respectively. We found that HAART use improved the short term survival after a pneumonia-related hospitalization also after adjusting for CD4+ cell count. Other prognostic factors were male sex, age, pre-existing comorbidity, low CD4 cell count, and older age.

Table 4. Short and long term impact of pneumonia on mortality among all HIV-infected individuals.

	No of deaths	Follow-up ^a	Mortality rate ^b	Crude MRR ratio	Adjusted ^c MRR
At any time after first hospitalization for pneumonia	263	3,131	0.23 (0.20-0.26)	3.56 (3.09-4.10)	2.79 (2.40-3.26)
Day 0-90 after admission	84	159	1.44 (1.17-1.79)	20.5 (16.3-25.7)	5.38 (4.27-6.78)

Day 91-365 after admission	54	420	0.35 (0.27-0.46)	4.98 (3.77-6.57)	1.80 (1.36-2.37)
Day 366+ after admission	125	2,552	0.13 (0.11-0.16)	1.90 (1.57-2.30)	1.62 (1.32-2.00)
No previous pneumonia	691	26,775	0.07 (0.07-0.08)	1 (ref)	1 (ref)

^a In years. ^b Per 1000 days. ^c Adjusted for use of HAART, history of AIDS, years since entering the DHCS, Charlson Comorbidity Index score, age, and current CD4+ cell count.

Comments: The evidence emerging from this study demonstrates that the chance of surviving an episode of pneumonia for an HIV-infected individual has greatly increased during the last decade. In a study of non-HIV infected individuals aged 40-64 hospitalized for the first time with pneumonia, 30-day mortality was 7.8%, and 90-day mortality was 11.6%⁸⁹. These estimates are comparable to what we found in HIV-infected individuals. Further, the overall impact on risk of death following a first hospitalization pneumonia was similar to the increased risk reported for “mild” AIDS-defining events (*i.e.*, pulmonary and extrapulmonary tuberculosis, *pneumocystis jiroveci* (*carinii*) pneumonia and esophageal candidiasis).¹⁰³

However, we did not include population controls in paper II. It is possible that the decline in mortality following hospitalization for pneumonia over time was caused by general improvements in management of pneumonia rather than by improvement in the management of HIV. Although this association has not been reported in other Danish studies (e.g. by RW Thomsen)⁸⁹ it cannot be ruled out that changes in pneumonia management guidelines during the study also had an impact on the prognosis. This study was the first to show that HAART use also affects prognosis in the presence of a pneumonia-related hospitalization. Other studies also suggested a CD4+ independent beneficial effect from HAART. In a CD4+ cell-count-adjusted subgroup analysis from the Strategies for Management of Antiretroviral Therapy (SMART) trial, the risk of opportunistic diseases and death was increased in HAART-naïve patients or those off-HAART for 6 months compared to those with suppressed HIV viral load in plasma.²⁰ In an observational study of asymptomatic HIV patients with CD4+ counts of 351 to 500 cells/μL, deferring HAART vs. initiating early HAART was associated with a mortality ratio of 1.7.⁸¹ The finding of a CD4+ independent positive effect of HAART on survival after pneumonia created an important basis for further research into this area..

5.3 PAPER III

MORBIDITY AND RISK OF SUBSEQUENT DIAGNOSIS OF HIV INFECTION: A POPULATION BASED CASE CONTROL STUDY IDENTIFYING INDICATOR DISEASES FOR HIV INFECTION

Background: Many individuals newly diagnosed with HIV present at a late stage of the disease with severe immune depletion, resulting in delayed initiation of antiretroviral therapy which worsens their prognosis⁵⁶ and increases further transmission of HIV.^{57,59,60} High risk behavior (e.g., injection drug use)⁵⁵ or the presence of diseases associated with HIV, so-called indicator diseases,⁶⁸ can be used to guide targeted HIV testing. HIV indicator diseases may be a result of individual risk behaviors or coexisting HIV infection. Several studies have attempted to identify indicator diseases within a narrow spectrum of conditions,¹⁰⁴⁻¹⁰⁷ but to date there has been no comprehensive study of HIV indicator diseases. In the absence of adequate data, guidance is based mainly on expert opinion.⁶⁸ The goal of this study was to delineate medical conditions that identify individuals at increased risk of subsequent HIV diagnosis.

Methods: In this population-based case control study, cases were persons with incident HIV infection diagnosed in Denmark between 1 January 1995 and 1 June 2008. Risk-set sampling was used to identify up to 19 age- and gender-matched population controls for each case, using the HIV diagnosis date as the index date for both cases and controls. We obtained prior hospital diagnoses for cases and controls from Danish medical databases. We first categorized these diagnoses into 22 major disease categories (excluding AIDS-defining diseases except tuberculosis) and then subdivided them into 161 subcategories, allowing us to examine specific diseases as potential HIV indicators by conditional logistic regression.

Results: The study included 2,036 HIV cases and 35,718 controls. In the first analysis, we studied associations between major disease categories and risk of subsequent HIV diagnosis. Several disease categories recorded in the 5 years prior to the index date were associated with an increased risk of HIV diagnosis. As expected, the strongest associations were found among categories of infections, hematological diseases, and substance abuse, but other disease categories were also associated with increased risk of HIV diagnosis including: non-AIDS defining cancers, 'ear, nose, and throat' diseases, skin diseases, and gastrointestinal diseases. In the following analysis, we studied associations between time of hospital contact and risk of subsequent HIV diagnosis. The main conclusion from this analysis was that different patterns of association occurred with some disease categories showing a gradually increased risk over time (lower respiratory tract infections, CNS infections, skin infections, other infections, and 'ear, nose, and throat' diseases); while other disease categories showed a near persistent increased risk (sexual transmitted infections [STIs] and viral hepatitis, substance abuse, and poisoning). In the final analysis, we subdivided the 22 major disease categories into 161 subcategories to pinpoint specific diseases as potential HIV indicators (Table 5). Not surprisingly, we found strong associations between all groups of STIs and viral hepatitis and subsequent HIV diagnosis. Several other specific groups of infectious diseases, including meningitis, herpes zoster, endocarditis, and malaria, were closely associated with later HIV diagnosis. Among hematological diseases and cancers, thrombocytopenia, anemia, lymphadenitis, non-AIDS defining lymphomas, and secondary and unspecified malignant neoplasm of lymph nodes were associated with later HIV diagnosis. Interestingly, genital cancers were not. In the group of

gastrointestinal diseases, diseases of the oral cavity, liver diseases, and fissures/abscesses of the anal cavity were strongly associated with later HIV diagnosis. Among skin diseases, seborrheic dermatitis was associated with increased risk of HIV diagnosis. Ischemic heart disease, including myocardial infarction and other cardiovascular diseases, were not associated with later HIV diagnosis, with the notable exception of thrombophlebitis. Overall, in the HIV cohort of 2,036 individuals, 782 (38.4%) had at least one hospital contact for one of the 52 specific diseases with an $OR \geq 3$, while this occurred for only 2,475 (6.9%) of 35,718 controls.

Table 5. Specific diseases (diagnosed in the 5 years before the index date) associated with at least 3-fold elevated risk of subsequent HIV diagnosis.

Disease category	Specific disease	Cases n=2,036	Controls n=35,718	aOR (95% CI) ^a
Infections				
STIs and viral hepatitis	Syphilis	15	2	94.7 (20.9 to 429)
STIs and viral hepatitis	Hepatitis A	14	4	41.6 (11.7 to 148)
STIs and viral hepatitis	Non "A" viral hepatitis	77	55	23.6 (16.5 to 33.7)
STIs and viral hepatitis	Anogenital herpes simplex	7	10	12.7 (4.65 to 34.8)
STIs and viral hepatitis	Condyloma	55	95	8.99 (6.32 to 12.8)
STIs and viral hepatitis	Other STIs	18	12	14.8 (6.35 to 34.6)
Lower respiratory tract infections	Unspecified pneumonia	126	290	7.56 (6.03 to 9.48)
Lower respiratory tract infections	Pneumococcal pneumonia	9	14	4.33 (1.63 to 11.5)
Lower respiratory tract infections	Influenza and viral pneumonia	9	43	3.21 (1.51 to 6.81)
CNS infections	Bacterial meningitis	5	9	14.7 (5.63 to 38.1)
CNS infections	Viral meningitis or encephalitis	9	25	6.33 (2.90 to 13.8)
CNS infections	Other CNS infections	9	10	5.51 (1.60 to 19.0)
Skin infections	Abscess, furuncle, carbuncle	137	409	5.15 (4.17 to 6.35)
Skin infections	Fungal skin infections	3	11	4.41 (1.18 to 16.5)
Skin infections	Erysipelas	25	76	3.92 (2.39 to 6.45)
Skin infections	Other skin infections	45	95	5.29 (3.56 to 7.86)
Other infections	Herpes zoster	22	8	33.7 (14.3 to 79.6)
Other infections	Candida infection	40	22	25.5 (14.6 to 44.6)
Other infections	Endocarditis	11	7	23.2 (8.71 to 61.9)
Other infections	Tuberculosis and other mycobacterial infections	24	21	15.2 (7.99 to 29.1)
Other infections	Malaria	10	12	9.53 (3.86 to 23.5)
Other infections	Mononucleosis	11	19	8.64 (4.04 to 18.5)
Other infections	Lymphangitis	5	8	7.88 (2.40 to 25.9)
Other infections	Unspecified viral illness	23	44	7.87 (4.56 to 13.6)
Other infections	Sepsis	23	34	4.90 (2.52 to 9.52)
Other infections	Infectious gastroenteritis	50	216	3.48 (2.49 to 4.87)
Other infections	Other types of infection	67	182	4.77 (3.46 to 6.56)
Haematological diseases and cancers				
Haematological diseases	Thrombocytopenia	15	10	24.0 (10.5 to 54.7)
Haematological diseases	Unspecified anaemia	24	44	7.26 (4.19 to 12.6)
Haematological diseases	Lymphoma	18	43	5.83 (3.22 to 10.5)
Haematological diseases	Aplastic and other specified anaemias	7	17	4.58 (2.38 to 8.79)
Haematological diseases	Lymphadenitis	13	42	3.44 (1.42 to 8.30)
Haematological diseases	Nutrition deficiency anaemia	7	27	3.11 (1.11 to 8.70)
Haematological diseases	Other haematological diseases	5	18	4.30 (1.54 to 12.0)
Non-AIDS defining cancers	Secondary and unspecified malignant neoplasm of lymph nodes	11	22	6.74 (3.14 to 14.5)
Substance abuse and poisoning				
Substance abuse	Substance abuse opioids	69	17	43.5 (24.6 to 76.8)
Substance abuse	Substance abuse other	51	55	6.54 (4.07 to 10.5)
Drug poisoning	Narcotics and hallucinogens	47	43	11.2 (7.08 to 17.8)
Other disease categories				
Ear, nose, and throat diseases	Other acute upper respiratory tract infection	10	30	5.02 (2.38 to 10.6)
Ear, nose, and throat diseases	Chronic disease of tonsils and adenoids	43	129	4.95 (3.45 to 7.09)
Skin diseases	Seborrhoeic dermatitis	9	8	11.8 (4.30 to 32.6)
Gastrointestinal diseases	Fissure/abscess of anal and rectal regions	50	202	4.35 (2.87 to 6.61)
Gastrointestinal diseases	Liver diseases	31	103	4.06 (2.27 to 7.25)
Gastrointestinal diseases	Disease of salivary glands, oral mucosa, tongue and lips	15	58	3.97 (2.88 to 5.48)

Lung diseases	Respiratory disease principally affecting the interstitium	7	13	9.22 (3.63 to 23.4)
Lung diseases	Lung abscess/empyema without pneumonia	5	11	6.42 (2.16 to 19.1)
Lung diseases	Pneumothorax	8	40	3.25 (1.98 to 5.35)
Lung diseases	Other lung diseases	21	95	3.00 (1.37 to 6.55)
Non-IHD vascular diseases	Thrombophlebitis	34	106	5.29 (3.51 to 7.96)
Neurological diseases	Facial nerve disorder	8	31	3.04 (1.46 to 6.35)
Neurological diseases	Polyneuropathy	9	47	4.52 (2.07 to 9.85)
Rheumatological diseases	Infectious arthropathy	14	75	3.18 (1.76 to 5.74)

^a Adjusted for other diseases within the same disease category (Appendix Table 1). Risk estimates for all 161 subcategories are shown in Appendix Table 2. aOR, adjusted odds ratio; CI, confidence interval; STIs, sexually transmitted infections; IHD, ischemic heart disease.

Comments: We identified several known and numerous unknown diseases, which were associated with increased risk of subsequent HIV diagnosis. This thorough delineation of HIV indicator diseases may markedly improve the efficacy of targeted HIV testing in hospital settings. Our results also highlight the different nature of these indicator diseases. Disease categories related to individual risk behaviors (e.g., drug abuse and STIs and viral hepatitis) were associated with an elevated risk that remained constant over time. Other disease categories, which may be related to coexisting HIV and immunodeficiency, such as respiratory infections, hematological diseases, and non-AIDS-defining cancers, showed gradually increasing risk over time.

HIV indicator diseases could potentially detect approximately two out of every five persons with HIV at an earlier stage. If combined with prompt HAART initiation, indicator disease-based HIV screening has the potential to reduce HIV-related morbidity and HIV transmission.^{61,81,83} However, this strategy needs to be combined with other HIV screening initiatives in order to identify the remaining 60% of persons with undiagnosed HIV. Nearly one-third of cases in our study had no hospital contacts in the 5 years prior to their HIV diagnosis. Therefore, national screening initiatives should include non-hospital based strategies such as community outreach programs aimed at high-risk groups (e.g. sex workers and drug users).^{108,109}

6 STRENGTHS AND WEAKNESSES OF THE STUDIES

6.1 CONSIDERATIONS ABOUT STUDY DESIGN

In 1946-48, the US Public Health Service conducted trials in which vulnerable populations in Guatemala—mentally incapacitated patients, prison inmates, sex workers, and soldiers— were intentionally exposed to sexually transmitted infections (syphilis, gonorrhea, and chancroid).¹¹⁰ This appalling and unethical use of humans as research subjects fortunately belongs to the past, but this implies that the only way to study HIV (and other serious diseases) as exposure is through observational studies. As mentioned in previous sections, observational studies come with a range of limitations and are subjects to numerous sources of bias and confounding.

6.1.1 CONSIDERATIONS ABOUT RANDOM AND SYSTEMATIC ERROR

In paper I, we used various strategies to minimize bias and confounding including matching of HIV patients with population controls (on age, gender, and municipality of residence), exclusion of persons with previous pneumonia-related hospitalization, age-stratification, minimizing loss to follow-up by tracking persons via CRS, multivariate analyses, and standardization of pneumonia classification. However, we could not control for two likely candidates for confounding and bias – smoking and knowledge of HIV status.

Knowledge of HIV status is a source of bias if physicians have a lower threshold for hospital admission of HIV-infected patients presenting with signs and symptoms of pneumonia than for a person without HIV. In that case, pneumonia would be diagnosed in hospitals more frequently in HIV-infected persons than in the general population, leading to overestimation of the IRRs. We could potentially have adjusted for this if we had had information on pneumonia severity on hospital admission (e.g. scoring by the Pneumonia Severity Index or CURB-65). The impact of this potential bias on our results is thus difficult to assess, but in paper II¹¹¹ we found that among people with HIV the mortality following first hospitalization for pneumonia was similar to that reported for people without HIV.⁸⁹ This may indicate that the severity of pneumonia is comparable for HIV and non-HIV infected individuals. Further, validation of diagnosis of pneumonia in HIV and non-HIV infected patients yielded similar results indicating that the pneumonia diagnosis was reliable in both populations.

Smoking is a well-established risk factor for pneumonia and may thus have affected the study results. Despite numerous registries in Denmark, there are no valid national registry data on individual smoking habits. Also, there are no reliable surrogate markers for smoking (e.g., chronic obstructive pulmonary disease) in this relatively young study population. Data from HIV cohorts suggests that smoking doubles the risk of

pneumonia.^{29,49} If 40% of the HIV population and 25% of the background population were smokers in our study, smoking could hypothetically account for 12% of the observed effect ($60 \times 1 + 40 \times 2 / 75 \times 1 + 25 \times 2 = 1.12$). Although smoking is a likely source of bias in this study, it is unlikely to account for the large difference in risk of pneumonia between people with and without HIV infection.


The comparison of IRs between HIV- and non-HIV-infected individuals could have been strengthened by inclusion of other known risk factors for pneumonia. We had incomplete data on BMI but useful information on alcohol abuse and comorbidity could have been retrieved from hospital diagnoses in the NHR. Although we failed to include this information in the published study, the impact comorbidity was subsequently investigated. Contrary to paper I, we used Charlson's Comorbidity Index (CCI)⁹¹ to adjust for comorbidity in paper II. Comorbidity is a major prognostic factor in pneumonia (as shown in paper II), but it has also been found to be a risk factor for pneumonia.^{48,89,112} Therefore, the lack of adjusting for comorbidity in paper I could be considered a limitation in the design. During the analyses for paper II, we repeated the main analyses from paper I incorporating the CCI score in both stratified and adjusted models. Interestingly, people without HIV had a mean CCI of 1.0 whereas people with HIV had a mean CCI of 0.5 (AIDS diagnosis was not included in the CCI score). Adjustment for comorbidity increased the IRR for pneumonia in people with HIV compared with people without HIV. Thus, lack of adjustment for comorbidity may actually have caused us to underestimate the effect of HIV infection in paper I.

However, as mentioned in the introduction there are many other risk factors for pneumonia than comorbidity, smoking, and age. As highlighted by paper III, individual risk behaviors in the HIV population may be different from the general population. For instance, drug and alcohol abuse, which are more common in the HIV population than in the general population, are well known risk factors for pneumonia and pneumococcal disease.^{32,44,48,112,113} Both types of abuse are often associated with other factors that predispose individuals to pneumonia such as poor housing, low socio-economic status, and low educational level.^{44,114} Controlling for these covariates may also have changed our risk estimates in paper I, but whether or not this would bring us closer to the "true" impact of HIV infection on the risk of pneumonia is debatable. Paper III and other recent studies^{80,81} suggest that the risk profile and lifestyle associated with a proportion of persons who subsequently become infected with HIV is a priori different from those who do not become infected with HIV. Hence, paper III illustrates some of the limitations in paper I and even when the most stringent methodological approaches are used, some degree of residual confounding will probably remain when comparing HIV with non-HIV-infected individuals.

We made no distinction between hospital-acquired pneumonia (HAP) and community-acquired pneumonia (CAP) in paper I or paper II. HAP is known to be associated with a poorer outcome than CAP. It is not possible to distinguish between HAP and CAP from the ICD-codes alone but the placement of the pneumonia code as primary or secondary diagnosis could have been used as a proxy to differentiate between CAP and HAP.

Temporal differences in the occurrence of CAP and HAP could explain some of the observed improvement in the prognosis following an episode of pneumonia from 1995 to 2008.

In paper III, although numerous diseases and conditions and their potential association with undiagnosed HIV infection were analyzed, some gender-specific conditions were not included in the study. For example, HIV screening is offered routinely to all pregnant women in Denmark. Pregnant women are not generally considered a high-risk group in our country but identifying those with undiagnosed HIV infection significantly reduce morbidity and mortality among the mothers and the risk of mother-to-child HIV transmission can be greatly reduced.^{73,115} It could be considered a weakness of the study that such gender-specific events were not analyzed and it is certainly an area of research that demands further attention.



7 CONCLUSIONS, INTERPRETATION, AND PERSPECTIVES

7.1 MAIN CONCLUSIONS

Paper I. In Denmark, the risk of pneumonia in persons with HIV has declined substantially after the introduction of HAART, but HIV remains a strong risk factor for hospitalization for pneumonia even in persons with high CD4⁺ cell counts. Use of HAART has a CD4⁺ cell count independent protective effect against pneumonia.

Paper II. The first hospitalization for pneumonia among HIV-infected individuals was associated with elevated risk of death up to more than a year later. Use of HAART decreased the risk, independent of current CD4⁺ cell count. The prognosis following pneumonia improved over calendar time.

Paper III. A wide range of medical conditions can identify persons with increased risk of HIV infection. These "HIV indicator diseases" identified more than one-third of all individuals diagnosed with HIV in the subsequent 5-year period.

7.2 INTERPRETATION

As mentioned in the introduction of this thesis, one of the major questions in today's HIV research field is which long term effects HIV infection and HAART have on morbidity and the expected lifespan of an HIV-infected individual. The 6-fold increased risk of hospitalization for pneumonia even among well-controlled HIV-infected persons compared with the background population suggests that there is an excess susceptibility to infections in this group of patients despite near-normal CD4⁺ cell counts (paper 1). However, the comparison of HIV-infected with HIV-uninfected individuals is not straightforward. How much of this excess morbidity is due to HIV infection in itself and how much can be attributed to other causes, for example lifestyle-associated factors, comorbidity, and chronic antiretroviral drug exposure (see Figure 5 below). Certainly, results from one of the sub-analysis in paper III indicate that a proportion of persons diagnosed with HIV in Denmark have a life-style, based on their medical history, which is a-priori different from those who do not become infected with HIV. This risk-taking behavior may also have a negative effect on their general health and predispose them to other diseases such as pneumonia. This argument is supported by studies showing excess risk of cardiovascular disease and other serious conditions in close relatives of HIV patients ^{116,117}. Thus, risk differences of common diseases (*i.e.* pneumonia, bone fracture, liver, kidney, and cardiovascular diseases) between HIV-infected populations and HIV-uninfected population may not only be due to the HIV infection itself, but also due to fundamental disparities between the two populations.

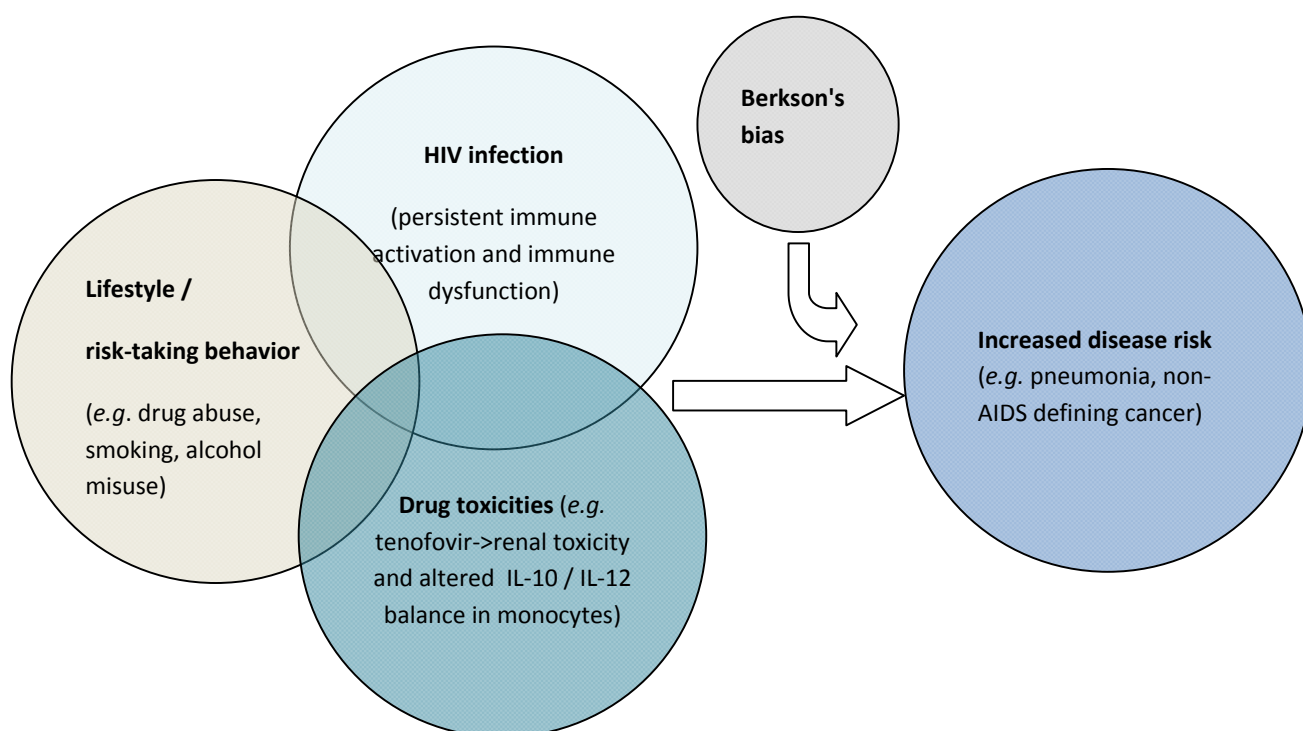


Figure 5. In HAART treated persons with undetectable viral load, several factors may play a role in the observed excess risk of pneumonia and other diseases such as non-AIDS defining cancers.

Selection (Berkson's) bias may also play a role in this finding as physicians may have lower threshold for hospital admission of HIV-infected patients presenting with signs and symptoms of pneumonia than for a person without HIV. This bias could have been addressed by studying disease severity - unfortunately, we did not have the data to do this. On the other hand, results from paper 3 show that the prognosis following pneumonia has significantly improved since the advent of HAART among people with HIV - and is now comparable to that of people without HIV infection. Similar prognosis following pneumonia indicates similar pneumonia severity in the two groups.

Current or cumulative exposure to certain antiretroviral drugs may increase the risk of renal disease, myocardial infarction, bone loss, and psychiatric disorders. In this thesis, we did not assess the effect of individual antiretroviral drug class exposure on pneumonia but we did show that HAART use was protective against pneumonia and against death following pneumonia independently of CD4+ cell count. In vitro data indicate that certain antiretroviral drugs may have immunomodulatory properties which affect the innate immune responses to bacterial pathogens (e.g. pretreatment with tenofovir shifts the interleukin-10 / interleukin-12 balance after infection with live bacteria in human peripheral blood mononuclear cells).¹¹⁸ Altogether, our results (paper I+II)

point towards significant CD4+ dependent and independent benefits from HAART use and for initiating treatment at an early stage of HIV infection.

In paper 3, we explored a great many diseases and disease groups, many of which were associated with later HIV infection. Due to the exploratory nature of the study we have not yet shown that testing patients with these diseases is an effective way to screen for HIV. Could implementation of indicator disease-based HIV screening improve the identification of undiagnosed HIV infection? We and others⁶⁸ argue that it could. In our study, HIV indicator diseases could potentially detect approximately two out of every five persons with HIV at an earlier stage. If combined with prompt HAART initiation, indicator disease-based HIV screening has the potential to reduce HIV-related morbidity and HIV transmission.^{61,81,83} However, this strategy is not a "magic bullet" and needs to be combined with other HIV screening initiatives in order to identify the remaining 60% of persons with undiagnosed HIV. Even if the US CDC's recommendations of routine HIV testing for all persons under the age of 65 who come into contact with health care system⁶⁴ were implemented in Denmark, we would still fail to identify the one-third of all incident cases who had no hospital contacts in the 5 years prior to their HIV diagnosis. Therefore, national screening initiatives should also include non-hospital based strategies such as community outreach programs aimed at high-risk groups (e.g. sex workers and drug users).^{108,109}

7.3 GENERALIZABILITY OF STUDY RESULTS

All three studies were based on data obtained from Danish clinical and administrative medical databases. The Danish health care system provides free, tax-supported medical care for all residents, including antiretroviral treatment of HIV. This implies that our results may not reflect trends in other settings due to population characteristics (race, age, sexual practices, immune status) and differences in health care systems (e.g., restricted/unrestricted access to HAART, organization, medical professionals' experience, vaccination policies). As far as for the excess risk of pneumonia and the prognosis following pneumonia, our data are comparable to those data from HIV cohorts in other developed countries.

Risk estimates for the HIV indicator diseases found in our study also reflect some general trends in the general population - for example outbreak of hepatitis A among men who have sex with men¹¹⁹ and malaria among non-Caucasian immigrants. Disease patterns are likely to differ between countries, which affect the strength of association between "indicator diseases" and undiagnosed HIV infection. However, a large HIV indicator diseases survey across Europe initiated in July 2010 focuses on a subset of diseases which we found also to be strongly associated with subsequent HIV infection (*i.e.*, sexually transmitted diseases, malignant lymphoma, cervical or anal dysplasia or cancer, herpes zoster, hepatitis B or C virus infection, ongoing mononucleosis-like illness, leukocytopenia or thrombocytopenia, and seborrheic dermatitis / exanthema. Hence, although the risk

estimate between indicator diseases and subsequent HIV infection will vary between countries, most of the indicator diseases in our study probably also indicate potentially undiagnosed HIV infection in other countries.

7.4 PERSPECTIVES

The challenges of treating HIV infection and controlling the HIV epidemic have changed dramatically over the past 30 years in the developed world. Today, 80-90% of HIV-infected individuals have undetectable viral load 6 months after initiating HAART, side effects from antiretroviral drug have diminished, and their life expectancy now approaches that of non-HIV-infected persons. Following the tremendous success of HAART, much attention has now been directed towards limiting residual non-AIDS morbidity such as liver, kidney and cardiovascular disease among those living with HIV. Our work shows that non-AIDS defining infections such as pneumonia should be included in this group of morbidities - regardless of its causes - and that preventing pneumonia is likely to reduce morbidity and mortality in HIV patients. Unfortunately, the effectiveness of the 23-valent pneumococcal polysaccharide vaccine against pneumococcal disease is far from perfect in immunosuppressed individuals but considerable effort are being made to develop more effective pneumococcal vaccines. We have also shown that use of HAART has both CD4+ cell count dependent and independent protective effects in pneumonia and thus, adds another good argument to the list for initiating HAART early during the course of HIV infection. However, despite three decades of concerted effort, controlling the HIV epidemic remains a tremendous public health challenge. Data from our study of HIV indicator diseases reveal a significant potential for earlier identification of individuals with undiagnosed HIV infection using disease-targeted HIV screening. Targeted testing for HIV in patients diagnosed with diseases associated with HIV can identify those with undiagnosed HIV infection, leading to earlier treatment and reduced HIV transmission. Implementation of indicator disease-based screening in national HIV testing programs should be strongly considered and its' impact on new HIV diagnoses, immune status on diagnose, and HIV transmission documented. Although the use of indicator diseases may enhance the identification of undiagnosed HIV-infected individuals, this strategy can only be supplementary to systematic HIV testing of risk groups identified through information about their behavioral risk-taking profiles.

8 SUMMARY

8.1 IN ENGLISH

This PhD thesis consists of three original research papers and a literature review. In 2007, when the work leading to this thesis was initiated, emerging evidence suggested that the risk of non-AIDS defining morbidity was increased among both treated and untreated HIV patients compared to HIV-uninfected individuals. Part of this excess morbidity was thought to be associated with late HIV diagnosis, resulting in severe immune depletion and delayed initiation of HIV treatment. Extensive research focusing on cardiovascular, liver, kidney, and metabolic disease was being conducted, whereas non-AIDS defining infections received relatively little attention. The aims of this thesis were therefore 1) to investigate temporal changes in the incidence of pneumonia among people with and without HIV infection and to identify risk factors for pneumonia in the HIV population; 2) to determine mortality among HIV patients following pneumonia and to identify prognostic factors; 3) to examine the relation between diseases diagnosed in hospitals and risk of subsequent HIV diagnosis. The studies were based on data from the Danish HIV cohort study and from Danish medical administrative databases.

We found that the risk of first-time hospitalization for pneumonia remained 6-fold higher in HIV-infected individuals than in the general population until 2007, despite a decrease in incidence after the introduction of HAART. The increased risk was observed even in persons with near-normal CD4⁺ cell counts. The strongest risk factors for pneumonia are low current CD4⁺ cell count, IDU as the mode of HIV transmission, and, among HAART-naïve patients, a high current viral load. HAART was associated with a decreased risk of pneumonia, but the protective effect of HAART was only observed at CD4⁺ counts ≤ 200 cells/ μ L. Reassuringly, short-term mortality after a first hospitalization for pneumonia among HIV-infected individuals decreased from the pre-HAART to the late-HAART era. Despite this decrease over time, an episode of hospitalization due to pneumonia remains associated with an increased mortality among HIV patients. Prognostic factors are male sex, age, pre-existing comorbidity, low CD4 cell count, older age, and absence of HAART treatment.

Use of HAART and current CD4⁺ cell count appear to be major independent risk and prognostic factors for pneumonia. Thus, early identification of newly infected individuals and prompt initiation of treatment could potentially reduce pneumonia-related morbidity and mortality among people with HIV. In the third study, we used prior hospital diagnoses to examine specific diseases as potential HIV indicators which could be used for targeted HIV screening in hospital settings. We found that several general disease categories were associated with an increased risk of subsequent HIV diagnosis including: sexually transmitted infections and viral hepatitis, hematological diseases, lower respiratory tract infections, CNS infections, skin infections, other infections, and substance abuse. Several specific diseases were associated with adjusted odds ratios above 20.

During recent years, national and international HIV treatment guidelines have emphasized the potential advantages from early initiation of antiviral therapy and increasingly higher CD4+ cell counts have been used as lower target for starting therapy among HIV patients. Our results supports a general protective effect from having high CD4+ cell counts against hospitalization for pneumonia and against dying following an episode of pneumonia, independent from use of HAART - likely due to reconstitution of other lymphocyte subsets and/or reduced immune activation. Considerable efforts are now being made to identify people with undiagnosed HIV infection - both to reduce the risk of severe immune depletion from occurring but also reduce the risk of onward HIV transmission. Our third study demonstrates the potential of using non-AIDS defining conditions to guide targeted HIV testing. In this study, HIV indicator diseases could potentially detect approximately two out of every five persons with HIV in Denmark at an earlier stage. If combined with prompt treatment, indicator disease-based HIV screening has the potential to reduce HIV-related morbidity and HIV transmission - though the exploratory nature of the study need confirmation from clinical studies. Thus, at the beginning of the forth decade of HIV epidemic mounting evidence calls for increased attention directed towards identifying people with undiagnosed HIV infection and initiating treatment before severe immune depletion occurs.

8.2 IN DANISH

Denne Ph.d.-afhandling består af original artikler og en litteraturgennemgang. I 2007, da det indledende arbejde til denne afhandling blev påbegyndt, var der begyndende tegn på, at risikoen for ikke-AIDS definerende sygdom var øget blandt både ubehandlede og behandlede HIV patienter sammenlignet med baggrundsbefolkningen. En del af denne øgede sygelighed mentes at være associeret med sen diagnose af HIV-smittede med betydeligt tab af immunfunktion og forsinket behandlingsopstart til følge. En del forskningsprojekter omhandlede kardiovaskulær, lever-, nyre- og metaboliske sygdomme, hvorimod relativt få havde interesseret sig for ikke-AIDS definerende infektioner.

Formålene med denne afhandling var derfor 1) at udforske ændringer i forekomsten af lungebetændelse over tid blandt folk med eller uden HIV infektion og at identificere risikofaktorer for lungebetændelse i HIV populationen; 2) at bestemme dødeligheden blandt HIV patienter efter lungebetændelse og at identificere prognostiske faktorer; 3) at undersøge sammenhængen mellem hospitalsdiagnoser og den efterfølgende risiko for at få stillet en HIV diagnose. Studierne blev lavet på baggrund af data fra den danske HIV kohorte og udtræk fra danske medicinske databaser.

Vi fandt at risikoen for førstegangssindlæggelse for lungebetændelse var 6 gange højere for HIV-smittede sammenlignet med baggrundsbefolkningen indtil 2007, selvom forekomsten faldt umiddelbart efter indførelse af HAART behandlingen i slutningen af 1996. Den øgede risiko blev også observeret blandt folk med god immunstatus og næsten-normale CD4+ celletal. De stærkeste risikofaktorer for lungebetændelse var lavt aktuelt CD4+ celletal, stofmisbrug som HIV smitemåde, og blandt ubehandlede patienter, høj virus mængde i blodet. HAART var associeret med en nedsat risiko for lungebetændelse, som dog kun sås ved CD4+ celletal under 200/ μ L. Heldigvis faldt dødeligheden efter en førstegangssindlæggelse for lungebetændelse fra perioden før HAART blev indført og frem til nu i (den "sene" HAART periode). Trods dette fald i dødelighed over tid, er en indlæggelse for lungebetændelse fortsat associeret med en betydelig dødelighed blandt HIV patienter. Prognostiske faktorer var at være mand, komorbiditet, lavt CD4+ celletal, høj alder og ingen HAART behandling.

Brug af HAART and nuværende CD4+ celletal synes at være betydningsfulde, uafhængige risiko- og prognostiske faktorer. Derfor kan tidlig identifikation af ny-smittede personer og hurtig behandlingsopstart være en måde at reducere sygelighed og dødelighed på blandt folk med HIV. I det tredje studie, brugte vi tidligere hospitalsdiagnoser til undersøge specifikke sygdomme som potentielle HIV indikatorer, som kunne bruges til målrettet HIV screening på hospitaler. Vi fandt, at adskillige overordnede sygdomskategorier var associeret med øget risiko for efterfølgende HIV diagnose, herunder: seksuelt overførte infektioner og viral hepatitis, hæmatologiske sygdomme, nedre luftvejsinfektioner, CNS-infektioner, hud-infektioner, andre infektioner og stofmisbrug. Nogle specifikke sygdomme var associeret med en justeret odds ratio på over 20.

Nationale og internationale retningslinjer for HIV behandling har gennem de senere år lagt stadig vægt på de potentielle fordele ved tidlig opstart af HAART. Det CD4+ celletal, der benyttes som grænse for hvornår behandling iværksættes, er gradvist blevet højere, hvilket har medført at flere personer er kommet i behandling på et tidligere tidspunkt end tilfældet var for bare 5 år siden. Vores resultater understøtter en generel beskyttende effekt af høje CD4+ celletal mod indlæggelse for lungebetændelse og mod død efter en lungebetændelse. De antyder også at HAART har en CD4+ celletal's uafhængig beskyttende effekt - sandsynligvis relateret til genetablering af andre lymfocyt populationer og reduceret immunaktivering. Betydelige tiltag er nu iværksat for at identificere for med udiagnosticeret HIV infektion - både for at reducere risikoen for irreversibelt tab af immunfunktion, men også for at reducere risikoen for HIV transmission. Vores tredje studie viste at HIV testning målrettet mod specifikke sygdomme kan bruges til opsporing af folk med udiagnosticeret HIV infektion. I dette studie kunne disse HIV indikatorsygdomme potentielt detektere 2 ud af 5 patienter med HIV på et tidligere stadie end det rent faktisk skete. Hvis indikator-baseret HIV screening kombineres med øjeblikkelig opstart af HAART, så har det potentialet til at kunne reducere både sygelighed og HIV transmission - selvom effekten af denne strategi selvsagt skal bekræftes i kliniske studier. Ved begyndelsen af HIV epidemiens fjerde årti peger tungtvejende data derfor på vigtigheden af øget opmærksomhed rettet mod at identificere folk med udiagnosticerede infektion og tilbyde dem hurtig behandlingsopstart før der sker en omfattende destruktion af deres immunforsvar og/eller de når at transmittre HIV til andre.

REFERENCES

1. Pneumocystis pneumonia--Los Angeles. MMWR Morb Mortal Wkly Rep 1981;30:250-2.
2. Barre-Sinoussi F, Chermann JC, Rey F, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science 1983;220:868-71.
3. Worobey M, Gemmel M, Teuwen DE, et al. Direct evidence of extensive diversity of HIV-1 in Kinshasa by 1960. Nature 2008;455:661-4.
4. UNAIDS report on the global AIDS epidemic 2010. Joint United Nations Programme on HIV/AIDS (UNAIDS), 2010. (Accessed 7 April, 2011, at http://www.unaids.org/globalreport/Global_report.htm.)
5. Simon V, Ho DD, Abdool Karim Q. HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. Lancet 2006;368:489-504.
6. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control 1992;41:1-19.
7. Fauci AS, Pantaleo G, Stanley S, Weissman D. Immunopathogenic mechanisms of HIV infection. Ann Intern Med 1996;124:654-63.
8. Dournon E, Matheron S, Rozenbaum W, et al. Effects of zidovudine in 365 consecutive patients with AIDS or AIDS-related complex. Lancet 1988;2:1297-302.
9. Reiss P, Lange JM, Boucher CA, Danner SA, Goudsmit J. Resumption of HIV antigen production during continuous zidovudine treatment. Lancet 1988;1:421.
10. Li TS, Tubiana R, Katlama C, Calvez V, Ait Mohand H, Autran B. Long-lasting recovery in CD4 T-cell function and viral-load reduction after highly active antiretroviral therapy in advanced HIV-1 disease. Lancet 1998;351:1682-6.
11. Gandhi T, Wei W, Amin K, Kazanjian P. Effect of maintaining highly active antiretroviral therapy on AIDS events among patients with late-stage HIV infection and inadequate response to therapy. Clin Infect Dis 2006;42:878-84.
12. Safrin S, Grunfeld C. Fat distribution and metabolic changes in patients with HIV infection. AIDS (London, England) 1999;13:2493-505.
13. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. Arch Intern Med 2006;166:1632-41.
14. Walmsley S. Protease inhibitor-based regimens for HIV therapy: safety and efficacy. Journal of acquired immune deficiency syndromes (1999) 2007;45 Suppl 1:S5-13; quiz S28-31.
15. Deeks SG, Phillips AN. HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. BMJ 2009;338:a3172.

16. Mocroft A, Reiss P, Gasiorowski J, et al. Serious fatal and nonfatal non-AIDS-defining illnesses in Europe. *J Acquir Immune Defic Syndr* 2010;55:262-70.
17. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* 2007;370:59-67.
18. Brenchley JM, Price DA, Schacker TW, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nature medicine* 2006;12:1365-71.
19. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* 2006;355:2283-96.
20. Emery S, Neuhaus JA, Phillips AN, et al. Major clinical outcomes in antiretroviral therapy (ART)-naive participants and in those not receiving ART at baseline in the SMART study. *J Infect Dis* 2008;197:1133-44.
21. Hanna DB, Gupta LS, Jones LE, Thompson DM, Kellerman SE, Sackoff JE. AIDS-defining opportunistic illnesses in the HAART era in New York City. *AIDS Care* 2007;19:264-72.
22. Podlekareva D, Mocroft A, Dragsted UB, et al. Factors associated with the development of opportunistic infections in HIV-1-infected adults with high CD4+ cell counts: a EuroSIDA study. *J Infect Dis* 2006;194:633-41.
23. Crothers K, Huang L, Goulet JL, et al. HIV infection and risk for incident pulmonary diseases in the combination antiretroviral therapy era. *Am J Respir Crit Care Med* 2011;183:388-95.
24. Harries AD, Zachariah R, Corbett EL, et al. The HIV-associated tuberculosis epidemic--when will we act? *Lancet* 2010;375:1906-19.
25. Lawn SD, Myer L, Edwards D, Bekker LG, Wood R. Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa. *Aids* 2009;23:1717-25.
26. Kesselring AM, Gras L, Wit FW, et al. Immune restoration and onset of new AIDS-defining events with combination antiretroviral therapy in HIV type-1-infected immigrants in the Netherlands. *Antiviral Therapy* 2010;15:871-9.
27. Serraino D, Puro V, Boumis E, et al. Epidemiological aspects of major opportunistic infections of the respiratory tract in persons with AIDS: Europe, 1993-2000. *AIDS (London, England)* 2003;17:2109-16.
28. Polsky B, Gold JW, Whimbey E, et al. Bacterial pneumonia in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1986;104:38-41.
29. Kohli R, Lo Y, Homel P, et al. Bacterial pneumonia, HIV therapy, and disease progression among HIV-infected women in the HIV epidemiologic research (HER) study. *Clin Infect Dis* 2006;43:90-8.
30. Feikin DR, Feldman C, Schuchat A, Janoff EN. Global strategies to prevent bacterial pneumonia in adults with HIV disease. *Lancet Infect Dis* 2004;4:445-55.
31. Barry PM, Zetola N, Keruly JC, Moore RD, Gebo KA, Lucas GM. Invasive pneumococcal disease in a cohort of HIV-infected adults: incidence and risk factors, 1990-2003. *AIDS (London, England)* 2006;20:437-44.

32. Grau I, Pallares R, Tubau F, et al. Epidemiologic changes in bacteremic pneumococcal disease in patients with human immunodeficiency virus in the era of highly active antiretroviral therapy. *Archives of Internal Medicine* 2005;165:1533-40.
33. Gilks CF, Ojoo SA, Ojoo JC, et al. Invasive pneumococcal disease in a cohort of predominantly HIV-1 infected female sex-workers in Nairobi, Kenya. *Lancet* 1996;347:718-23.
34. Barry PM, Zetola N, Keruly JC, Moore RD, Gebo KA, Lucas GM. Invasive pneumococcal disease in a cohort of HIV-infected adults: incidence and risk factors, 1990-2003. *AIDS* 2006;20:437-44.
35. Grau I, Pallares R, Tubau F, et al. Epidemiologic changes in bacteremic pneumococcal disease in patients with human immunodeficiency virus in the era of highly active antiretroviral therapy. *ArchInternMed* 2005;165:1533-40.
36. Dworkin MS, Ward JW, Hanson DL, Jones JL, Kaplan JE. Pneumococcal disease among human immunodeficiency virus-infected persons: incidence, risk factors, and impact of vaccination. *Clinical Infectious Diseases* 2001;32:794-800.
37. Gebo KA, Moore RD, Keruly JC, Chaisson RE. Risk factors for pneumococcal disease in human immunodeficiency virus-infected patients. *Journal of Infectious Diseases* 1996;173:857-62.
38. Teshale EH, Hanson D, Flannery B, et al. Effectiveness of 23-valent polysaccharide pneumococcal vaccine on pneumonia in HIV-infected adults in the United States, 1998-2003. *Vaccine* 2008.
39. Tumbarello M, Tacconelli E, De Gaetano K, et al. Bacterial pneumonia in HIV-infected patients: Analysis of risk factors and prognostic indicators. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology* 1998;18:39-45.
40. Penaranda M, Falco V, Payeras A, et al. Effectiveness of polysaccharide pneumococcal vaccine in HIV-infected patients: a case-control study. *Clinical Infectious Diseases* 2007;45:e82-e7.
41. Payeras A, Martinez P, Mila J, et al. Risk factors in HIV-1-infected patients developing repetitive bacterial infections: Toxicological, clinical, specific antibody class responses, opsonophagocytosis and Fc(gamma)RIIa polymorphism characteristics. *Clinical and Experimental Immunology* 2002;130:271-8.
42. Veras MA, Enanoria WT, Castilho EA, Reingold AL. Effectiveness of the polysaccharide pneumococcal vaccine among HIV-infected persons in Brazil: a case control study. *BMCInfectDis* 2007;7:119.
43. Guerrero M, Kruger S, Saitoh A, et al. Pneumonia in HIV-infected patients: a case-control survey of factors involved in risk and prevention. *AIDS* 1999;13:1971-5.
44. Dworkin MS, Ward JW, Hanson DL, et al. Pneumococcal disease among human immunodeficiency virus-infected persons: incidence, risk factors, and impact of vaccination. *Clin Infect Dis* 2001;32:794-800.
45. Hirschtick RE, Glassroth J, Jordan MC, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary Complications of HIV Infection Study Group. *The New England journal of medicine* 1995;333:845-51.

46. Floris-Moore M, Lo Y, Klein RS, et al. Gender and hospitalization patterns among HIV-infected drug users before and after the availability of highly active antiretroviral therapy. In: *Journal of acquired immune deficiency syndromes* (1999). United States; 2003:331-7.
47. Sullivan JH, Moore RD, Keruly JC, Chaisson RE. Effect of antiretroviral therapy on the incidence of bacterial pneumonia in patients with advanced HIV infection. *Am J Respir Crit Care Med* 2000;162:64-7.
48. Tumbarello M, Tacconelli E, de Gaetano Donati K, Cauda R. HIV-associated bacterial pneumonia in the era of highly active antiretroviral therapy. *Journal of acquired immune deficiency syndromes and human retrovirology : official publication of the International Retrovirology Association* 1999;20:208-9.
49. Gordin FM, Roediger MP, Girard PM, et al. Pneumonia in HIV-infected persons: increased risk with cigarette smoking and treatment interruption. *Am J Respir Crit Care Med* 2008;178:630-6.
50. Lopez-Palomo C, Martin-Zamorano M, Benitez E, et al. Pneumonia in HIV-infected patients in the HAART era: incidence, risk, and impact of the pneumococcal vaccination. *Journal of medical virology* 2004;72:517-24.
51. Curran A, Falco V, Crespo M, et al. Bacterial pneumonia in HIV-infected patients: use of the pneumonia severity index and impact of current management on incidence, aetiology and outcome. *HIV Med* 2008;9:609-15.
52. Valdiserri RO. Late HIV diagnosis: Bad medicine and worse public health. *PLoS Med* 2007;4:975-6.
53. Hall HI, Song R, Rhodes P, et al. Estimation of HIV incidence in the United States. *Jama* 2008;300:520-9.
54. Coenen T, Lundgren J, Lazarus JV, Matic S. Optimal HIV testing and earlier care: the way forward in Europe. *HIV Med* 2008;9 Suppl 2:1-5.
55. Mathers BM, Degenhardt L, Ali H, et al. HIV prevention, treatment, and care services for people who inject drugs: a systematic review of global, regional, and national coverage. *Lancet* 2010;375:1014-28.
56. Chadborn TR, Delpech VC, Sabin CA, Sinka K, Evans BG. The late diagnosis and consequent short-term mortality of HIV-infected heterosexuals (England and Wales, 2000-2004). *Aids* 2006;20:2371-9.
57. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med* 2000;342:921-9.
58. Wawer MJ, Gray RH, Sewankambo NK, et al. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. *J Infect Dis* 2005;191:1403-9.
59. Donnell D, Baeten JM, Kiarie J, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet* 2010;375:2092-8.
60. Montaner JS, Lima VD, Barrios R, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. *Lancet* 2010;376:532-9.

61. Wood E, Kerr T, Marshall BD, et al. Longitudinal community plasma HIV-1 RNA concentrations and incidence of HIV-1 among injecting drug users: prospective cohort study. *BMJ* 2009;338:b1649.
62. Montaner JS, Hogg R, Wood E, et al. The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic. *Lancet* 2006;368:531-6.
63. Check Hayden E. 'Seek, test and treat' slows HIV. *Nature* 2010;463:1006.
64. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep* 2006;55:1-17; quiz CE1-4.
65. Krentz HB, Auld MC, Gill MJ. The high cost of medical care for patients who present late (CD4 < 200 cells/ μ L) with HIV infection. *HIV Med* 2004;5:93-8.
66. Paltiel AD, Weinstein MC, Kimmel AD, et al. Expanded screening for HIV in the United States - An analysis of cost-effectiveness. *New England Journal of Medicine* 2005;352:586-95.
67. Mounier-Jack S, Nielsen S, Coker RJ. HIV testing strategies across European countries. *HIV Med* 2008;9 Suppl 2:13-9.
68. Gazzard B, Clumeck N, d'Arminio Monforte A, Lundgren JD. Indicator disease-guided testing for HIV--the next step for Europe? *HIV Med* 2008;9 Suppl 2:34-40.
69. Ancelle-Park R. Expanded European AIDS case definition. *Lancet* 1993;341:441.
70. Marks G, Crepaz N, Senterfitt JW, Janssen RS. Meta-analysis of high-risk sexual behavior in persons aware and unaware they are infected with HIV in the United States: implications for HIV prevention programs. *J Acquir Immune Defic Syndr* 2005;39:446-53.
71. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *The New England journal of medicine* 1994;331:1173-80.
72. Humphrey JH, Marinda E, Mutasa K, et al. Mother to child transmission of HIV among Zimbabwean women who seroconverted postnatally: prospective cohort study. *Bmj* 2010;341:c6580.
73. Lalletant M, Jourdain G. Preventing mother-to-child transmission of HIV-protecting this generation and the next. *The New England journal of medicine* 2010;363:1570-2.
74. Sterne JA, May M, Costagliola D, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet* 2009;373:1352-63.
75. Muller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis* 2010;10:251-61.
76. Lawn SD, Wood R. Immune reconstitution inflammatory syndrome. *Lancet Infect Dis* 2010;10:833-4.

77. Emery S, Neuhaus JA, Phillips AN, et al. Major clinical outcomes in antiretroviral therapy (ART)-naive participants and in those not receiving ART at baseline in the SMART study. *J Infect Dis* 2008;197:1133-44.
78. Sabin CA, Smith CJ, Gumley H, et al. Late presenters in the era of highly active antiretroviral therapy: uptake of and responses to antiretroviral therapy. *Aids* 2004;18:2145-51.
79. Titanji K, De Milito A, Cagigi A, et al. Loss of memory B cells impairs maintenance of long-term serologic memory during HIV-1 infection. *Blood* 2006;108:1580-7.
80. Sogaard OS, Schonheyder HC, Bukh AR, et al. Pneumococcal conjugate vaccination in persons with HIV: the effect of highly active antiretroviral therapy. *Aids* 2010;24:1315-22.
81. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of Early versus Deferred Antiretroviral Therapy for HIV on Survival. *N Engl J Med* 2009.
82. Paltiel AD, Walensky RP, Schackman BR, et al. Expanded HIV screening in the United States: Effect on clinical outcomes, HIV transmission, and costs. *Annals of Internal Medicine* 2006;145:797-806.
83. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet* 2009;373:48-57.
84. Jensen-Fangel S, Pedersen C, Larsen CS, Tauris P, Moller A, Obel N. Changing demographics in an HIV-infected population: results from an observational cohort study in Western Denmark. *Scandinavian journal of infectious diseases* 2001;33:765-70.
85. Obel N, Engsig FN, Rasmussen LD, Larsen MV, Omland LH, Sorensen HT. Cohort Profile: The Danish HIV Cohort Study. *Int J Epidemiol* 2008.
86. Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Danish medical bulletin* 2006;53:441-9.
87. Frank L. Epidemiology. When an entire country is a cohort. *Science* 2000;287:2398-9.
88. Nickelsen TN. Data validity and coverage in the Danish National Health Registry. A literature review. *Ugeskrift for laeger* 2001;164:33-7.
89. Thomsen RW, Riis A, Norgaard M, et al. Rising incidence and persistently high mortality of hospitalized pneumonia: a 10-year population-based study in Denmark. *Journal of internal medicine* 2006;259:410-7.
90. de Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity. a critical review of available methods. *J Clin Epidemiol* 2003;56:221-9.
91. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-83.
92. Carr A, Grund B, Neuhaus J, et al. Asymptomatic myocardial ischaemia in HIV-infected adults. *AIDS (London, England)* 2008;22:257-67.

93. Danish National Board of H. Tobaksskaderaadet. In: Danish National Board of Health; 2008.
94. Fletcher RWF, S. W. Clinical epidemiology: the essentials. Fourth ed: Lippincott Williams & Wilkins; 2005.
95. Richardson DB. An incidence density sampling program for nested case-control analyses. *Occup Environ Med* 2004;61:e59.
96. Friis-Moller N, Reiss P, Sabin CA, et al. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med* 2007;356:1723-35.
97. Obel N, Thomsen HF, Kronborg G, et al. Ischemic heart disease in HIV-infected and HIV-uninfected individuals: a population-based cohort study. *Clin Infect Dis* 2007;44:1625-31.
98. Thio CL, Seaberg EC, Skolasky R, Jr., et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet* 2002;360:1921-6.
99. Kimmel PL, Barisoni L, Kopp JB. Pathogenesis and treatment of HIV-associated renal diseases: lessons from clinical and animal studies, molecular pathologic correlations, and genetic investigations. *Annals of Internal Medicine* 2003;139:214-26.
100. Betz ME, Gebo KA, Barber E, et al. Patterns of diagnoses in hospital admissions in a multistate cohort of HIV-positive adults in 2001. *Medical care* 2005;43:III3-14.
101. Morris A. Intensive Care of Human Immunodeficiency Virus-infected Patients during the Era of Highly Active Antiretroviral Therapy. *Am J Respir Crit Care Med* 2002;166:262-7.
102. Sogaard OS, Lohse N, Gerstoft J, et al. Hospitalization for Pneumonia among Individuals With and Without HIV Infection, 1995-2007: A Danish Population-Based, Nationwide Cohort Study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2008.
103. Mocroft A, Sterne JA, Egger M, et al. Variable impact on mortality of AIDS-defining events diagnosed during combination antiretroviral therapy: not all AIDS-defining conditions are created equal. *Clin Infect Dis* 2009;48:1138-51.
104. Bini EJ, Currie SL, Shen H, et al. National multicenter study of HIV testing and HIV seropositivity in patients with chronic hepatitis C virus infection. *J Clin Gastroenterol* 2006;40:732-9.
105. Bottieau E, Clerinx J, Van den Enden E, et al. Infectious mononucleosis-like syndromes in febrile travelers returning from the tropics. *J Travel Med* 2006;13:191-7.
106. Klein D, Hurley LB, Merrill D, Quesenberry CP, Jr. Review of medical encounters in the 5 years before a diagnosis of HIV-1 infection: implications for early detection. *J Acquir Immune Defic Syndr* 2003;32:143-52.
107. Noskin GA, Glassroth J. Bacterial pneumonia associated with HIV-1 infection. *Clin Chest Med* 1996;17:713-23.
108. de la Fuente L, Delgado J, Hoyos J, et al. Increasing early diagnosis of HIV through rapid testing in a street outreach program in Spain. *AIDS Patient Care STDS* 2009;23:625-9.

109. Wolfe D, Carrieri MP, Shepard D. Treatment and care for injecting drug users with HIV infection: a review of barriers and ways forward. *Lancet* 2010;376:355-66.
110. Frieden TR, Collins FS. Intentional infection of vulnerable populations in 1946-1948: another tragic history lesson. *Jama* 2010;304:2063-4.
111. Sogaard OS, Lohse N, Gerstoft J, et al. Mortality after hospitalization for pneumonia among individuals with HIV, 1995-2008: a Danish cohort study. *PLoS One* 2009;4:e7022.
112. Penaranda M, Falco V, Payeras A, et al. Effectiveness of polysaccharide pneumococcal vaccine in HIV-infected patients: a case-control study. *Clin Infect Dis* 2007;45:e82-7.
113. Teshale EH, Hanson D, Flannery B, et al. Effectiveness of 23-valent polysaccharide pneumococcal vaccine on pneumonia in HIV-infected adults in the United States, 1998--2003. *Vaccine* 2008;26:5830-4.
114. Veras MA, Enanoria WT, Castilho EA, Reingold AL. Effectiveness of the polysaccharide pneumococcal vaccine among HIV-infected persons in Brazil: a case control study. *BMC Infect Dis* 2007;7:119.
115. Moszynski P. Global elimination of mother to child HIV transmission is now achievable, say agencies. *Bmj* 2010;341:c5152.
116. Hansen AB, Lohse N, Gerstoft J, et al. Cause-specific excess mortality in siblings of patients co-infected with HIV and hepatitis C virus. *PLoS One* 2007;2:e738.
117. Rasmussen LD, Omland LH, Pedersen C, et al. Risk of myocardial infarction in parents of HIV-infected Individuals: a population-based Cohort Study. *BMC Infect Dis* 2010;10:169.
118. Melchjorsen J, Risør RW, Sogaard OS, et al. Tenofovir selectively regulates production of inflammatory cytokines and shifts the IL-12 / IL-10 balance in human primary cells. *JAIDS* 2011;in press.
119. Mazick A, Howitz M, Rex S, et al. Hepatitis A outbreak among MSM linked to casual sex and gay saunas in Copenhagen, Denmark. *Euro Surveill* 2005;10:111-4.

109. Wolfe D, Carrieri MP, Shepard D. Treatment and care for injecting drug users with HIV infection: a review of barriers and ways forward. *Lancet* 2010;376:355-66.
110. Frieden TR, Collins FS. Intentional infection of vulnerable populations in 1946-1948: another tragic history lesson. *Jama* 2010;304:2063-4.
111. Sogaard OS, Lohse N, Gerstoft J, et al. Mortality after hospitalization for pneumonia among individuals with HIV, 1995-2008: a Danish cohort study. *PLoS One* 2009;4:e7022.
112. Penaranda M, Falco V, Payeras A, et al. Effectiveness of polysaccharide pneumococcal vaccine in HIV-infected patients: a case-control study. *Clin Infect Dis* 2007;45:e82-7.
113. Teshale EH, Hanson D, Flannery B, et al. Effectiveness of 23-valent polysaccharide pneumococcal vaccine on pneumonia in HIV-infected adults in the United States, 1998--2003. *Vaccine* 2008;26:5830-4.
114. Veras MA, Enanoria WT, Castilho EA, Reingold AL. Effectiveness of the polysaccharide pneumococcal vaccine among HIV-infected persons in Brazil: a case control study. *BMC Infect Dis* 2007;7:119.
115. Moszynski P. Global elimination of mother to child HIV transmission is now achievable, say agencies. *Bmj* 2010;341:c5152.
116. Hansen AB, Lohse N, Gerstoft J, et al. Cause-specific excess mortality in siblings of patients co-infected with HIV and hepatitis C virus. *PLoS One* 2007;2:e738.
117. Rasmussen LD, Omland LH, Pedersen C, et al. Risk of myocardial infarction in parents of HIV-infected Individuals: a population-based Cohort Study. *BMC Infect Dis* 2010;10:169.
118. Melchjorsen J, Risør RW, Sogaard OS, et al. Tenofovir selectively regulates production of inflammatory cytokines and shifts the IL-12 / IL-10 balance in human primary cells. *JAIDS* 2011;in press.
119. Mazick A, Howitz M, Rex S, et al. Hepatitis A outbreak among MSM linked to casual sex and gay saunas in Copenhagen, Denmark. *Euro Surveill* 2005;10:111-4.

Hospitalization for Pneumonia among Individuals With and Without HIV Infection, 1995–2007: A Danish Population-Based, Nationwide Cohort Study

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Background. Human immunodeficiency virus (HIV)-infected individuals with high CD4⁺ cell counts may have increased susceptibility to other infections. We compared incidence rates of pneumonia among individuals with and without HIV infection and explored risk factors for pneumonia in the HIV-infected population.

Methods. This was an observational cohort study conducted during 1995–2007. Each member of a Danish population-based nationwide cohort of HIV-infected individuals was matched with up to 99 control individuals from the general population. Data on age, mortality, emigration, and hospital discharge diagnoses from 1977 onward were obtained from nationwide administrative databases. Individuals without previous hospitalization for pneumonia were observed from the date of HIV diagnosis until the first hospitalization to treat pneumonia (excluding pneumonia attributable to *Pneumocystis jiroveci*). Risk factors were assessed by Poisson regression.

Results. The study included 3516 persons with HIV infection and 328,738 persons without HIV infection, which provided 23,677 person-years and 2,944,760 person-years of observation, respectively. Incidence rates of pneumonia in HIV-infected individuals decreased from 50.6 hospitalizations per 1000 person-years (95% confidence interval [CI], 42.9–59.7 hospitalizations per 1000 person-years) during 1995–1996 to 19.7 hospitalizations per 1000 person-years (95% CI, 16.2–23.8 hospitalizations per 1000 person-years) during 2005–2007. Compared with control individuals, incidence rate ratios were 34.6 (95% CI, 28.4–41.8) during 1995–1996; 6.3 (95% CI, 5.1–7.7) during 2005–2007; and 5.9 (95% CI, 4.2–7.6) during 2005–2007 for the subgroup with a CD4⁺ cell count >500 cells/ μ L. Injection drug use, low current CD4⁺ cell count, nadir CD4⁺ cell count, increasing age, and no current receipt of highly active antiretroviral therapy increased the risk of pneumonia.

Conclusions. The risk of pneumonia in persons with HIV infection has decreased substantially since the introduction of highly active antiretroviral therapy, but HIV infection remains a strong risk factor for the need for hospitalization to treat pneumonia, even in persons with high CD4⁺ cell counts.

HAART has markedly reduced the incidence of AIDS and death among HIV-infected persons [1–3], but morbidity and mortality remain high, compared with those for persons without HIV infection [1]. Contributing factors are low CD4⁺ cell counts attributable to non-adherence to treatment, drug resistance, delayed HIV

diagnosis [4], adverse effects of antiretroviral drugs [5], coexisting chronic infections (e.g., hepatitis B and/or C virus infection) [6, 7], or lifestyle-associated factors, such as injection drug use (IDU) and smoking [8]. Compared with the general population, persons with HIV infection have increased rates of non-AIDS-defining malignancies [9] and cardiovascular [10, 11], liver [12], and renal diseases [13], even among patients with full virological suppression and high CD4⁺ cell counts.

Bacterial pneumonia (first incidence or recurring) is a common hospital diagnosis among persons with HIV infection, including those receiving HAART [14, 15], and respiratory failure is the leading cause of intensive

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care unit admissions among HIV-infected patients [16]. A number of studies have reported increased rates of pneumonia among persons with HIV infection, compared with rates in the general population [17–20], but the impact of HAART and CD4⁺ cell count on risk of pneumonia in HIV-infected patients is still controversial.

We aimed to compare population-based incidence rates (IRs) of first-time hospitalizations for pneumonia among persons with and without HIV infection in Denmark, to estimate changes in IRs and IR ratios (IRRs) over time and according to age in the 2 populations, to estimate the influence of immunocompetence defined by CD4⁺ cell count, and to explore potential risk factors for non-AIDS-defining pneumonia among HIV-infected individuals.

PATIENTS AND METHODS

Study design and setting. We conducted a nationwide population-based cohort study among persons with and without HIV infection in Denmark during 1995–2007. The estimated prevalence of HIV infection in the adult population of Denmark, with a population of 5.4 million, is 0.07% [21]. Treatment for HIV infection occurs in only 8 specialized health care centers. The Danish health care system provides free, tax-supported medical care for all residents, including antiretroviral treatment of HIV infection.

Study Population

Inclusion criteria. We included persons who were ≥ 16 years of age and had no recorded hospitalization for pneumonia before study inclusion.

Persons with HIV infection. The Danish HIV Cohort Study is a prospective, open, nationwide, population-based cohort of all HIV-infected individuals seen in Danish HIV clinics since 1 January 1995. Study methods were described in detail elsewhere [21, 22]. The study is ongoing, with continual enrollment of both patients with new diagnoses and new immigrants to Denmark who have HIV infection. Use of the Danish 10-digit personal identification number prevents multiple registrations of the same patient and allows tracking of deaths and losses to follow-up because of emigration. Study data are updated annually, with information about antiretroviral treatment, development of opportunistic infections and other AIDS-defining illnesses, and laboratory values, including viral load and CD4⁺ cell count.

Population control individuals without HIV infection. The Danish Civil Registration System includes information about each individual's personal identification number, sex, date and place of birth, place of residence, citizenship status, and continually updated information on vital status [23]. For each person living in Denmark at the time of HIV diagnosis, we aimed to identify 99 population control individuals—

matched on the basis of sex, age (month and year of birth), and municipality—as the corresponding patient on the day the patient received the diagnosis of HIV infection. Because of shortage of eligible control individuals in some municipalities, we identified an average of 94.8 population control individuals per HIV-infected patient.

Identification of patients hospitalized with pneumonia.

The Danish National Hospital Registry contains information about all patients discharged from Danish hospitals since 1977. Its records for each hospitalization include personal identification number, hospital department involved, discharge diagnoses, and dates of admission and discharge. Diagnoses are coded by the treating physician according to the *International Classification of Diseases, 8th Revision* (ICD-8), through the end of 1993 and, likewise, to the 10th revision (ICD-10) thereafter. For persons with HIV infection and the general population control individuals, we used the National Hospital Registry to identify all hospital stays with a discharge diagnosis of pneumonia, through identification of ICD-8 codes 480.XX–486.XX, 073.XX, and 471.XX and ICD-10 codes J11.0 (influenza with pneumonia), J12.X–J18.X (pneumonia), A481.X, (ornithosis), or A709.X (legionellosis). Thus, both community-acquired and hospital-acquired incidences of pneumonia were included. Criteria for hospital admission of HIV-infected patients and the general population were unchanged during the study. The onset of pneumonia was defined as the date of hospital admission. Because HIV-infected patients have an increased risk of receiving a diagnosis of pneumonia while visiting HIV centers, outpatient visits were not included. Also, AIDS-defining *Pneumocystis jirovecii* pneumonia was not included as an episode of pneumonia. To limit the study to first-time hospitalizations to treat pneumonia, individuals with a recorded episode of pneumonia between 1977 and 1 January 1995 were excluded.

Validation of discharge diagnoses. For a sample of 77 HIV-infected patients with a discharge diagnosis of pneumonia, we validated pneumonia diagnoses identified in the National Hospital Registry by reviewing medical records. We confined the review to Aarhus County, because data quality in the National Hospital Registry is considered to be uniform throughout the country [24]. Pneumonia diagnoses recorded in the National Hospital Registry for patients without HIV infection were validated previously [25], and we used the same criteria for patients with HIV infection. A discharge diagnosis of pneumonia was considered to be confirmed if an infiltrate was documented in a chest radiograph and if ≥ 1 of the following clinical or laboratory findings was present: body temperature $\geq 37.5^{\circ}\text{C}$, cough, dyspnea, chest pain or rales coincident with the area of infiltrate, increased amount of sputum, purulent sputum, microorganism isolated from blood culture, leukocyte count $\geq 12 \times 10^9$ cells/L, or C-reactive protein concentration >100 mg per dL. We computed the percentage of episodes recorded in

Table 1. Characteristics of the HIV-infected and control populations at study entry.

Variable	HIV-infected patients (n = 3516)	Control individuals (n = 328,738)
Age at entry, median years (interquartile range)	37.0 (31.0–44.5)	36.6 (30.8–44.2)
Duration of follow-up, median years (interquartile range)	6.6 (3.1–10.8)	10.1 (5.9–12.3)
Lost to follow-up	141 (4.0)	12,833 (3.9)
Sex		
Female	797 (22.7)	76,008 (23.1)
Male	2719 (77.3)	252,730 (76.9)
Ethnicity		
White	2890 (82.2)	...
Black	425 (12.1)	...
Asian	111 (3.2)	...
Inuit	28 (0.8)	...
Other	60 (1.7)	...
Mode of or risk group for HIV exposure		
MSM	1682 (47.8)	...
Heterosexual intercourse	1265 (36.0)	...
Injection drug use	375 (10.7)	...
Other	69 (2.0)	...
Unknown	117 (3.3)	...
AIDS status at study entry		
Positive	463 (13.2)	...
Negative	3053 (86.8)	...
CD4 ⁺ cell count at study entry, ^a median cells/ μ L (interquartile range)	313 (100–460)	...

NOTE. Data are no. (%) of individuals, unless otherwise indicated. MSM, men having sex with men.

^a Date of measurement closest to date of entry and not >180 days apart.

the National Hospital Registry that fulfilled the aforementioned criteria.

Definitions. HAART was defined as either a 3-drug regimen that included a nonnucleoside reverse-transcriptase inhibitor, a protease inhibitor, and/or abacavir or a 2-drug regimen with a combination of a nonnucleoside reverse-transcriptase inhibitor and a boosted protease inhibitor.

CD4⁺ cell count and viral load were estimated by using the most recent measurement. Nadir CD4⁺ cell count was defined as the lowest CD4⁺ cell count ever previously measured for that patient.

Statistical Analyses

Variables. The following variables were used in our analyses: sex, ethnicity, most likely mode of HIV acquisition, AIDS status [26, 27], and the time-varying covariates (TVCs) of current CD4⁺ cell count, nadir CD4⁺ cell count (TVC), current viral load (TVC), receipt of HAART (yes vs. no; TVC), and age (15–39 years, 40–49 years, 50–59 years, and ≥ 60 years; TVC). Median and interquartile ranges were determined for age and CD4⁺ cell count. For other variables, frequencies and percentages were computed.

Time at risk. Subjects were observed from 1 January 1995 or the date of HIV diagnosis, whichever was later. Population

control individuals entered the study on the same day as their matched HIV-infected person. We computed time from the date of first observation until the date of first hospitalization for pneumonia, death, emigration, or 1 May 2007, whichever came first.

IR, IRR, and cumulative risk. IRs of pneumonia hospitalization were computed for HIV-infected patients and for control individuals in the 4 age strata and in 6 time periods (1995–1996, 1997–1998, 1999–2000, 2001–2002, 2003–2004, and 2005–1 May 2007). In an analysis restricted to HIV-infected patients with current CD4⁺ cell counts >500 and their respective uninfected control individuals, we compared IR in the last time period. We computed IRRs and 5- and 10-year cumulative risk of pneumonia after 1 January 1997.

Poisson regression analysis. We used a Poisson regression model to explore risk factors for first-time hospitalization for pneumonia for all individuals with HIV infection. Variables entered into the model were ethnicity (white vs. nonwhite), most likely mode of infection (IDU vs. non-IDU), sex, age, receipt of HAART (yes vs. no), and nadir and current CD4⁺ cell counts. Viral load values were log-transformed, and the effect of current viral load was examined in a separate model limited to HAART-naïve subjects. The effect of nadir CD4⁺ cell count among individuals receiving HAART was estimated for

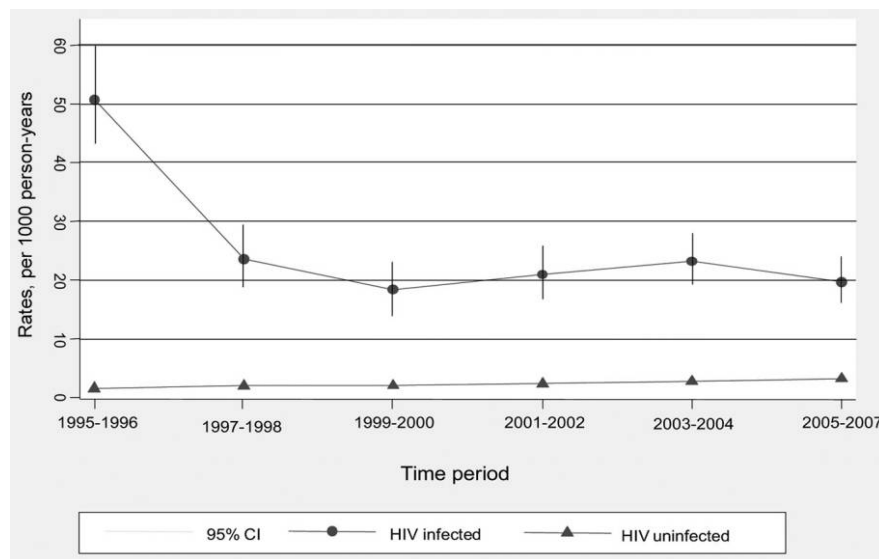


Figure 1. Incidence of first-time hospitalization to treat pneumonia in Denmark among individuals with and without HIV infection, 1995–2007

subjects with current CD4⁺ cell counts >300 cells/ μ L. The effect of HAART was estimated in 5 strata of CD4⁺ cell counts. In addition, we conducted a sensitivity analysis that excluded individuals with IDU as their most likely mode of HIV transmission. We did not include AIDS in these analyses, because nadir CD4⁺ cell count and AIDS are dependent covariates, and adjustment for AIDS could cancel out the effect of nadir CD4⁺ cell count. We used Stata software, version 9.2 (StataCorp) for statistical analyses. The study was approved by the Danish Data Protection Agency.

RESULTS

Study population. There were 3944 HIV-infected individuals and 373,856 matched population control individuals initially eligible for the study. We excluded 428 HIV-infected patients and 5996 members of the general population who had been hospitalized for pneumonia before study entry. Exclusion of the 428 HIV-infected patients entailed exclusion of an additional 39,121 matched control individuals from the general population. A total of 3516 HIV-infected patients and 328,738

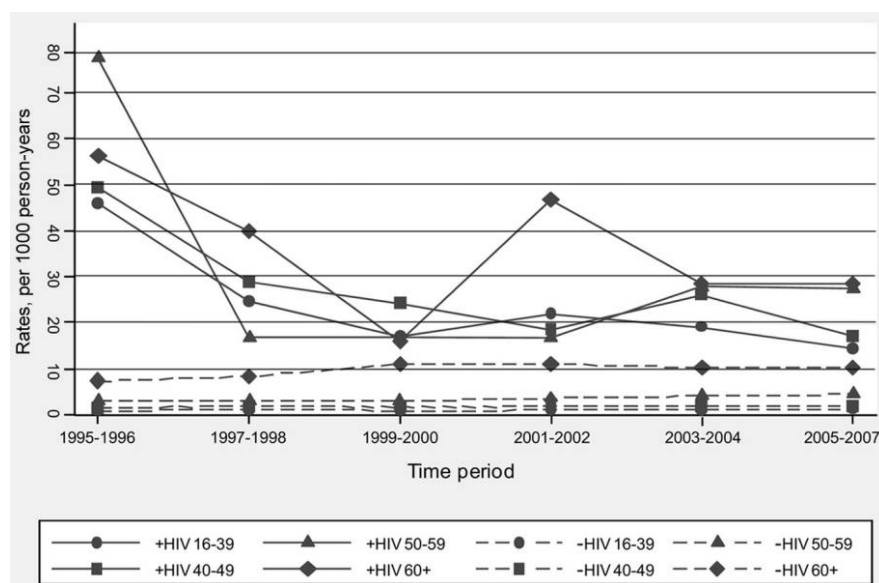


Figure 2. Incidence rates of first-time hospitalization to treat pneumonia by HIV infection status and age group, 1995–2007

Table 2. Incidence rate ratios for HIV-infected individuals by time and age.

Period	Incidence rate ratio (95% CI)				
	16–39 years	40–49 years	50–59 years	≥60 years	All ages
1995–1996	54.2 (40.5–72.0)	31.9 (21.8–45.8)	24.9 (15.1–39.5)	8.0 (2.1–21.7)	34.6 (28.4–41.8)
1997–1998	18.7 (13.0–26.3)	13.8 (8.8–20.8)	5.6 (2.2–11.8)	4.8 (1.3–12.5)	12.2 (9.5–15.5)
1999–2000	17.9 (11.9–26.3)	13.5 (8.6–20.5)	4.9 (2.2–9.4)	1.5 (0.2–5.3)	9.3 (7.2–12.0)
2001–2002	21.5 (15.1–30.0)	9.2 (5.8–14.1)	4.9 (2.6–8.5)	4.2 (1.9–8.1)	9.0 (7.1–11.2)
2003–2004	15.5 (10.5–22.3)	12.8 (9.0–17.8)	6.8 (4.2–10.3)	2.8 (1.2–5.5)	8.6 (7.0–10.5)
2005–2007 ^a	11.3 (7.3–16.8)	9.5 (6.6–13.4)	6.1 (4.1–9.0)	2.7 (1.5–4.6)	6.3 (5.1–7.7)

^a Through 1 May 2007.

population control individuals were included in the analysis, contributing 23,767 and 2,944,760 person-years of follow-up, respectively. Characteristics of study populations are shown in table 1. One hundred forty HIV-infected individuals (4.0%) and 12,833 control individuals (3.9%) were lost to follow-up, primarily because of emigration (116 [3.3%] and 10,096 [3.1%], respectively). A first-time hospitalization for pneumonia was identified for 582 persons with HIV infection and for 7042 persons without HIV infection.

Validation of pneumonia diagnoses. Seventy-three (95%) of 77 patients with HIV infection (95% CI, 87%–98%) who were registered as having pneumonia in the National Hospital Registry had their diagnoses confirmed by data in their medical records. In an earlier validation of pneumonia diagnoses among 100 patients without HIV infection, the diagnosis was confirmed for 90 (90%; 95% CI, 82%–95%) on the basis of their medical records [25].

IR, IRR, and cumulative risk. The overall IRs of hospitalization with pneumonia among HIV-infected persons decreased from 50.6 hospitalizations per 1000 person-years (95% CI, 42.9–59.7 hospitalizations per 1000 person-years) during 1995–1996 to 18.3 hospitalizations per 1000 person-years (95% CI, 14.4–23.2 hospitalizations per 1000 person-years) during 1999–2000 (figure 1) and remained stable, with a rate of 19.7 hospitalizations per 1000 person-years (95% CI, 16.2–23.8 hospitalizations per 1000 person-years) during 2005–2007. The IR among persons without HIV infection during 1995–2007 was 2.4 hospitalizations per 1000 person-years (95% CI, 2.3–2.4 hospitalizations per 1000 person-years) and increased from 1.5 hospitalizations per 1000 person-years (95% CI, 1.3–1.6 hospitalizations per 1000 person-years) during 1995–1996 to 3.1 hospitalizations per 1000 person-years (95% CI, 3.0–3.3 hospitalizations per 1000 person-years) during 2005–2007. Figure 2 shows that the decrease over time occurred in all age groups. The 5-year risk of pneumonia after 1 January 1997 was 11.0% (95% CI, 9.5%–12.7%) for HIV-infected patients and 1.0% (95% CI, 1.0%–1.0%) for control individuals. The corresponding 10-year risk was 21.3% (95% CI, 19.4%–23.4%) for HIV-

infected patients and 2.4% (95% CI, 2.3%–2.5%) for control individuals. The overall IRR for hospitalization to treat pneumonia among HIV-infected patients, compared with control individuals, decreased over time, from 34.6 (95% CI, 28.4–41.8) during 1995–1996 to 9.3 (95% CI, 7.2–12.0) during 1999–2000 and to 6.3 (95% CI, 5.1–7.7) during 2005–2007 (table 2). During 2005–2007, IRs of pneumonia for those with CD4⁺ cell counts >500 cells/ μ L and their corresponding control individuals were 16.1 hospitalizations per 1000 person-years (95% CI, 12.0–21.6 hospitalizations per 1000 person-years) and 2.8 hospitalizations per 1000 person-years (95% CI, 2.6–3.0 hospitalizations per 1000 person-years), respectively, resulting in an IRR of 5.9 hospitalizations per 1000 person-years (95% CI, 4.2–7.9 hospitalizations per 1000 person-years).

Risk factors for hospitalization with pneumonia among persons with HIV infection. Table 3 shows IRs of a first pneumonia hospitalization for persons with HIV infection, by potential risk factors for pneumonia, as well as crude and adjusted IRRs. Factors associated with increased risk of pneumonia were low current CD4⁺ cell count, low nadir CD4⁺ cell count, IDU, and male sex, whereas current receipt of HAART was protective. Among HAART-naïve individuals, high current viral load was associated with an increased risk of pneumonia in the adjusted estimates. A sensitivity analysis excluding individuals with IDU as their most likely mode of HIV transmission provided estimates very similar to those displayed in table 3. Among patients receiving HAART with current CD4⁺ cell counts >300 cells/ μ L, nadir CD4⁺ cell count was not associated with increased risk of pneumonia; adjusted IRRs were 1.1 (95% CI, 0.7–1.8), 1.1 (95% CI, 0.7–1.9), 0.8 (95% CI, 0.4–1.6), and 1.3 (95% CI, 0.8–2.3) for nadir CD4⁺ cell counts of 201–300, 101–200, 51–100, and \leq 50 cells/ μ L, respectively, compared with those whose CD4⁺ cell counts were never <300 cells/ μ L. Figure 3 shows the CD4⁺ cell count-independent protective effect of HAART on crude and adjusted IRRs for the 5 levels of current CD4⁺ cell counts, comparing HAART-naïve with HAART-experienced individuals.

Table 3. Incidence rates of a first hospitalization to treat pneumonia in persons with HIV infection, by potential risk factors for pneumonia and with crude and adjusted incidence rate ratios.

Variable	No. of cases of pneumonia	Incidence rate ^a (95% CI)	Incidence rate ratio (95% CI)	
			Crude	Adjusted ^b
Current CD4 ⁺ cell count ^c				
≥501	103	11.8 (9.7–14.3)	1 (Reference)	1 (Reference)
401–500	45	12.7 (9.7–17.0)	1.1 (0.7–1.5)	1.0 (0.7–1.4)
301–400	88	22.9 (18.6–28.3)	2.0 (1.5–2.6)	1.7 (1.3–2.3)
201–300	84	26.3 (21.2–32.6)	2.3 (1.7–3.0)	1.6 (1.2–2.2)
101–200	80	36.6 (29.4–45.5)	3.2 (2.4–4.3)	2.3 (1.6–3.3)
51–100	55	76.7 (59.9–100)	6.7 (4.8–9.2)	5.0 (3.3–7.6)
0–50	84	117 (94.2–144)	11.1 (8.3–14.8)	9.2 (6.0–14.3)
Nadir CD4 ⁺ cell count ^c				
≥301	75	12.5 (10.0–15.7)	1 (Reference)	1 (Reference)
201–300	96	19.8 (16.2–24.2)	1.6 (1.2–2.1)	1.7 (1.2–2.4)
101–200	128	24.2 (20.3–28.7)	1.9 (1.5–2.6)	2.0 (1.4–2.9)
51–100	82	29.2 (23.5–36.2)	2.3 (1.7–3.2)	1.7 (1.1–2.6)
0–50	158	39.9 (34.1–46.6)	4.1 (2.8–5.9)	1.7 (1.1–2.5)
Age, ^c years				
15–39	247	22.6 (19.9–25.5)	1 (Reference)	1 (Reference)
40–49	192	25.0 (21.7–28.8)	1.1 (0.9–1.3)	1.1 (0.9–1.4)
50–59	102	26.3 (21.7–32.0)	1.2 (0.9–1.5)	1.5 (1.2–1.9)
≥60	41	32.3 (23.8–43.9)	1.4 (1.0–2.0)	2.1 (1.5–3.0)
Ethnicity				
White	498	25.3 (23.1–27.6)	1 (Reference)	1 (Reference)
Nonwhite	83	20.5 (16.5–25.4)	0.8 (0.6–1.0)	1.1 (0.9–1.4)
Injection drug use ^d				
No	453	20.9 (19.0–23.0)	1 (Reference)	1 (Reference)
Yes	129	60.5 (50.9–71.9)	2.9 (2.4–3.5)	2.6 (2.1–3.3)
Receipt of HAART ^c				
Naive	321	33.6 (29.7–37.9)	1 (Reference)	1 (Reference)
Experienced	261	20.0 (18.0–22.4)	0.6 (0.5–0.7)	0.7 (0.5–0.8)
Sex				
Female	116	20.5 (17.1–24.6)	1 (Reference)	1 (Reference)
Male	466	25.7 (23.5–28.2)	1.3 (1.0–1.5)	1.3 (1.0–1.6)
Viral load, ^{c,e} copies/mL				
<10 ³	12	14.3 (8.1–25.2)	1 (Reference)	1 (Reference)
10 ³ –10 ⁵	64	18.8 (14.7–24.0)	1.4 (1.1–1.7)	1.2 (0.7–2.3)
>10 ⁵	27	58.1 (39.8–84.7)	3.8 (2.9–4.9)	2.0 (1.0–4.1)

NOTE. Missing values are not shown.

^a No. of hospitalizations per 1000 person-years.

^b Adjusted for all variables in the table except viral load.

^c Time-varying covariate.

^d The most likely mode of HIV acquisition.

^e Includes HAART-naive individuals only.

DISCUSSION

To our knowledge, this population-based study is the first to explore on a national level the relative risk of pneumonia among HIV-infected patients. We found that the risk of first-time hospitalization for pneumonia remained 6-fold higher for HIV-infected individuals than for the general population until 2007, despite a decrease in incidence of pneumonia among HIV-infected persons after the introduction of HAART. The increased risk was observed even in persons with nearly normal CD4⁺ cell counts. The strongest risk factors for pneumonia

were low current CD4⁺ cell count, IDU as the mode of HIV transmission, and, among HAART-naive patients, a high current viral load. HAART was associated with a decreased risk of pneumonia, but the protective effect of HAART was observed only for patients with CD4⁺ counts ≤200 cells/μL.

The strengths of our study include the use of population-based, nationwide cohorts; access to complete hospitalization data; minor loss to follow-up; and availability of electronically collected longitudinal data on viral load and CD4⁺ cell counts. This is one of the largest studies of the incidence of pneumonia

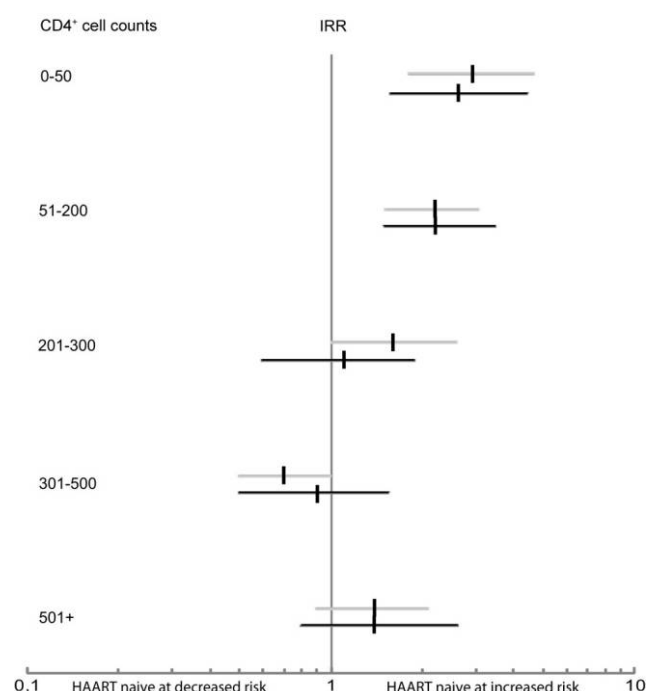


Figure 3. Relationship between use of HAART and risk of pneumonia, in comparison of HAART-naive and HAART-experienced individuals, by CD4⁺ cell count strata. Point estimates and 95% CIs are indicated by vertical and horizontal bars, respectively. Gray bars indicate crude estimates. Black bars indicate estimates adjusted for nadir CD4⁺ cell count, age, injection drug use as mode of HIV transmission, sex, and ethnicity. IRR, incidence rate ratio.

among HIV-infected individuals, yielding estimates with high statistical precision. Because we considered only the first hospitalization for pneumonia, our estimates were not biased by multiple pneumonia episodes occurring in highly susceptible individuals.

Our study also had limitations. Data on specific pathogens and pneumococcal vaccination status were not available. Therefore, we do not know the percentage of pneumonia cases caused by bacteria and whether this percentage differed between persons with and without HIV infection. Previous studies have found identifiable bacterial pathogens in 24%–38% of HIV-infected patients with pneumonia [17, 28], which is comparable to findings in persons without HIV infection [29]. In Denmark, the 23-valent polysaccharide vaccine is not routinely administered to HIV-infected individuals or to elderly persons (age, ≥ 65 years). Recruitment for a recent Danish trial showed that <10% of HIV-infected persons had been vaccinated within the previous 5 years (O.S.S., unpublished data). We therefore assume that pneumococcal vaccination had very little influence on our results.

Physicians may have a lower threshold for hospital admission of HIV-infected patients presenting with signs and symptoms of pneumonia than for a person without HIV infection. In that

case, pneumonia would be diagnosed in hospitals more frequently among HIV-infected persons than among the general population, leading to an overestimation of the IRR. However, this information bias is unlikely to be the sole cause of the higher risks observed. First, validation of diagnosis of pneumonia among patients with and without HIV infection was found to be comparable. Second, the general improvement in the immunocompetence of the HIV-infected population during the study period has made their hospitalization pattern approach what is seen in control individuals (N.O., unpublished data).

Finally, we did not have data on smoking, a well-known risk factor for pneumonia that may be more common among HIV-infected individuals, particularly among injection drug users. A recent cohort study found that 40% of HIV-infected individuals were smokers [30], compared with 27% of the Danish population as a whole in 2006 [31]. This difference is small and could not have accounted for our findings.

Our data extend previous research. Grau et al. [18] reported a 3-fold decrease in the incidence of invasive pneumococcal disease in the HAART era (1997–2002), compared with the pre-HAART era (1986–1996), that was similar to the decrease we observed in incidence of pneumonia between 1995–1996 and 1999–2000. Although our overall IRR for pneumonia did decrease between 1999–2000 and 2005–2007, the IR of pneumonia among persons with HIV infection remained stable for each age stratum during the same period (figure 2). The 12-fold higher incidence among HIV-infected versus HIV-uninfected individuals that was determined in the HIV Epidemiologic Research study by Kohli et al. [17] of primarily female injection drug users was based on incidence data from 1993–2000; therefore, it did not fully capture the decrease in IRRs over time that we observed between the pre-HAART and the late-HAART era. Many studies based on data from the early-HAART and pre-HAART era would, therefore, produce higher IRs than we observed after 2000 [17–20]. Availability of less toxic antiretroviral drugs in recent years has increased drug adherence, leading to the improved immune status of many HIV-infected individuals [32]. IRs for pneumonia increased over time in the background population; this is in line with results from a recent study [25]. Most risk factors identified in our study corroborated the findings of other studies [17–20, 28]. However, the increased risk of pneumonia in individuals with a current CD4⁺ cell count as high as 301–400 cells/ μ L supports recommendations for HAART initiation for patients with higher CD4⁺ cell counts [33].

The increased incidence of pneumonia among persons with HIV infection, even among those with nearly normal CD4⁺ cell counts, indicates that HIV infection increases the susceptibility to pneumonia beyond what is indicated by CD4⁺ cell counts. Possible mechanisms could be loss of immunological and ep-

ithelial integrity [34, 35], fibrosis of lymphatic tissue [36], and loss of IL-17–expressing CD4⁺ T lymphocytes from the gastrointestinal tract, leading to microbial translocation and generalized immune activation [34, 37], as shown in patients who had effective treatment despite high CD4⁺ cell counts. In animal studies, HAART seems to reduce microbial translocation [34], which may explain why HAART was associated with a decreased risk of pneumonia in treatment-naïve and treatment-experienced individuals in the same low CD4⁺ cell strata. In addition, some reports have shown that HIV-infected persons in the HAART era may have a high prevalence of other chronic conditions (e.g., heart disease and cirrhosis), which may be additional risk factors for pneumonia [10–12].

In conclusion, introduction of HAART has substantially decreased the risk of pneumonia in HIV-infected patients. Although a high CD4⁺ count protects against pneumonia, persons with HIV infection and high CD4⁺ cell counts still have increased risk of the need for hospitalization to treat pneumonia compared with persons without HIV infection.

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References

- Lohse N, Hansen AB, Pedersen G, et al. Survival of persons with and without HIV infection in Denmark, 1995–2005. *Ann Intern Med* **2007**; 146:87–95.
- Palella FJ Jr, Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr* **2006**; 43:27–34.
- Hogg RS, Heath KV, Yip B, et al. Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. *JAMA* **1998**; 279:450–4.
- Lohse N, Jorgensen LB, Kronborg G, et al. Genotypic drug resistance and long-term mortality in patients with triple-class antiretroviral drug failure. *Antivir Ther* **2007**; 12:909–17.
- Safrin S, Grunfeld C. Fat distribution and metabolic changes in patients with HIV infection. *AIDS* **1999**; 13:2493–505.
- Weis N, Lindhardt BO, Kronborg G, et al. Impact of hepatitis C virus coinfection on response to highly active antiretroviral therapy and outcome in HIV-infected individuals: a nationwide cohort study. *Clin Infect Dis* **2006**; 42:1481–7.
- Hansen AB, Lohse N, Gerstoft J, et al. Cause-specific excess mortality in siblings of patients co-infected with HIV and hepatitis C virus. *PLoS ONE* **2007**; 2:e738.
- Saves M, Chene G, Ducimetiere P, et al. Risk factors for coronary heart disease in patients treated for human immunodeficiency virus infection compared with the general population. *Clin Infect Dis* **2003**; 37:292–8.
- Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* **2007**; 370:59–67.
- DAD Study Group, Friis-Moller N, Reiss P, et al. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med* **2007**; 356:1723–35.
- Obel N, Thomsen HF, Kronborg G, et al. Ischemic heart disease in HIV-infected and HIV-uninfected individuals: a population-based cohort study. *Clin Infect Dis* **2007**; 44:1625–31.
- Thio CL, Seaberg EC, Skolasky R Jr, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the multicenter cohort study (MACS). *Lancet* **2002**; 360:1921–6.
- Kimmel PL, Barisoni L, Kopp JB. Pathogenesis and treatment of HIV-associated renal diseases: lessons from clinical and animal studies, molecular pathologic correlations, and genetic investigations. *Ann Intern Med* **2003**; 139:214–26.
- Betz ME, Gebo KA, Barber E, et al. Patterns of diagnoses in hospital admissions in a multistate cohort of HIV-positive adults in 2001. *Med Care* **2005**; 43(Suppl 9):III3–14.
- Floris-Moore M, Lo Y, Klein RS, et al. Gender and hospitalization patterns among HIV-infected drug users before and after the availability of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* **2003**; 34:331–7.
- Morris A, Creasman J, Turner J, Luce JM, Wachter RM, Huang L. Intensive care of human immunodeficiency virus-infected patients during the era of highly active antiretroviral therapy. *Am J Respir Crit Care Med* **2002**; 166:262–7.
- Kohli R, Lo Y, Homel P, et al. Bacterial pneumonia, HIV therapy, and disease progression among HIV-infected women in the HIV Epidemiologic Research (HER) study. *Clin Infect Dis* **2006**; 43:90–8.
- Grau I, Pallares R, Tubau F, et al. Epidemiologic changes in bacteremic pneumococcal disease in patients with human immunodeficiency virus in the era of highly active antiretroviral therapy. *Arch Intern Med* **2005**; 165:1533–40.
- Barry PM, Zetola N, Keruly JC, Moore RD, Gebo KA, Lucas GM. Invasive pneumococcal disease in a cohort of HIV-infected adults: incidence and risk factors, 1990–2003. *AIDS* **2006**; 20:437–44.
- Tumbarello M, Tacconelli E, de Gaetano Donati K, Cauda R. HIV-associated bacterial pneumonia in the era of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr Hum Retrovirol* **1999**; 20:208–9.
- Lohse N, Hansen AB, Jensen-Fangel S, et al. Demographics of HIV-1 infection in Denmark: results from the Danish HIV Cohort Study. *Scand J Infect Dis* **2005**; 37:338–43.
- Jensen-Fangel S, Pedersen C, Larsen CS, Tauris P, Moller A, Obel N. Changing demographics in an HIV-infected population: results from an observational cohort study in western Denmark. *Scand J Infect Dis* **2001**; 33:765–70.
- Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish civil registration system: a cohort of eight million persons. *Dan Med Bull* **2006**; 53:441–9.
- Nickelsen TN. Data validity and coverage in the Danish national health registry: a literature review. *Ugeskr Laeger* **2001**; 164:33–7.
- Thomsen RW, Riis A, Norgaard M, et al. Rising incidence and persistently high mortality of hospitalized pneumonia: a 10-year population-based study in Denmark. *J Intern Med* **2006**; 259:410–7.
- Centers for Disease Control and Prevention. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep* **1992**; 41(RR-17):1–19.
- Ancelle-Park R. Expanded European AIDS case definition. *Lancet* **1993**; 341:441.
- Hirschtick RE, Glassroth J, Jordan MC, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus: pulmonary

- complications of HIV infection study group. *N Engl J Med* **1995**;333: 845–51.
29. Fine MJ, Stone RA, Singer DE, et al. Processes and outcomes of care for patients with community-acquired pneumonia: results from the pneumonia Patient Outcomes Research Team (PORT) cohort study. *Arch Intern Med* **1999**; 159:970–80.
30. Carr A, Grund B, Neuhaus J, et al. Asymptomatic myocardial ischaemia in HIV-infected adults. *AIDS* **2008**; 22:257–67.
31. Danish National Board of Health. Tobaksskaderaadet. **2008**. Available at: http://www.sst.dk/Forebyggelse/Alkohol_narkotika_og_tobak/Tobak/Tal_og_undersogelser/Danskernes_rygevaner/Udvikling_2006.aspx?lang=da. Accessed 1 April 2008.
32. Walmsley S. Protease inhibitor-based regimens for HIV therapy: safety and efficacy. *J Acquir Immune Defic Syndr* **2007**; 45(Suppl 1):S5–13.
33. Hammer SM, Saag MS, Schechter M, et al. Treatment for adult HIV infection: 2006 recommendations of the international AIDS society—USA panel. *Top HIV Med* **2006**; 14:827–43.
34. Brenchley JM, Price DA, Schacker TW, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nat Med* **2006**; 12:1365–71.
35. Mehandru S, Poles MA, Tenner-Racz K, et al. Lack of mucosal immune reconstitution during prolonged treatment of acute and early HIV-1 infection. *PLoS Med* **2006**; 3:e484.
36. Schacker TW, Brenchley JM, Beilman GJ, et al. Lymphatic tissue fibrosis is associated with reduced numbers of naive CD4⁺ T cells in human immunodeficiency virus type 1 infection. *Clin Vaccine Immunol* **2006**; 13:556–60.
37. Raffatellu M, Santos RL, Verhoeven DE, et al. Simian immunodeficiency virus–induced mucosal interleukin-17 deficiency promotes *Salmonella* dissemination from the gut. *Nat Med* **2008**; 14:421–8.

Mortality after Hospitalization for Pneumonia among Individuals with HIV, 1995–2008: A Danish Cohort Study

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Abstract

Background: HIV-infected persons are at increased risk of pneumonia, even with highly active antiretroviral treatment (HAART). We examined the impact of pneumonia on mortality and identified prognostic factors for death among HIV-infected.

Methodology/Principal Findings: In a nationwide, population-based cohort of individuals with HIV, we included persons hospitalized with pneumonia from the Danish National Hospital Registry and obtained mortality data from the Danish Civil Registration System. Comparing individuals with and without pneumonia, we used Poisson regression to estimate relative mortality and logistic regression to examine prognostic factors for death following pneumonia. From January 1, 1995, to July 1, 2008, we observed 699 episodes of first hospitalization for pneumonia among 4,352 HIV patients. Ninety-day mortality after pneumonia decreased from 22.4% (95% confidence interval [CI]: 16.5%–28.9%) in 1995–1996 to 8.4% (95% CI: 6.1%–11.6%) in 2000–2008. Mortality remained elevated for more than a year after hospitalization for pneumonia: adjusted mortality rate ratio 5.38 (95% CI: 4.27–6.78), 1.80 (95% CI: 1.36–2.37), and 1.62 (95% CI: 1.32–2.00) for days 0–90, 91–365, and 366+, respectively. The following variables predicted mortality within 90 days following hospitalization for pneumonia (adjusted Odds Ratios): male sex (3.77, 95% CI: 1.37–10.4), Charlson Comorbidity Index score ≥ 2 (3.86, 95% CI: 2.19–6.78); no current HAART (3.58, 95% CI: 1.83–6.99); history of AIDS (2.46, 95% CI: 1.40–4.32); age per 10 year increase (1.43, 95% CI: 1.11–1.85); and CD4+ cell count ≤ 200 (2.52, 95% CI: 1.37–4.65).

Conclusions/Significance: The first hospitalization for pneumonia among HIV-infected individuals was associated with elevated risk of death up to more than a year later. Use of HAART decreased the risk, independent of current CD4+ cell count. Prognosis following pneumonia improved over calendar time.

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Introduction

Early in the HIV epidemic it was recognized that morbidity and mortality due to pneumonia were higher in HIV-infected persons than in the general population [1]. In 1993 the United States Centers for Disease Control and Prevention categorized two or more episodes of bacterial pneumonia as an AIDS-defining event [2]. The introduction of highly active antiretroviral therapy (HAART) markedly reduced the incidence of AIDS and death among HIV-infected persons [3,4,5], and improved immune function also led to fewer pneumonia-related hospitalizations [6,7]. However, more than a decade after the widespread introduction of HAART in high-income countries, the risk of pneumonia among HIV-infected persons remains high compared to persons without HIV [7]. A better understanding of modifiable prognostic factors for death after pneumonia could

potentially reduce mortality from this illness. In this cohort study we estimated the impact of a first hospitalization for pneumonia on mortality among Danish HIV patients, examined changes over calendar time in mortality following hospitalization for pneumonia, and identified prognostic factors for death following pneumonia.

Methods

Study design and setting

We conducted a nationwide, population-based cohort study among HIV-infected persons in Denmark from 1995 to 2008. Treatment for HIV infection in Denmark is restricted to 8 specialized centers. The Danish health care system provides free, tax-supported medical care for all residents, including antiretroviral treatment of HIV.

The Danish HIV Cohort Study (DHCS)

The DHCS has established a prospective, dynamic, nationwide, population-based cohort of all HIV-infected individuals seen in Danish HIV clinics since 1 January 1995. DHCS has been described in detail elsewhere [8,9]. The study is ongoing, with continuous enrolment of both newly diagnosed patients and immigrants with HIV infection. Study data are updated annually with information on antiretroviral treatment, development of opportunistic infections and other AIDS-defining illnesses, and laboratory data including plasma HIV RNA (viral load (VL)) and CD4⁺ cell count.

Danish Civil Registration System (CRS)

CRS is a national registry of all Danish residents, which contains information on date of birth, sex, date of migration, and date of death. A 10-digit personal registration number (CPR number), assigned at birth, uniquely identifies each person since 1968. The CRS is updated within a week of a person's birth, death, or emigration. Use of the CPR number enables Danish HIV clinics to avoid multiple registrations of the same patient and allows tracking of deaths and persons lost to follow-up due to emigration.

The Danish National Hospital Registry (NHR)

NHR contains information on all patients discharged from Danish hospitals since 1977. Records for each hospitalization include CPR number, hospital department, inpatient and outpatient discharge diagnoses, and dates of admission and discharge. Diagnoses are coded by the treating physician according to the International Classification of Diseases, 8th revision (ICD-8) until the end of 1993 and 10th revision (ICD-10) thereafter.

Identification of pneumonia

We identified the first hospitalization for pneumonia following HIV diagnosis. We used the NHR to identify all hospital stays with a discharge diagnosis of pneumonia using ICD-8 codes 471.x (influenza with pneumonia), 480.x-486.x (pneumonia), 073.x (ornithosis) and ICD-10 codes J11.0 (influenza with pneumonia), J12.x-J18.x (pneumonia), A481.x, (ornithosis), or A709.x (legionellosis). Thus, both community-acquired and hospital-acquired pneumonias were included. The pneumonia diagnoses recorded in the NHR were validated in a previous report [7]. Pneumonia onset was defined as the date of hospital admission. Since we have not validated pneumonia diagnoses in emergency room and outpatient settings, outpatient diagnoses were not included. AIDS-defining *Pneumocystis jiroveci* pneumonia was not counted as an episode of pneumonia.

Study population

Our study population consisted of persons in DHCS who were at least 16 years old on the date of HIV diagnosis and who had no recorded hospitalization for pneumonia before entering DHCS. Study subjects were followed from their registration in DHCS to death, loss to follow-up or 1 July 2008, whichever came first.

Definitions

HAART was defined as either a 3-drug regimen that included a non-nucleoside reverse transcriptase inhibitor, a protease inhibitor, and/or abacavir; or a 2-drug regimen with a combination of a non-nucleoside reverse transcriptase inhibitor and a boosted protease inhibitor.

CD4⁺ cell counts and viral load (VL) were estimated between measurements by carrying forward the value from the most recent

measurement. **Nadir CD4⁺ cell count** was defined as the lowest CD4⁺ cell count ever measured for a given patient.

Comorbidity was assessed with the Charlson Comorbidity Index (CCI). The index, which includes 19 major disease categories, has been adapted and validated for use with hospital discharge data in ICD databases for predicting short- and long-term mortality [10]. A CCI score was computed for each patient based on all available foregoing NHR discharge diagnoses. A previous AIDS diagnosis (conferring 6 CCI points) was not included in our computations [11].

Hepatitis C co-infection was defined as patients having at least 1 positive result on a hepatitis C virus (HCV)-antibody test or a positive result on HCV RNA test.

The endpoint, defined a priori, was all-cause mortality following the hospital admission date for pneumonia. Causes of death, extracted from patient files and available in the DHCS database, were divided into HIV-related causes (AIDS-defining illnesses and bacterial infections, corresponding to ICD-10 codes A02, A07.2-07.3, A15-19, A31, A81.2, B00, B20-25, B37-39, B45, B58, C46, C53, C83.4, C83.9, F02.4, and J13-17 [pneumonia]), serious non-AIDS causes (cardiovascular disease [i.e. myocardial infarction or stroke], end stage renal and liver disease, COPD, and non-AIDS-defining malignancies), unnatural causes (i.e. drug overdose, suicide, accident) and other/unknown causes.

Statistical analyses

We first computed 30-day and 90-day cumulative mortality following the first hospitalization for pneumonia and constructed Kaplan-Meier survival curves, stratified into 3 calendar periods: 1995-1996 ("pre-HAART era"), 1997-1999 ("early HAART era"), and 2000-2008 ("late HAART era").

We then assessed the effect of a first hospitalization for pneumonia on mortality. We compared the mortality rate in persons who had no previous history of pneumonia (reference group) with that of persons with a first hospitalization for pneumonia within the last 0-90 days, within the last 91-365 days, and more than 365 days ago. Poisson regression analysis was used to adjust for potential confounders. The following time-dependent variables were forced into the model based on their presumed association with pneumonia and/or effect on mortality: CCI score (0-1/2+), age (10-year intervals), and CD4⁺ cell count (continuous). Other variables were examined and included in the final model if they changed the effect measure by 10% or more. Constant variables were sex (male/female), hepatitis C coinfection (yes/no), injection drug use (IDU) as presumed mode of HIV infection (yes/no), and race (Caucasian/non-Caucasian). Time-dependent variables were history of AIDS (yes/no), current HAART (yes/no), years since entering the DHCS, and calendar time period (1995-96 vs. 1997-2008). Causes of death were tabulated for all four time periods.

Finally, we used logistic regression to identify prognostic factors for 30-day and 90-day mortality following hospitalization for pneumonia. In the unadjusted analyses we included all the variables listed above as of the time of admission, as well as log-transformed HIV RNA (continuous). In the adjusted analyses of 30-day and 90-day mortality we included all variables from the unadjusted analyses in the models, except: nadir CD4⁺ cell count because this variable and history of AIDS are interdependent (adjustment for nadir CD4⁺ cell count thus could cancel out the effect of previous AIDS); IDU as mode of HIV exposure which is interdependent with hepatitis C status; and HIV RNA which is interdependent with use of HAART.

We used Stata software, version 9.2 (StataCorp, College Station, TX, USA) for statistical analyses. The study was approved by the Danish Data Protection Agency. In Denmark, a national board

(The Danish Data protection Agency) approved the studies. Informed consent was waived. Informed consent was not required by Danish law in order to conduct cohort studies.

Results

DHCS study population

Between 1 January 1995 and 1 July 2008, 699 episodes of an initial hospitalization for pneumonia were observed among 4,352 persons who were at least 16 years old and had no recorded hospitalization for pneumonia before entering the DHCS cohort. Characteristics of persons in our study population at the time of the initial hospitalization for pneumonia are shown in Table 1. Less than half (43.3%) received HAART and the median CD4+ cell count was 281 cells/ μ l.

Impact of hospitalization for pneumonia on survival among HIV patients

Overall 30-day risk of death after first hospitalization for pneumonia was 6.4% (95% CI: 4.8%–8.5%) (see Figure 1). It was 7.9% (95% CI: 4.6%–13.5%) in 1995–1996, 7.6% (95% CI: 4.1%–13.6%) in 1997–1999, and 5.5% (95% CI: 3.7%–8.2%) in 2000–2008. Overall 90-day risk of death was 12.0% (95% CI: 9.8%–14.7%), decreasing from 22.4% (95% CI: 16.5%–28.9%) in 1995–1996 to 11.4% (95% CI: 7.0%–18.1%) in 1997–1999, and to 8.4% (95% CI: 6.1%–11.6%) in 2000–2008.

The effect of first-time hospitalization for pneumonia on mortality among all HIV-infected persons is shown in Table 2. Adjusting for use of HAART, history of AIDS, years since entering the DHCS, CCI score, age, and current CD4+ cell count, the relative mortality during the first 90 days after an initial hospitalization for pneumonia, compared to those with no previous hospitalization for this indication, was 5.38 (adjusted mortality rate ratio [MRR_{adj}], 95% CI: 4.27–6.78). Mortality was also elevated for days 91–365 (MRR_{adj} = 1.80, 95% CI: 1.36–2.37) and days 366+ (MRR_{adj} = 1.62, 95% CI: 1.32–2.00). Causes of death for persons in all four time strata are presented in Table 3. Among those who died within days 0–90, days 91–365, and after 365 days, 61.9%, 53.7%, and 28.8%, respectively, had an HIV-related cause of death.

Prognostic factors for short-term mortality following hospitalization for pneumonia

In the adjusted logistic regression analysis, the following variables were associated with increased 30-day mortality after a first hospitalization for pneumonia (Table 4): CCI score ≥ 2 (OR_{adj} = 4.07, 95% CI: 2.03–8.17), male sex (OR_{adj} = 3.86, 95% CI: 1.05–14.2), no current HAART (OR_{adj} = 3.19, 95% CI: 1.42–7.16), history of AIDS (OR_{adj} = 2.78, 95% CI: 1.34–5.78), latest CD4+ cell count ≤ 200 cells/ μ l (OR_{adj} = 2.72, 95% CI: 1.28–5.78) and age (OR_{adj} = 1.53 per 10 year increase, 95% CI: 1.11–2.12).

Variables associated with increased 90-day mortality were (Table 5): CCI score ≥ 2 (OR_{adj} = 3.86, 95% CI: 2.19–6.78), male sex (OR_{adj} = 3.77, 95% CI: 1.37–10.4), no current HAART (OR_{adj} = 3.56, 95% CI: 1.83–6.99), previous AIDS (OR_{adj} = 2.46, 95% CI: 1.40–4.32), CD4+ cell count ≤ 200 (OR_{adj} = 2.52, 95% CI: 1.37–4.65) and age (OR_{adj} = 1.43 per 10 year increase, 95% CI: 1.11–1.85). Among patients on HAART neither the duration of HAART use or HIV RNA (<50 vs. ≥ 50 copies/ml) were protective (data not shown).

Discussion

This study found that short-term mortality after a first hospitalization for pneumonia among HIV-infected individuals decreased

Table 1. Baseline characteristics of HIV-infected individuals at time of first admission for pneumonia.

Variable	Numbers (N = 699)
Median age, years (interquartile range)	42.2 (35.2–50.1)
Sex, n (%)	
Female	146 (20.9)
Male	553 (79.1)
Race, n (%)	
Caucasian	588 (84.2)
Black	73 (10.5)
Asian	12 (1.7)
Inuit	10 (1.4)
Other	15 (2.2)
Mode of HIV exposure, n (%)	
MSM	299 (42.8)
Heterosexual	204 (29.2)
IV drug use	147 (21.0)
Other	28 (4.0)
Unknown	21 (3.0)
Hepatitis C co-infected, n (%)	
Yes	191 (27.3)
No	508 (72.7)
History of AIDS, n (%)	
Yes	236 (33.8)
No	463 (66.2)
Years since entering DHCS ^a , (interquartile range)	3.30 (1.18–7.01)
On HAART, n (%)	
Yes	403 (57.7)
No	296 (43.3)
Median current CD4+ cell count ^b , cells/ μ l (interquartile range)	281 (117–462)
Median days since last CD4+ cell count measurement, (interquartile range)	47 (17–87)
Nadir CD4+ cell count, cells/ μ l (interquartile range)	139 (48–240)
Median HIV RNA ^a , log(copies/ml), (interquartile range)	
On HAART	1.6 (1.3–4.1)
HAART-naïve	4.6 (4.0–5.0)
Median days since last HIV RNA measurement, (interquartile range)	48 (19–85)
Charlson Comorbidity Index score, n (%)	
0–1	532 (76.1)
≥ 2	167 (23.9)

^aDHCS: Danish HIV Cohort Study.

^bLast measurement before date of pneumonia.

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from the pre-HAART to the late-HAART era. Despite this decrease over time, an episode of hospitalization due to pneumonia remains associated with an increased mortality among HIV patients. Prognostic factors were male sex, age, pre-existing comorbidity, low CD4 cell count, older age, and absence of HAART treatment. Several studies have shown that persons on HAART have a reduced

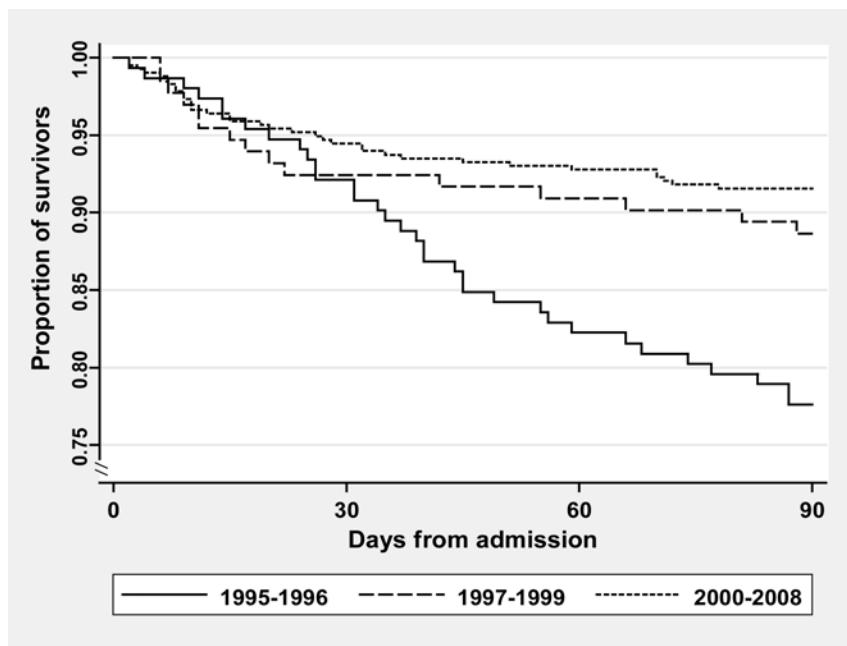


Figure 1. Mortality after first hospitalization for pneumonia among persons with HIV by time period.

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risk of pneumonia compared to those not on HAART [6,7,12]. However, our study is the first to show that HAART use also affects prognosis in the presence of a pneumonia-related hospitalization.

The strengths of our study include use of a population-based, nationwide cohort with nearly complete inclusion and minor loss to follow-up; access to complete hospitalization data and vital

statistics; and availability of electronically collected longitudinal data on viral load and CD4+ cell counts. The quality of the data minimized selection and information biases. Because we considered only the first hospitalization for pneumonia, our estimates were not biased by multiple pneumonia episodes occurring in highly susceptible individuals.

Table 2. Short- and long-term impact of pneumonia on mortality among all HIV-infected individuals.

	No of deaths	Follow-up ^a	MR ^b	Crude MRR ratio	Adjusted ^c MRR
At any time after first hospitalization for pneumonia	263	3,131	0.23 (0.20–0.26)	3.56 (3.09–4.10)	2.79 (2.40–3.26)
Day 0–90 after admission	84	159	1.44 (1.17–1.79)	20.5 (16.3–25.7)	5.38 (4.27–6.78)
Day 91–365 after admission	54	420	0.35 (0.27–0.46)	4.98 (3.77–6.57)	1.80 (1.36–2.37)
Day 366+ after admission	125	2,552	0.13 (0.11–0.16)	1.90 (1.57–2.30)	1.62 (1.32–2.00)
No previous pneumonia	691	26,775	0.07 (0.07–0.08)	1 (ref)	1 (ref)

^aIn years.

^bPer 1000 days.

^cAdjusted for use of HAART, history of AIDS, years since entering the DHCS, Charlson Comorbidity Index score, age, and current CD4+ cell count.

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Table 3. Causes of death among HIV patients with and without pneumonia.

	HIV-related ^a	Serious non-AIDS conditions ^b	Unnatural ^c	Other/unknown	No of deaths
Day 0–90 after pneumonia, n (%)	52 (61.9)	15 (17.9)	2 (2.4)	15 (17.9)	84 (100)
Day 91–365 after pneumonia, n (%)	29 (53.7)	7 (13.0)	3 (5.6)	15 (27.8)	54 (100)
Day 366+ after pneumonia, n (%)	36 (28.8)	36 (28.8)	5 (4.0)	48 (38.4)	125 (100)
No previous pneumonia, n (%)	296 (42.8)	145 (21.0)	42 (6.1)	208 (30.1)	691 (100)

^aAIDS-defining illnesses and bacterial infections.

^bCardiovascular disease [i.e. myocardial infarction or stroke], end stage renal and liver disease, COPD, and non-AIDS-defining malignancies.

^cI.e. drug overdose, suicide, and accident.

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Table 4. Prognostics factors associated with 30-day mortality after first hospitalization for pneumonia among HIV-infected individuals.

		30 day mortality							
		n	Deaths	Mortality (%)	OR (95% CI)	p	OR _{adj} (95% CI) ^a	Coefficient (SE)	p
Intercept								−7.29 (1.11)	
Age (per 10 year increase)		699	45	6.4	1.47 (1.13–1.90)	0.004	1.53 (1.11–2.12)	0.43 (0.17)	0.010
CD4+ cell count ^b <200 cells/μl	No	411	16	3.9	1 (ref)		1 (ref)	0 (ref)	
	Yes	241	27	11.1	3.11 (1.64–5.91)	0.001	2.72 (1.28–5.78)	1.00 (0.38)	0.009
	missing data	47	2	4.3	1.10 (0.24–4.93)	0.904	1.50 (0.29–7.74)	0.40 (0.84)	0.631
Charlson Comorbidity index	0–1	532	20	3.8	1 (ref)		1 (ref)	0 (ref)	
	≥2	167	25	15.0	4.51 (2.43–8.35)	<0.001	4.07 (2.03–8.17)	1.40 (0.36)	<0.001
History of AIDS	No	236	18	3.9	1 (ref)		1 (ref)	0 (ref)	
	Yes	463	27	11.4	3.19 (1.72–5.93)	<0.001	2.78 (1.34–5.78)	1.02 (0.37)	0.006
On HAART	Yes	347	17	4.9	1 (ref)		1 (ref)	0 (ref)	
	No	352	28	7.9	1.68 (0.90–3.12)	0.103	3.19 (1.42–7.16)	1.16 (0.41)	0.005
Sex	Female	146	3	2.0	1 (ref)		1 (ref)	0 (ref)	
	Male	553	42	7.6	3.92 (1.20–12.8)	0.024	3.86 (1.05–14.2)	1.35 (0.66)	0.042
Race	Non-caucasian	111	5	4.5	1 (ref)		1 (ref)	0 (ref)	
	Caucasian	588	40	6.8	1.55 (0.60–4.01)	0.369	0.47 (0.16–1.43)	−0.75 (0.57)	0.185
Calendar period	1995–1996	152	12	7.9	1 (ref)		1 (ref)	0 (ref)	
	1997–2008	547	33	6.0	0.75 (0.38–1.49)	0.409	0.61 (0.23–1.57)	−0.50 (0.49)	0.305
Hepatitis C co-infected	No		31	6.1	1 (ref)		1 (ref)	0 (ref)	
	Yes		14	7.3	1.22 (0.63–2.34)	0.556	1.58 (0.74–3.39)	0.46 (0.39)	0.240
Mode of HIV exposure	Non-IDU	552	35	6.3	1 (ref)				
	IDU	147	10	6.8	1.08 (0.52–2.23)	0.839
		699	45	6.4	0.78 (0.61–0.99)	0.046
Nadir CD4+ cell count (per 100 cells/μl decrease)									
HIV RNA, (per log10 increase in copies/ml) ^b	On HAART	403	24	6.0	2.76 (0.40–19.2)	0.304
	HAART-naïve	296	21	7.1	0.36 (0.02–5.57)	0.468

^aThis logistic regression model is adjusted for all variables in the table except: IDU as mode of HIV exposure which is interdependent to hepatitis C status, Nadir CD4+ cell count which is interdependent to AIDS and HIV RNA which is interdependent to use of HAART.

^bLast measurement before date of pneumonia. *adj* = Adjusted; OR = Odds Ratio; CI = Confidence Interval.

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Our study had a number of limitations. First, previous studies have found identifiable bacterial pathogens in 24%–38% of HIV-infected patients with pneumonia [13,14]. As data on specific pathogens were not available, we do not know the percentage of pneumonia cases in our study population caused by bacteria and how this may have affected prognosis. Second, causes of death registered in DHCS were based on information extracted from medical records. Thus the exact cause of death may be uncertain or, in some cases, multifactorial. For this reason we chose to group causes of death into broader categories to determine whether HIV was the key factor. We were unable to adjust for use of opportunistic infection prophylaxis, smoking status, and/or pneumococcal vaccination status since these data were not available in DHCS database. Our results are restricted to inpatients. Finally, despite our efforts to control for potential confounders, it is possible that the observed protective effect of HAART was due to confounding by indication (*i.e.*, patients on HAART had an *a priori* reduced risk of death for example due to a healthier lifestyle compared to HAART-naïve patients).

The incidence rates of pneumonia in HIV-infected individuals decreased from 51 hospitalizations per 1000 person-years during

1995–1996 to 20 hospitalizations per 1000 person-years during 2005–2007 [7]. In our study population, 30-day mortality did not change over calendar time and was comparable to the mortality risk of 6%–8% following pneumonia found in other studies of HIV-infected persons [6,13], and consistent with the finding that most pneumonia-related deaths occur within 30 days of hospital admission [15].

Contrary to studies on invasive pneumococcal disease [16], we found a decline in 90-day mortality from the pre-HAART era to the HAART era. We even may have underestimated the decline in mortality over calendar time because the median age in our cohort increased from 1995 to 2008. Therefore, while the acute course of pneumonia has change little over time, the reduction in 90-day mortality may be due to reduced risk of death from sequelae following the initial episode of pneumonia [17], perhaps stemming from a general improvement in immune function after introduction of HAART.

In a study of non-HIV infected individuals aged 40–64 hospitalized for the first time with pneumonia, 30-day mortality was 7.8%, and 90-day mortality was 11.6% [18]. These estimates are comparable to what we found in HIV-infected individuals.

Table 5. Prognostics factors for 90-day mortality after first hospitalization for pneumonia among HIV-infected individuals.

		90 day mortality							
		n	Deaths	Mortality (%)	OR (95% CI)	p	OR _{adj} (95% CI) ^a	Coefficient (SE)	p
Intercept								−6.82 (1.01)	
Age (per 10 year increase)		699	84	12.0	1.36 (1.11–1.66)	0.003	1.43 (1.11–1.85)	0.36 (0.13)	0.007
CD4+ cell count ^b <200 cells/μl	No	411	28	6.8	1 (ref)		1 (ref)	0 (ref)	
	Yes	241	49	20.3	3.49 (2.13–5.73)	<0.001	2.52 (1.37–4.65)	0.93 (0.31)	0.003
	missing data	47	7	14.9	2.39 (0.98–5.83)	0.055	1.91 (0.67–5.43)	0.65 (0.53)	0.223
Charlson Comorbidity index	0–1	532	44	8.2	1 (ref)		1 (ref)	0 (ref)	
	≥2	167	40	24.0	3.49 (2.18–5.59)	<0.001	3.86 (2.19–6.78)	1.35 (0.29)	<0.001
History of AIDS	No	236	35	7.6	1 (ref)		1 (ref)	0 (ref)	
	Yes	463	49	20.8	3.20 (2.01–5.11)	<0.001	2.46 (1.40–4.32)	0.90 (0.29)	0.002
On HAART	Yes	347	25	7.2	1 (ref)		1 (ref)	0 (ref)	
	No	352	59	16.8	2.59 (1.58–4.25)	<0.001	3.58 (1.83–6.99)	1.27 (0.34)	<0.001
Sex	Female	146	5	3.4	1 (ref)		1 (ref)	0 (ref)	
	Male	553	79	14.3	4.40 (1.79–10.9)	0.001	3.77 (1.37–10.4)	1.33 (0.52)	0.010
Race	Non-caucasian	111	5	4.5	1 (ref)		1 (ref)	0 (ref)	
	Caucasian	588	79	13.4	3.29 (1.30–8.32)	0.012	1.15 (0.41–3.24)	0.14 (0.53)	0.791
Calender period	1995–1996	152	34	22.4	1 (ref)		1 (ref)	0 (ref)	
	1997–2008	547	50	9.1	0.35 (0.22–0.56)	<0.001	0.80 (0.39–1.64)	−0.22 (0.36)	0.548
Hepatitis C co-infected	No	508	63	12.4	1 (ref)		1 (ref)	0 (ref)	
	Yes	191	21	11.0	0.87 (0.52–1.47)	0.610	1.13 (0.61–2.11)	0.12 (0.32)	0.701
Mode of HIV exposure	Non-IDU	552	66	12.0	1 (ref)				
	IDU	147	8	12.3	1.03 (0.59–1.79)	0.924
Nadir CD4+ cell count (per 100 cells/μl decrease)		699	84	12.0	1.38 (1.13–1.69)	0.002
HIV RNA, (per log10 increase in copies/ml) ^b	On HAART	403	39	9.2	2.27 (0.43–12.1)	0.337
	HAART-naïve	296	45	14.9	0.24 (0.03–2.18)	0.206

^aThis logistic regression model was adjusted for all variables in the table except: IDU as mode of HIV exposure which is interdependent to hepatitis C status, Nadir CD4+ cell count which is interdependent to AIDS and HIV RNA which is interdependent to use of HAART.

^bLast measurement before date of pneumonia. *adj* = Adjusted; OR = Odds Ratio; CI = Confidence Interval.

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Further, the overall impact on risk of death following a first hospitalization pneumonia was similar to the increased risk recently reported for “mild” AIDS-defining events (*i.e.*, pulmonary and extrapulmonary tuberculosis, *pneumocystis jirovecii* (carinii) pneumonia and esophageal candidiasis) [19].

Others have found a four to five-fold increased risk of death (follow-up ≤51 months) among HIV-infected persons with pneumonia, compared to those without pneumonia [6,13], which is in accordance with our findings. Contrary to other studies [20], however, we found that the increased risk of death persisted beyond one year. Although unmeasured confounding factors cannot be ruled out as a contributory cause of the increased long term risk of death, pneumonia could also be viewed as a marker of immune system frailty that may not be reflected by the CD4+ cell count.

We found that HAART use improved the prognosis after a pneumonia-related hospitalization also after adjusting for CD4+ cell count, which is in line with results from earlier studies [21,22,23]. In a CD4+ cell-count-adjusted subgroup analysis from the Strategies for Management of Antiretroviral Therapy (SMART) trial, the risk of opportunistic diseases and death was increased in HAART-naïve patients or those off-HAART for 6 months compared to those with suppressed HIV viral load in

plasma [21]. In an observational study of asymptomatic HIV patients with CD4+ counts of 351 to 500 cells/μl, deferring HAART vs. initiating early HAART was associated with a mortality ratio of 1.7 [23]. Brenchley and colleagues demonstrated that microbial translocation and immune activation were higher among HAART-naïve than those on HAART [24]. Whether increased immune activation influences an individual's ability to survive a serious infection such as pneumonia remains to be determined.

We observed a lower short term mortality among females than males. In the HIV Epidemiologic Research (HER) Study on pneumonia Kohli et al. found in-hospital mortality after bacterial pneumonia to be 7.7% among females [6,7]. In our study, in which only 20.9% of the subjects were females, 30 day mortality was very low (2.0% compared to 7.6% for males). All-cause mortality rates may be moderately lower among females than males with HIV [4], but the considerable effect of gender on short term mortality found in our study may have been caused by chance and should be interpreted with caution.

In conclusion, a first hospitalization for pneumonia in HIV-infected individuals predicted an increased risk of death beyond one year. Among those hospitalized with pneumonia, use of HAART was associated with a reduced risk of death, independent

of CD4 cell counts. While the former finding may indicate that acquisition of pneumonia is a marker of frailty, the latter may indicate that this frailty can be partly offset by use of HAART. These findings support the need for additional research to assess the role of HAART in reducing morbidity and mortality associated with non-AIDS-defining infections. Promotion of early HAART initiation may not only lead to reduced mortality after pneumonia, it may also reduce the risk of acquiring pneumonia severe enough to require hospitalization [6,7]. Finally, it is reassuring that the prognosis following pneumonia has improved over calendar time.

References

1. Polsky B, Gold JW, Whimbey E, Dryjanski J, Brown AE, et al. (1986) Bacterial pneumonia in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 104: 38–41.
2. (1992) 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recommendations and reports: Morbidity and mortality weekly report* 41: 1–19.
3. Hogg RS, Heath KV, Yip B, Craib KJ, O'Shaughnessy MV, et al. (1998) Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. *JAMA* 279: 450–454.
4. Lohse N, Hansen AB, Pedersen G, Kronborg G, Gerstoft J, et al. (2007) Survival of persons with and without HIV infection in Denmark, 1995–2005. *Ann Intern Med* 146: 87–95.
5. Palella FJ, Jr., Delaney KM, Moorman AC, Loveless MO, Fuhrer J, et al. (1998) Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 338: 853–860.
6. Kohli R, Lo Y, Homel P, Flanigan TP, Gardner LI, et al. (2006) Bacterial pneumonia, HIV therapy, and disease progression among HIV-infected women in the HIV epidemiologic research (HER) study. *Clin Infect Dis* 43: 90–98.
7. Sogaard OS, Lohse N, Gerstoft J, Kronborg G, Ostergaard L, et al. (2008) Hospitalization for Pneumonia among Individuals With and Without HIV Infection, 1995–2007: A Danish Population-Based, Nationwide Cohort Study. *Clin Infect Dis* 47: 1347–1353.
8. Obel N, Engsig FN, Rasmussen LD, Larsen MV, Omland LH, et al. (2008) Cohort Profile: The Danish HIV Cohort Study. *Int J Epidemiol*.
9. Lohse N, Hansen AB, Jensen-Fangel S, Kronborg G, Kvinesdal B, et al. (2005) Demographics of HIV-1 infection in Denmark: results from the Danish HIV Cohort Study. *Scand J Infect Dis* 37: 338–343.
10. de Groot V, Beckerman H, Lankhorst GJ, Bouter LM (2003) How to measure comorbidity. a critical review of available methods. *J Clin Epidemiol* 56: 221–229.
11. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 40: 373–383.
12. Gordin FM, Roediger MP, Girard PM, Lundgren JD, Miro JM, et al. (2008) Pneumonia in HIV-infected persons: increased risk with cigarette smoking and treatment interruption. *Am J Respir Crit Care Med* 178: 630–636.
13. Hirschtick RE, Glassroth J, Jordan MC, Wilcosky TC, Wallace JM, et al. (1995) Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary Complications of HIV Infection Study Group. *N Engl J Med* 333: 845–851.
14. Fine MJ, Stone RA, Singer DE, Coley CM, Marrie TJ, et al. (1999) Processes and outcomes of care for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team (PORT) cohort study. *Arch Intern Med* 159: 970–980.
15. Mortensen EM, Coley CM, Singer DE, Marrie TJ, Obrosky DS, et al. (2002) Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. *Arch Intern Med* 162: 1059–1064.
16. Grau I, Pallares R, Tubau F, Schulze MH, Llopi F, et al. (2005) Epidemiologic changes in bacteremic pneumococcal disease in patients with human immunodeficiency virus in the era of highly active antiretroviral therapy. *Arch Intern Med* 165: 1533–1540.
17. Mortensen EM, Kapoor WN, Chang CC, Fine MJ (2003) Assessment of mortality after long-term follow-up of patients with community-acquired pneumonia. *Clin Infect Dis* 37: 1617–1624.
18. Thomsen RW, Riis A, Norgaard M, Jacobsen J, Christensen S, et al. (2006) Rising incidence and persistently high mortality of hospitalized pneumonia: a 10-year population-based study in Denmark. *J Intern Med* 259: 410–417.
19. Mocroft A, Sterne JA, Egger M, May M, Grabar S, et al. (2009) Variable impact on mortality of AIDS-defining events diagnosed during combination antiretroviral therapy: not all AIDS-defining conditions are created equal. *Clin Infect Dis* 48: 1138–1151.
20. Kaplan V, Clermont G, Griffin MF, Kasal J, Watson RS, et al. (2003) Pneumonia: still the old man's friend? *Arch Intern Med* 163: 317–323.
21. Emery S, Neuhaus JA, Phillips AN, Babiker A, Cohen CJ, et al. (2008) Major clinical outcomes in antiretroviral therapy (ART)-naïve participants and in those not receiving ART at baseline in the SMART study. *J Infect Dis* 197: 1133–1144.
22. Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, et al. (2003) Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet* 362: 22–29.
23. Kitahata MM, Gange SJ, Abraham AG, Merriman B, Saag MS, et al. (2009) Effect of Early versus Deferred Antiretroviral Therapy for HIV on Survival. *N Engl J Med*.
24. Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, et al. (2006) Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nature Med* 12: 1365–1371.

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Author Contributions

Conceived and designed the experiments: OSS NL HS NO. Performed the experiments: OSS. Analyzed the data: OSS NL HS. Contributed reagents/materials/analysis tools: OSS JG GK L CP GP NO. Wrote the paper: OSS NL JG GK L CP GP HS NO.

Morbidity and Risk of Subsequent Diagnosis of HIV Infection: A Population Based Case Control Study Identifying Indicator Diseases for HIV infection

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ABSTRACT

Objective To examine associations between diseases diagnosed in hospitals and risk of subsequent HIV diagnosis.

Design Population-based case control study.

Setting All hospitals in Denmark.

Participants Cases were persons with incident HIV infection diagnosed in Denmark between 1 January 1995 and 1 June 2008. Risk-set sampling was used to identify 19 age- and gender-matched population controls for each HIV case, using the HIV diagnosis date as the index date for both cases and controls.

Main outcome measures Prior hospital diagnoses were obtained from Danish medical databases. These diagnoses were first categorized into 22 major disease categories (excluding AIDS-defining diseases except tuberculosis) and then subdivided them into 161 subcategories, allowing us to examine specific diseases as potential HIV indicators by conditional logistic regression.

Results The study included 2,036 HIV cases and 35,718 controls. Persons with the following disease categories had a high risk of HIV diagnosis during the subsequent 5-year period: sexually transmitted infections and viral hepatitis (adjusted odds ratio [aOR]=12.3 (95% CI, 9.60 to 15.7), haematological diseases (aOR=4.28 (3.13 to 5.85)), lower respiratory tract infections (aOR=3.98 (3.14 to 5.04)), CNS infections (aOR=3.44 (1.74 to 6.80)), skin infections (aOR=3.05, (2.47 to 3.75)), other infections (aOR=4.64 (3.89 to 5.54)), and substance abuse (aOR=2.60, (2.06 to 3.29)). Several specific diseases were associated with aORs >20 including syphilis, hepatitis A, non "A" viral hepatitis, herpes zoster, candida infection, endocarditis, thrombocytopenia, and opioid abuse.

Conclusion: Targeted testing for HIV in patients diagnosed with diseases associated with HIV may lead to earlier treatment and thereby reduced morbidity, mortality and HIV transmission.

INTRODUCTION

Despite three decades of concerted effort, the HIV epidemic remains a tremendous public health challenge in both low- and high-income countries.^{1,2} Many individuals newly diagnosed with HIV present at a late stage of the disease with severe immune depletion, resulting in delayed initiation of antiretroviral therapy (ART) which worsens their prognosis³ and increases further transmission of HIV.⁴⁻⁶ Recently, the European Center for Disease Control and Prevention's Dublin Declaration Progress Report 2010 concluded that "the rates of late diagnosis remain unacceptably high" in Europe and Central Asia.⁷ Thus, intensified HIV testing and treatment has been advocated to lower the prevalence of undiagnosed HIV infection and to control the HIV epidemic.^{8,9}

The U.S. Centers for Disease Control and Prevention (CDC) recommend routine HIV testing for all persons under age 65 who come into contact with the US health care system.¹⁰ While this approach may be cost-effective in areas with high HIV prevalence¹¹ and does prolong life expectancy,³ alternative approaches such as targeted HIV testing may be more appropriate in other settings with lower HIV prevalence or in different health care systems.²

Targeted HIV testing based on risk groups (e.g. injecting drug users [IDU])¹², presence of AIDS-defining illnesses, or coming from a high-HIV prevalence country is practised in most European countries.¹³ However, many opportunities for HIV testing are missed by the health care system prior to HIV diagnosis.¹⁴ In 2007, the pan-European initiative "HIV in Europe" recommended that targeted testing based on the presence of diseases associated with HIV, so-called indicator diseases,¹⁵ should be developed as an additional tool to guide targeted HIV testing. HIV indicator diseases may be a result of individual risk behaviours or coexisting HIV infection. Several studies have identified indicator diseases within a narrow spectrum of conditions,¹⁶⁻¹⁹ but to date there has been no comprehensive study of HIV indicator diseases. In the absence of adequate data, guidance is based mainly on expert opinion.¹⁵ There is substantial information regarding the prevalence of indicator diseases in the HIV-infected population. In contrast, the relative risk of HIV

among patients with indicator diseases remains poorly described. The goal of this study was to delineate medical conditions that identify individuals at increased risk of subsequent HIV diagnosis.

METHODS

We conducted a population-based nested case control study among persons with and without an incident HIV diagnosis in Denmark. The adult population of Denmark is 4.3 million with an estimated HIV infection prevalence of 0.09%.²⁰ The Danish healthcare system provides free, tax-supported medical care for all residents, including antiretroviral treatment of HIV.

Data sources

The civil registration system (CRS) number, assigned at birth, uniquely identifies each person living in Denmark since 1968 and is used for personal identification in all Danish administrative and medical databases. Further, those who live or work in Denmark legally for a certain amount of time must register with the CRS. We used this unique 10-digit CRS-number to link data among the following registries: *The Danish HIV Cohort Study* (DHCS) is a prospective, open, nationwide, population-based cohort of all HIV-infected individuals receiving care in Danish HIV clinics since 1 January 1995.²⁰ The study is ongoing, with continuous enrolment of newly diagnosed patients. *The Danish Civil Registration System* records demographic information, vital status, and immigration and emigration dates for all Danish citizens beginning in 1967.²¹ *The Danish National Registry of Patients* (DNRP) contains information on all patients discharged from Danish hospitals since 1977.²² It includes diagnoses coded by the treating physician according to the *International Classification of Diseases*, 8th revision (ICD-8) up to the end of 1993 and according to the 10th revision (ICD-10) thereafter. The registry covers public as well as private hospitals and so constitutes a virtually complete population-based database. *The Danish Cancer Registry* (DCR) has recorded all incident cancers in Denmark since 1943, classifying cancers registered after 1977 according to ICD-10.²³

Study population

Cases. Cases were identified from DHCS and included all individuals who (I) were diagnosed with HIV between 1 January 1995 and 1 June 2008; (II) were at least 16 years of age on the date of HIV diagnosis; and (III) were living in Denmark for at least 5 years prior to HIV diagnosis.

Population controls. Controls not diagnosed with HIV were identified from the CRS using incidence density sampling, which involves matching each case to a sample of those who are at risk at the time of case occurrence.²⁴ To ensure sufficient statistical power to detect differences in the occurrence of rare events, we sampled for each case 19 random population controls that were alive on the HIV diagnosis date of their respective case, had the gender and were born on the date of birth of the HIV patient. Population controls could only be sampled once. The date of HIV diagnosis/sampling constituted the *index date* for both cases and controls. Controls who, according to the CRS, had not been living in Denmark for at least 5 years prior to the index date were excluded. Hence, although some controls (and cases) did not go to hospital in the 5-year period prior to their sampling date / HIV diagnosis, they were all living in Denmark during this period and therefore at risk of both exposure and outcome.

Identification of hospital diagnoses and grouping of disease categories

For all study subjects we extracted hospital diagnoses from all outpatient contacts and hospital stays from the DNRP and DCR, up to the day prior to the index date. ICD-10 codes were the primary source for grouping diseases. We defined 22 disease categories of interest according to the type and anatomical location of the disease (Appendix Table 1). ICD-8 codes were translated to the corresponding ICD-10 disease categories and first-time diagnoses were assigned to the appropriate category. In addition, a total of 161 subcategories were created for the 22 disease categories, allowing us to examine specific diseases as potential HIV indicators (Appendix Table 1). Except for tuberculosis, we excluded AIDS-defining diseases, because their association with HIV infection is well established.²⁵

Statistical analyses

For cases and controls, we tabulated gender, age (16 to 39 years, 40 to 49 years, 50 to 59 years, and 60+ years), and hospital contact(s) in the 5-year period prior to the index date for each of the 22 disease categories (yes/no). For cases, the following variables were also included: race, most likely mode of HIV acquisition, presence of AIDS²⁵ at diagnosis, first CD4⁺ cell count, and HIV RNA measurement (within 180 days of HIV diagnosis). Frequencies and percentages were computed for all variables.

Conditional logistic regression analyses

For each of the 22 disease categories, conditional logistic regression analysis was used to estimate odds ratios (OR), which is an unbiased estimate of the incidence rate ratio (IRR) for subsequent HIV diagnosis; unadjusted ORs as well as ORs adjusted for the remaining 21 disease categories were estimated.²⁴ Observation data were subsequently stratified into three time periods prior to the index date (less than 1 year, 1 to 2 years, and 3 to 5 years,) to explore changes in ORs in the years following a given disease or disease category. We used first-time diagnoses registered within each time stratum for a given disease/disease category. Adjusted ORs were calculated for each disease category and time period (adjusted for the remaining 21 disease categories). To identify specific HIV-indicator diseases, we explored risk estimates for the 161 specific subcategories within each of the 22 disease categories. We computed both unadjusted odds ratios for each subcategory and odds ratios adjusted for other diseases within the same disease category (Appendix Table 1). In all analyses, only first-time diagnoses for a given disease/disease category were utilized.

The Danish Data Protection Agency approved the establishment of the cohort and the linkage between the four registries in this study (J. no. 2008-41-1781). The study was not subject to approval by the ethics committee because data collection did not involve direct patient contact.

RESULTS

We identified 2,363 individuals diagnosed with HIV between 1 January 1995 and 1 June 2008 and 38,684 controls. Of these, 327 cases and 2,966 controls were excluded because they immigrated to Denmark less than 5 years prior to their index date. Thus, a total of 2,036 cases and 35,718 controls were included resulting in an average of 17.5 controls per case.

In the 5 years prior to their index date, there were a total of 138,416 hospital contacts for both cases and controls, of which 34,520 represented a first-time diagnosis for one of the 22 disease categories. Table 1 shows characteristics of cases and controls on their index date. In the 5 years preceding the index date, 69.8% of cases (1,421 of 2,036 cases) and 53.6% of controls (19,148 of 35,718 controls) had at least one hospital contact for one of the 22 disease categories delineated below.

Disease category and risk of subsequent HIV diagnosis

Several disease categories were associated with an increased relative risk of HIV diagnosis during the following 5-year period (Figure 1). Persons diagnosed for the first time with a disease in the category “sexually transmitted infections (STIs) and viral hepatitis” had the highest risk of subsequent HIV diagnosis (adjusted OR [aOR] = 12.3 [95% CI, 9.60 to 15.7]). Also persons with infections (lower respiratory tract infections (aOR=3.98 (3.14 to 5.04)), CNS infections (aOR=3.44 (1.74 to 6.80)), skin infections (aOR=3.05 (2.47 to 3.75)), other infections (aOR=4.64 (3.89 to 5.54))), haematological diseases (aOR=4.28 (3.13 to 5.85)), non-AIDS defining cancers (aOR=1.72 (1.24 to 2.40)), substance abuse (aOR=2.60 (2.06 to 3.29)), poisoning (aOR=2.00 (1.54 to 2.60)), ear, nose, and throat diseases (aOR=1.84 (1.53 to 2.21)), skin diseases (aOR=1.52 (1.16 to 2.01)), and gastrointestinal diseases (aOR=1.39 (1.20 to 1.60)) had higher risk of HIV diagnosis during the following 5 years. Seven disease categories were not associated with subsequent HIV diagnosis: eye diseases, kidney diseases, lung diseases, ischemic heart disease

(IHD), non-IHD vascular diseases, neurological diseases, and trauma. A decreased risk of subsequent HIV diagnosis was found for persons with rheumatological diseases (aOR=0.72 (0.62 to 0.85), non-diabetes endocrine diseases (aOR=0.60 (0.42 to 0.86), and diabetes (aOR=0.40 (0.23 to 0.69).

Time trends in risk of HIV diagnosis following hospital contact

Figure 2 shows the relative risk of subsequent HIV in 3 time periods: <1 year, 2-3 years, and 3-5 years after each of the 22 disease categories. The time trends can be categorized in four main groups: 1) no time trend (eye diseases, lung diseases, kidney diseases, IHD, neurological diseases, trauma, rheumatological diseases, non-diabetic endocrine diseases, and diabetes); 2) A highly increased risk of HIV in the first year after diagnosis and no or only a slightly increased risk thereafter (haematological diseases, non-AIDS malignancy, skin diseases, gastrointestinal diseases, and non-IHD vascular diseases); 3) gradually decreased risk of HIV over time (lower respiratory tract infections, CNS infections, skin infections, other infections, and ear, nose, and throat diseases); 4) persistently increased risk both in the short and the long term (STIs and viral hepatitis, substance abuse, and poisoning).

Specific HIV-indicator diseases

To determine whether any specific diseases were strong indicators of subsequent HIV diagnosis, we further divided the 22 disease categories into 161 subcategories. Table 2 reports risk estimates for subcategories associated with at least a 3-fold elevated risk of subsequent HIV diagnosis (all 161 subcategories shown in Appendix Table 2). We found strong associations between all groups of STIs and viral hepatitis and subsequent HIV diagnosis. Several other specific groups of infectious diseases, including meningitis, herpes zoster, endocarditis, and malaria, were closely associated with later HIV diagnosis. Among haematological diseases and cancers: thrombocytopenia, anaemia, lymphadenitis, non-AIDS defining lymphomas, and secondary and

unspecified malignant neoplasm of lymph nodes were associated with later HIV diagnosis. Genital cancers were not. In the group of gastrointestinal diseases, diseases of the oral cavity, liver diseases, and fissures/abscesses of the anal cavity were strongly associated with later HIV diagnosis. Among skin diseases, seborrheic dermatitis was associated with increased risk of HIV diagnosis. Ischaemic heart disease, including myocardial infarction (aOR=0.81 (0.39 to 1.69)) and other cardiovascular diseases, were not associated with later HIV diagnosis, with the notable exception of thrombophlebitis (aOR=5.29 (3.51 to 7.96)).

Among fourteen individuals diagnosed with hepatitis A infection, 12 (85.7%) were men who had sex with men (MSM). Five (50%) of ten cases with malaria were non-Caucasian immigrants. In 62 of 68 cases (91.2%) with opioid abuse-related diagnoses, IDU was registered as the mode of HIV transmission.

First-time diagnoses for the 52 diseases in Table 2 represented 3,257 (1.9%) of all 138,416 hospital contacts registered in the 5 years prior to the index date. In the HIV cohort of 2,036 individuals, 782 (38.4%) had at least one hospital contact for an indicator disease, while this occurred for only 2,475 (6.9%) of 35,718 controls. For the 1,826 cases not reporting IDU as mode of HIV infection, 613 (34.1%) had a first-time hospital contact for diseases listed in Table 2.

DISCUSSION

We found that HIV indicator diseases identified over one-third of all individuals who would become diagnosed with HIV in the subsequent 5-year period. Recognition of these HIV indicator diseases could aid healthcare personnel in identifying individuals at increased risk of undiagnosed HIV. The time-dependent association between the date of diagnosis of some disease categories and HIV diagnosis suggests that for several categories repeated (e.g. yearly) HIV testing is advisable.

To our knowledge, this is the first population-based study conducted to identify HIV indicator diseases across all disease categories. While some indicator diseases we identified were previously recognized,^{15-17 26} the size of our study population and completeness of hospitalization data allowed us to provide risk estimates with high statistical precision for the majority of disease groups. Our results thus can be used to guide strategies for targeted HIV testing in the hospital settings.

Our study also had some limitations. As in other observational HIV cohort studies, an unknown proportion of people with HIV may have died without being diagnosed with the condition. Thus, we may have underestimated the relative risk of subsequent HIV diagnosis after life-threatening conditions such as cancer.²⁶ Additionally, we had access only to hospital diagnoses, which may have caused us to underestimate the occurrence of diseases diagnosed outside the hospital system, such as syphilis, fungal skin infections, and herpes zoster. If patients at risk of HIV are more prone to be diagnosed in a hospital setting this will lead to a potential overestimation of the predictive value of some HIV predictor diseases if compared with those from a non-hospital setting. Another potential shortcoming is inaccuracies in diagnoses reported to national hospital databases. However, the positive predictive value of registry diagnoses (i.e. the proportion of subjects with a given registry diagnosis which is correct when compared to medical records) is generally high (70% to 99%).^{22 27} Furthermore, risk of subsequent HIV diagnosis may be elevated if a given disease diagnosis increases the likelihood of HIV testing, regardless of its actual association with HIV infection. This phenomenon would produce a close association between the timing of the disease and HIV diagnoses. Although persons with some disease categories had increased risk of HIV in the first year thereafter (Figure 2), the increased risk of subsequent HIV diagnosis was also observed more than 1 year after the disease. Hence, this phenomenon could only have a moderate effect on the 5-year estimates. Finally, it should be noted that due to our use of hospital diagnoses, we were unable to identify clinical features that may further enhance the predictive value of given indicator diseases (e.g. “florid or hard to treat” fungal skin infection).

HIV indicator diseases can be grouped into three major types. First, disease manifestations of acute HIV infection (e.g. acute viral illness or lymphadenitis); second, diseases associated with coexisting HIV infection (e.g. herpes zoster or thrombocytopenia); and third, diseases associated with behaviour that increases the risk of acquiring HIV (e.g. hepatitis and opioid abuse). The latter group is highlighted in Figure 2, which shows that disease categories related to individual risk behaviours (e.g. STIs and viral hepatitis) are associated with an elevated risk that remained constant over time. Other disease categories which may be related to coexisting HIV, such as respiratory infections, haematological diseases, and non-AIDS-defining cancers, showed a highly increased risk of HIV in the first year after the diagnosis. The close connection between the date of hospital contact and date of HIV diagnosis suggests that the hospital contacts led to subsequent HIV testing as part of the recommended medical work-up (e.g. following lymphoma diagnosis).¹⁵ Among specific HIV indicator diseases, acute hepatitis A virus (HAV) infection was associated with high risk of subsequent HIV diagnosis. The strong association between acute HAV infection and MSM suggests that HAV infection is a proxy for high-risk sexual behaviour in our study population.²⁸ Our data also indicate that endocrine and rheumatological diseases (except infectious arthropathy) are associated with decreased risk of HIV which may be related to low-risk sexual behaviour among individuals with these chronic diseases.²⁹

Targeted HIV testing is practiced in many countries^{2 13 15} and may be more cost-effective than universal HIV testing in low HIV prevalence regions like Denmark.^{30 31} However, until now the lack of a thorough delineation of HIV indicator diseases has markedly reduced the efficacy of targeted HIV testing². Another barrier to HIV screening is the acceptance of testing among patients³². While the acceptance of universal opt-out HIV testing among emergency department patients has varied greatly^{33 34} and was as low as 24% in a recent trial,³⁵ physician recommended HIV testing is more acceptable for most patients.³² Thus, expanding targeted HIV testing using indicator diseases may be an agreeable approach for patients. In our study, HIV indicator diseases could potentially detect approximately two out of every five persons with HIV at an earlier stage. If the earlier

diagnosis leads to earlier ART initiation, indicator disease-based HIV screening has the potential to reduce both HIV-related morbidity and HIV transmission.³⁶⁻³⁸ This screening strategy should of course be added to the usual HIV screening initiatives to ensure un-delayed diagnosis of the remaining 60% of persons with HIV. Almost one-third of cases in our study had no hospital contacts in the 5 years prior to their HIV diagnosis. Therefore, national screening initiatives could aim to expand current non-hospital based strategies such as community outreach programs aimed at high-risk groups (e.g. sex workers and drug users).^{39 40}

In conclusion, knowledge of HIV indicator diseases may optimize national HIV testing programs but the effectiveness of indicator disease-based HIV screening needs confirmation in clinical studies. Although the use of indicator diseases may enhance the identification of undiagnosed HIV-infected individuals, this strategy can only be supplementary to systematic HIV testing of risk groups identified through information about their behavioural risk-taking profiles.

What is already known on this subject

Certain diseases are associated with increased risk of undiagnosed HIV infection

Targeted HIV screening based on these diseases has been proposed as the next step in controlling the HIV epidemic in Europe

However, to date, indicator diseases for HIV infection have not been delineated thoroughly

What this paper adds

HIV indicators diseases can be found within a wide range of medical specialties

Targeted HIV screening based on these newly identified indicator diseases can identify people with undiagnosed HIV infection at an earlier disease stage, which improves their prognosis and reduces further transmission of HIV

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Conflicts of interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) no authors have support from any companies for the submitted work; (2) all authors have no relationships with companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) all authors have no non-financial interests that may be relevant to the submitted work.

Role of the funding sources

No funding sources had roles in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author had the final responsibility to submit for publication.

Contributors

OSS, NL, JG, HTS, and NO contributed to conception and design of the study. Data collection and linkages were undertaken by OSS, LØ, GK, BR, JG, and NO. Data analysis was performed by OSS and NL. OSS, NL, LØ, GK, BR, JG, HTS, and NO interpreted the results. OSS drafted the report. OSS, NL, LØ, GK, BR, JG, HTS, and NO contributed to editing and review of the report.

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REFERENCES

1. Hall HI, Song R, Rhodes P, Prejean J, An Q, Lee LM, et al. Estimation of HIV incidence in the United States. *Jama* 2008;300(5):520-9.
2. Coenen T, Lundgren J, Lazarus JV, Matic S. Optimal HIV testing and earlier care: the way forward in Europe. *HIV Med* 2008;9 Suppl 2:1-5.
3. Chadborn TR, Delpech VC, Sabin CA, Sinka K, Evans BG. The late diagnosis and consequent short-term mortality of HIV-infected heterosexuals (England and Wales, 2000-2004). *Aids* 2006;20(18):2371-9.
4. Donnell D, Baeten JM, Kiarie J, Thomas KK, Stevens W, Cohen CR, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet* 2010;375(9731):2092-8.
5. Montaner JS, Lima VD, Barrios R, Yip B, Wood E, Kerr T, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. *Lancet* 2010;376(9740):532-39.
6. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med* 2000;342(13):921-9.
7. Prevention ECfDCa. HIV testing: increasing uptake and effectiveness in the European Union.: ECDC, Stockholm 2010.
8. Marks G, Crepaz N, Janssen RS. Estimating sexual transmission of HIV from persons aware and unaware that they are infected with the virus in the USA. *Aids* 2006;20(10):1447-50.
9. Montaner JS, Hogg R, Wood E, Kerr T, Tyndall M, Levy AR, et al. The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic. *Lancet* 2006;368(9534):531-6.
10. Branson BM, Handsfield HH, Lampe MA, Janssen RS, Taylor AW, Lyss SB, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep* 2006;55(RR-14):1-17; quiz CE1-4.
11. Paltiel AD, Weinstein MC, Kimmel AD, Seage GR, Losina E, Zhang H, et al. Expanded screening for HIV in the United States - An analysis of cost-effectiveness. *N Engl J Med* 2005;352(6):586-95.
12. Mathers BM, Degenhardt L, Ali H, Wiessing L, Hickman M, Mattick RP, et al. HIV prevention, treatment, and care services for people who inject drugs: a systematic review of global, regional, and national coverage. *Lancet* 2010;375(9719):1014-28.
13. Mounier-Jack S, Nielsen S, Coker RJ. HIV testing strategies across European countries. *HIV Med* 2008;9 Suppl 2:13-9.
14. Burns FM, Johnson AM, Nazroo J, Ainsworth J, Anderson J, Fakoya A, et al. Missed opportunities for earlier HIV diagnosis within primary and secondary healthcare settings in the UK. *Aids* 2008;22(1):115-22.
15. Gazzard B, Clumeck N, d'Arminio Monforte A, Lundgren JD. Indicator disease-guided testing for HIV--the next step for Europe? *HIV Med* 2008;9 Suppl 2:34-40.
16. Bini EJ, Currie SL, Shen H, Brau N, Schmidt W, Anand BS, et al. National multicenter study of HIV testing and HIV seropositivity in patients with chronic hepatitis C virus infection. *J Clin Gastroenterol* 2006;40(8):732-9.
17. Bottieau E, Clerinx J, Van den Enden E, Van Esbroeck M, Colebunders R, Van Gompel A, et al. Infectious mononucleosis-like syndromes in febrile travelers returning from the tropics. *J Travel Med* 2006;13(4):191-7.
18. Klein D, Hurley LB, Merrill D, Quesenberry CP, Jr. Review of medical encounters in the 5 years before a diagnosis of HIV-1 infection: implications for early detection. *J Acquir Immune Defic Syndr* 2003;32(2):143-52.

19. Noskin GA, Glassroth J. Bacterial pneumonia associated with HIV-1 infection. *Clin Chest Med* 1996;17(4):713-23.
20. Obel N, Engsig FN, Rasmussen LD, Larsen MV, Omland LH, Sorensen HT. Cohort Profile: The Danish HIV Cohort Study. *Int J Epidemiol* 2008.
21. Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Danish medical bulletin* 2006;53(4):441-49.
22. Nickelsen TN. Data validity and coverage in the Danish National Health Registry. A literature review. *Ugeskrift for laeger* 2001;164(1):33-37.
23. Olsen JH, Andersen A, Dreyer L, Pukkala E, Tryggvadottir L, Gerhardsson de Verdier M, et al. Summary of avoidable cancers in the Nordic countries. *APMIS Suppl* 1997;76:141-6.
24. Richardson DB. An incidence density sampling program for nested case-control analyses. *Occup Environ Med* 2004;61(12):e59.
25. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR. Recommendations and reports:* 1992;41(RR-17):1-19.
26. Chiao EY, Dezube BJ, Krown SE, Wachsman W, Brock MV, Giordano TP, et al. Time for oncologists to opt in for routine opt-out HIV testing? *Jama* 2010;304(3):334-9.
27. Sogaard OS, Lohse N, Gerstoft J, Kronborg G, Ostergaard L, Pedersen C, et al. Hospitalization for pneumonia among individuals with and without HIV infection, 1995-2007: a Danish population-based, nationwide cohort study. *Clin Infect Dis* 2008;47(10):1345-53.
28. Mazick A, Howitz M, Rex S, Jensen IP, Weis N, Katzenstein TL, et al. Hepatitis A outbreak among MSM linked to casual sex and gay saunas in Copenhagen, Denmark. *Euro Surveill* 2005;10(5):111-4.
29. Lindau ST, Gavrilova N. Sex, health, and years of sexually active life gained due to good health: evidence from two US population based cross sectional surveys of ageing. *BMJ* 2010;340:c810.
30. Paltiel AD, Walensky RP, Schackman BR, Seage GR, Mercincavage LM, Weinstein MC, et al. Expanded HIV screening in the United States: Effect on clinical outcomes, HIV transmission, and costs. *Ann Intern Med* 2006;145(11):797-806.
31. Sanders GD, Bayoumi AM, Sundaram V, Bilir SP, Neukermans CP, Rydzak CE, et al. Cost-effectiveness of screening for HIV in the era of highly active antiretroviral therapy. *N Engl J Med* 2005;352(6):570-85.
32. Haukoos JS, Hopkins E, Byyny RL. Patient acceptance of rapid HIV testing practices in an urban emergency department: assessment of the 2006 CDC recommendations for HIV screening in health care settings. *Ann Emerg Med* 2008;51(3):303-9, 09 e1.
33. Brown J, Shesser R, Simon G, Bahn M, Czarnogorski M, Kuo I, et al. Routine HIV screening in the emergency department using the new US Centers for Disease Control and Prevention Guidelines: results from a high-prevalence area. *J Acquir Immune Defic Syndr* 2007;46(4):395-401.
34. Kendrick SR, Kroc KA, Couture E, Weinstein RA. Comparison of point-of-care rapid HIV testing in three clinical venues. *Aids* 2004;18(16):2208-10.
35. Haukoos JS, Hopkins E, Conroy AA, Silverman M, Byyny RL, Eisert S, et al. Routine opt-out rapid HIV screening and detection of HIV infection in emergency department patients. *Jama* 2010;304(3):284-92.
36. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet* 2009;373(9657):48-57.
37. Kitahata MM, Gange SJ, Abraham AG, Merriman B, Saag MS, Justice AC, et al. Effect of Early versus Deferred Antiretroviral Therapy for HIV on Survival. *N Engl J Med* 2009.
38. Wood E, Kerr T, Marshall BD, Li K, Zhang R, Hogg RS, et al. Longitudinal community plasma HIV-1 RNA concentrations and incidence of HIV-1 among injecting drug users: prospective cohort study. *BMJ* 2009;338:b1649.

39. de la Fuente L, Delgado J, Hoyos J, Belza MJ, Alvarez J, Gutierrez J, et al. Increasing early diagnosis of HIV through rapid testing in a street outreach program in Spain. *AIDS Patient Care STDS* 2009;23(8):625-9.
40. Wolfe D, Carrieri MP, Shepard D. Treatment and care for injecting drug users with HIV infection: a review of barriers and ways forward. *Lancet* 2010;376(9738):355-66.

Table 1. Baseline characteristics* of HIV cases and HIV-uninfected controls.

	Cases (n=2,036)	Controls (n=35,718)
Sex, n (%)		
Female	380 (18.7)	6,555 (18.4)
Male	1,656 (81.3)	30,819 (81.6)
Age at diagnosis, n (%)		
16-39 years	1,122 (55.1)	18,899 (52.91)
40-49 years	510 (25.1)	9,266 (25.9)
50-59 years	290 (14.2)	5,410 (15.2)
60+ years	114 (5.6)	2,143 (6.0)
Hospital contact, n (%)†		
Yes	1,421 (69.8)	19,148 (53.6)
No	615 (30.2)	16,570 (46.4)
Race, n (%)		
Caucasian	1,798 (88.7)	—
Black	119 (5.9)	—
Asian	55 (2.7)	—
Inuit	19 (0.9)	—
Other	36 (1.8)	—
Mode of HIV exposure, n (%)		
MSM	975 (47.9)	—
Heterosexual	722 (35.5)	—
IDU	210 (10.3)	—
Other	49 (2.4)	—
Unknown	80 (3.9)	—
AIDS at diagnosis, n (%)		
No	1,847 (90.7)	—
Yes	189 (9.3)	—
First CD4 ⁺ count (cells/μL)‡		
<350	999 (49.1)	—
≥350	829 (40.7)	—
missing	208 (10.2)	—
First HIV RNA measurement (copies/mL)‡		
≤10 ⁴	343 (16.9)	—
>10 ⁴ & ≤10 ⁵	622 (30.6)	—
>10 ⁵	660 (32.4)	—
missing	411 (20.2)	—

* Baseline was defined as the index date which was the date of HIV diagnosis for cases and their corresponding controls (matched on the day the case was diagnosed with HIV). † In the 5 years prior to the index date for at least one of the 22 disease categories in Appendix Table 1. ‡ Within 180 days of HIV diagnosis. The table shows data on HIV cases and HIV-uninfected controls with at least 5 years of continuous observation prior to the index date. MSM, men who have sex with men; IDU, injection drug use

Table 2. Specific diseases (diagnosed in the 5 years before the index date) associated with at least 3-fold elevated risk of subsequent HIV diagnosis.

Disease category	Specific disease	Cases n=2,036	Controls n=35,718	aOR (95% CI) ^a
Infections				
STIs and viral hepatitis	Syphilis	15	2	94.7 (20.9 to 429)
STIs and viral hepatitis	Hepatitis A	14	4	41.6 (11.7 to 148)
STIs and viral hepatitis	Non "A" viral hepatitis	77	55	23.6 (16.5 to 33.7)
STIs and viral hepatitis	Anogenital herpes simplex	7	10	12.7 (4.65 to 34.8)
STIs and viral hepatitis	Condyloma	55	95	8.99 (6.32 to 12.8)
STIs and viral hepatitis	Other STIs	18	12	14.8 (6.35 to 34.6)
Lower respiratory tract infections	Unspecified pneumonia	126	290	7.56 (6.03 to 9.48)
Lower respiratory tract infections	Pneumococcal pneumonia	9	14	4.33 (1.63 to 11.5)
Lower respiratory tract infections	Influenza and viral pneumonia	9	43	3.21 (1.51 to 6.81)
CNS infections	Bacterial meningitis	5	9	14.7 (5.63 to 38.1)
CNS infections	Viral meningitis or encephalitis	9	25	6.33 (2.90 to 13.8)
CNS infections	Other CNS infections	9	10	5.51 (1.60 to 19.0)
Skin infections	Abscess, furuncle, carbuncle	137	409	5.15 (4.17 to 6.35)
Skin infections	Fungal skin infections	3	11	4.41 (1.18 to 16.5)
Skin infections	Erysipelas	25	76	3.92 (2.39 to 6.45)
Skin infections	Other skin infections	45	95	5.29 (3.56 to 7.86)
Other infections	Herpes zoster	22	8	33.7 (14.3 to 79.6)
Other infections	Candida infection	40	22	25.5 (14.6 to 44.6)
Other infections	Endocarditis	11	7	23.2 (8.71 to 61.9)
Other infections	Tuberculosis and other mycobacterial infections	24	21	15.2 (7.99 to 29.1)
Other infections	Malaria	10	12	9.53 (3.86 to 23.5)
Other infections	Mononucleosis	11	19	8.64 (4.04 to 18.5)
Other infections	Lymphangitis	5	8	7.88 (2.40 to 25.9)
Other infections	Unspecified viral illness	23	44	7.87 (4.56 to 13.6)
Other infections	Sepsis	23	34	4.90 (2.52 to 9.52)
Other infections	Infectious gastroenteritis	50	216	3.48 (2.49 to 4.87)
Other infections	Other types of infection	67	182	4.77 (3.46 to 6.56)
Haematological diseases and cancers				
Haematological diseases	Thrombocytopenia	15	10	24.0 (10.5 to 54.7)
Haematological diseases	Unspecified anaemia	24	44	7.26 (4.19 to 12.6)
Haematological diseases	Lymphoma	18	43	5.83 (3.22 to 10.5)
Haematological diseases	Aplastic and other specified anaemias	7	17	4.58 (2.38 to 8.79)
Haematological diseases	Lymphadenitis	13	42	3.44 (1.42 to 8.30)
Haematological diseases	Nutrition deficiency anaemia	7	27	3.11 (1.11 to 8.70)
Haematological diseases	Other haematological diseases	5	18	4.30 (1.54 to 12.0)
Non-AIDS defining cancers	Secondary and unspecified malignant neoplasm of lymph nodes	11	22	6.74 (3.14 to 14.5)
Substance abuse and poisoning				
Substance abuse	Substance abuse opioids	69	17	43.5 (24.6 to 76.8)
Substance abuse	Substance abuse other	51	55	6.54 (4.07 to 10.5)
Drug poisoning	Narcotics and hallucinogens	47	43	11.2 (7.08 to 17.8)
Other disease categories				
Ear, nose, and throat diseases	Other acute upper respiratory tract infection	10	30	5.02 (2.38 to 10.6)
Ear, nose, and throat diseases	Chronic disease of tonsils and adenoids	43	129	4.95 (3.45 to 7.09)
Skin diseases	Seborrheic dermatitis	9	8	11.8 (4.30 to 32.6)
Gastrointestinal diseases	Fissure/abscess of anal and rectal regions	50	202	4.35 (2.87 to 6.61)
Gastrointestinal diseases	Liver diseases	31	103	4.06 (2.27 to 7.25)
Gastrointestinal diseases	Disease of salivary glands, oral mucosa, tongue and lips	15	58	3.97 (2.88 to 5.48)
Lung diseases	Respiratory disease principally affecting the interstitium	7	13	9.22 (3.63 to 23.4)
Lung diseases	Lung abscess/empyema without pneumonia	5	11	6.42 (2.16 to 19.1)
Lung diseases	Pneumothorax	8	40	3.25 (1.98 to 5.35)
Lung diseases	Other lung diseases	21	95	3.00 (1.37 to 6.55)
Non-IHD vascular diseases	Thrombophlebitis	34	106	5.29 (3.51 to 7.96)
Neurological diseases	Facial nerve disorder	8	31	3.04 (1.46 to 6.35)
Neurological diseases	Polyneuropathy	9	47	4.52 (2.07 to 9.85)

Rheumatological diseases	Infectious arthropathy	14	75	3.18 (1.76 to 5.74)
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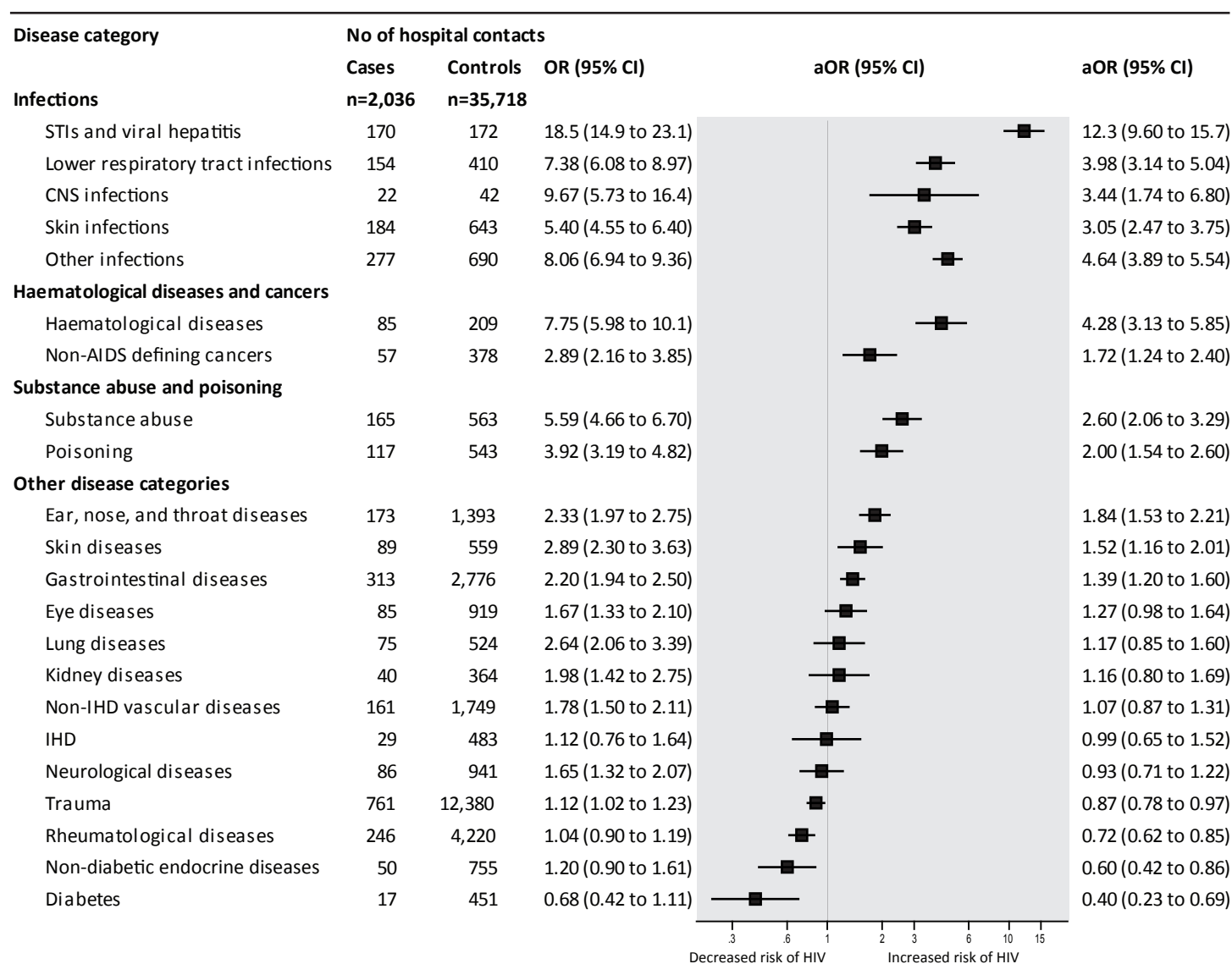
^a Adjusted for other diseases within the same disease category (Appendix Table 1). Risk estimates for all 161 subcategories are shown in Appendix Table 2. aOR, adjusted odds ratio; CI, confidence interval; STIs, sexually transmitted infections; IHD, ischemic heart disease.

FIGURE LEGENDS

Figure 1. Association between subsequent risk of HIV diagnosis and hospital contact for 22 major disease categories in the 5 years prior to the index date.

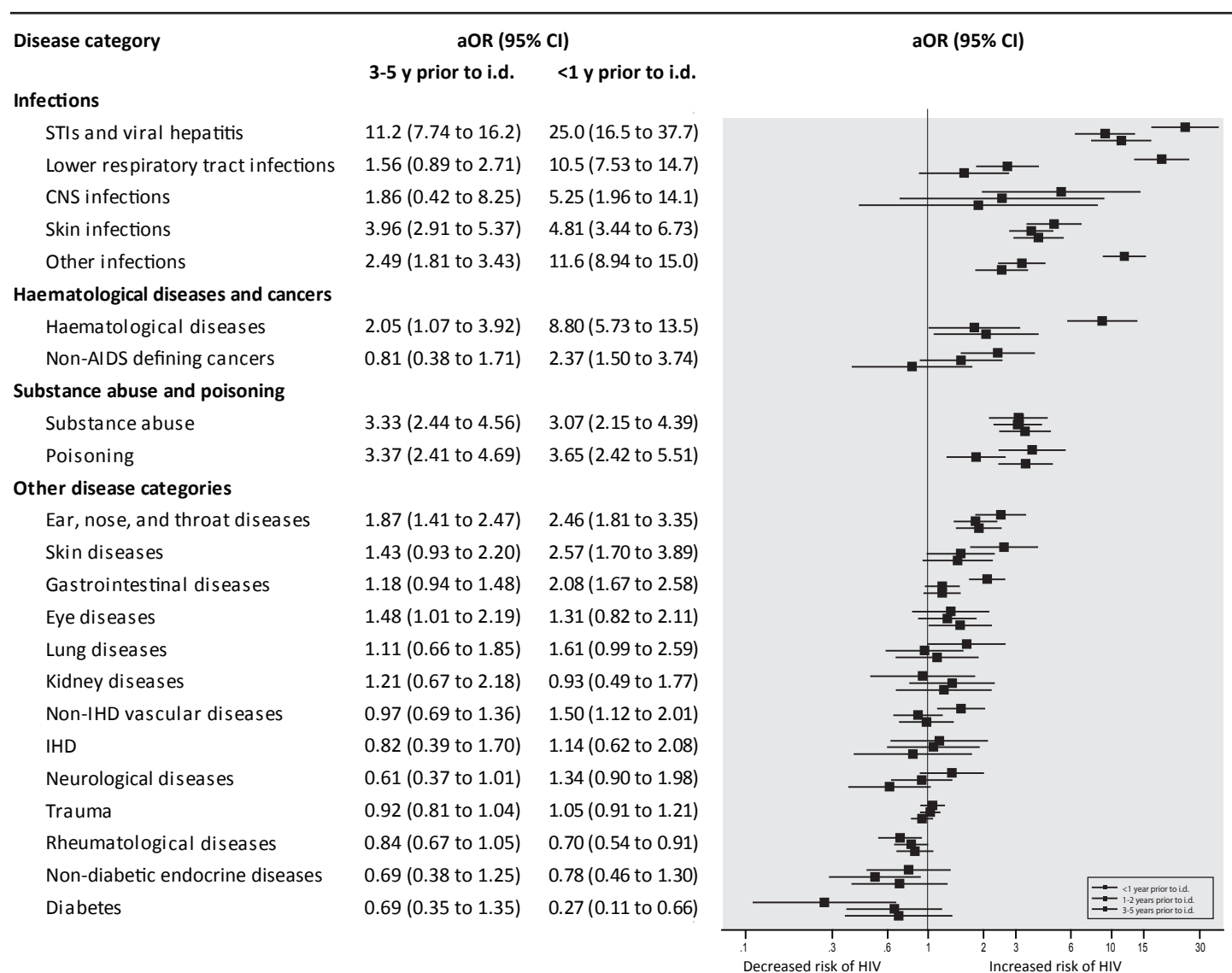
Figure 2. Association between risk of subsequent HIV diagnosis and time of hospital contact.

Figure 1.



Adjusted risk ratio of HIV diagnosis for 22 major disease categories with 95% confidence intervals was determined by conditional logistic regression. Risk estimates are shown as squares with the corresponding confidence intervals shown as lines. The analyses included cases (n=2,036) and their matched controls (n=35,718) with a minimum of 5 years of continuous follow-up prior to the index date, cases and controls. aOR, adjusted odds ratio (adjustment for all other disease categories); CI, confidence interval; i.d., index date; STIs, sexually transmitted infections; IHD, ischaemic heart disease.

Figure 2.



The adjusted odds ratio of subsequent HIV diagnosis for 22 major disease categories with 95% confidence intervals was determined by conditional logistic regression (with adjustment for all other disease categories in the same observation period). Only cases and their respective controls under observation from the beginning of the strata up to the index date were included in each of the analyses. For each disease category three risk estimates are shown as squares with the corresponding 95% confidence intervals shown as lines. In the order from top to bottom the three observation periods are: <1 year prior to index date, cases (n=2,036) and controls (n=35,718); 1-2 years prior to the index date, cases (n=2,036) and controls (n=35,718); 3-5 years prior to the index date, cases (n=2,036) and controls (n=35,718). The exact risk estimates for the first and last observation period are shown in the two columns. aOR, adjusted odds ratio; CI, confidence interval; i.d., index date; STIs, sexually transmitted infections; IHD, ischaemic heart disease.

Supplementary Table 1. *International Classification of Diseases* , version 8 and version 10 codes used for the analyses.

	ICD-8 codes	ICD-10 codes
Sexually transmitted infections (STI) and viral hepatitis	07000-07099, 09000-09999	A50-A649, B15-B199
<i>Subcategory</i>		
Syphilis	09000-09799	A50-A539
Condyloma	09990-09999	A630, A630A
Anogenital herpes simplex		A60-A609
Hepatitis A		B15-B159
Non "A" viral hepatitis	07000-07099	B16-B199
Other STIs	09800-09989	A54-A599, A61-A629, A631-A649
Lower respiratory tract infections (LRTI)	46600-48699, 07399	J09-J229, A481, A709, J851
<i>Subcategory</i>		
Bronchitis and non-specific LRTIs	46600-46699	J20-J229
Influenza and viral pneumonia	47000-48099	J09-J129
Pneumococcal pneumonia	48100-48199	J13-J139
Other bacterial pneumonia	07399, 48200-48299	A481, A709, J14-J159
Unspecified pneumonia	48300-48699	J16-J189, J851
CNS infections	03609, 06200-06599, 07929 32000-32409	G00-G099, A390, A81-A899
<i>Subcategory</i>		
Bacterial meningitis	03609, 32000-32019	A390, G00-G019
Viral meningitis or encephalitis	06200-06599, 07929	A81-A899
Other CNS infections	32020-32409	G02-G099
Skin infections	68000-68299, 68400-68699, 03599	L00-L039, L05-L089, A46-A469, B35-B369
<i>Subcategory</i>		
Erysipelas	03599	A46-A469, L032
Pilonidal cyst	68500-68599	L05-L059
Abscess, furuncle, carbuncle	68200-68299	L02-L031, L033-L039
Fungal skin infections		B35-B369
Other skin infections	68000-68199, 68400-68499, 68600-68699	L00-L019, L08-L089
Other infections	00009-03590, 03610-06199, 06600-06999, 07100-07390, 07400-07982, 07984-08999, 10000-13499, 13600-13609, 42100-42199, 57193, 59009- 59099, 59500-59509, 59700- 59709	A00-A020, A022-A071, A078-A099, A15- A310-389, A391-A459, A47-A480, A482- A499, A65-A708, A71-A809, A900-B149, B25- B251, B258-B299, B31-B349, B370, B372- B379, B40-B450, B459-B581, B583-B589, B60-B999, I33-I339, I38-I399, I891-I891C, K930, N10-N129, N300-N309, N34-N341, N390, O230-D0234
<i>Subcategory</i>		
Infectious gastroenteritis	00009-00999	A00-A020, A022-A071, A078-A099
Malaria	08400-08499	B50-B549
Mononucleosis	07500-07509	B27-B279
Candida infections		B370, B372-B379
Herpes zoster	05300-05399	B019-B029
Sepsis	03800-03899	A40-A419
Pyelonephritis	59000-59019	N10-N129
Cystitis	59500-59509	N300-N309
Endocarditis	42100-42199	I33-I339, I38-I399

Mycobacterial infections including tuberculosis	01100-01999	A15-A199, A311-A319, B90-B909
Lymphangitis		I891-I891C
Unspecified viral illness	07999	B349
Other specified infections	<i>remaining codes</i>	<i>remaining codes</i>
Haematological disease	20100-20199, 28000-28999	C81-C833, C835-C836, C838-C859, D50-D779, I880-I889
<i>Subcategory</i>		
Nutrition deficiency anaemia	28000-28199	D50-D539
Hemolytic anaemia	28200-28399	D50-D539
Unspecified anaemia	28599	D649
Aplastic and other specified anaemia	28400-28589	D60-D648
Coagulation defect, purpura and non-thrombocytopenic hemorrhagic dis.	28600-28709, 28720-28799	D65-D692, D698-D699
Thrombocytopenia	28710-28719	D693-D696
Lymphadenitis	28910-28939, 68300-68399	L04-L049, I880-I889
Lymphoma	20100-20199	C81-C833, C835-C836, C838-C859
Other haematological diseases	<i>remaining codes</i>	<i>remaining codes</i>
Non-AIDS defining cancers	14009-17409, 18100-20799	C00-C459, C47-C529, C54-C833, C835-C836, C838-C999
<i>Subcategory</i>		
Digestive tract cancer	14009-15999	C00-C269
Respiratory tract cancer	16000-16999	C30-C399
Malignant skin cancer	17200-17399	C43-C449
Secondary and unspecified malignant neoplasm of lymph nodes	19600-19699	C77-C779
Genital cancer	18100-18799	C51-C529, C54-C639
Other cancer type	<i>remaining codes</i>	<i>remaining codes</i>
Substance abuse	29100-29199, 30309-30499	F10-F199
<i>Subcategory</i>		
Substance abuse alcohol	29100-29199, 30300-30399	F10-F109
Substance abuse opioids	30400-30419	F11-F119
Substance abuse other	30420-30499	F12-F199
Drug poisoning	96000-98999	T36-T659
<i>Subcategory (poisoning by)</i>		
Narcotics and hallucinogens	96500-96509, 96790-96799	T40-T409
Other psychotropic drugs	97000-97199	T43-T439
Nonopioid analgesics, antipyretics and antirheumatics	96510-96599	T39-T399
Antiepileptic, sedative-hypnotic and antiparkinsonism drugs	96700-96789	T42-T429
Systemic antibiotics, other systemic anti-infectives and antiparasitics	96000-96199	T36-T379
Alcohol	97900-98099	T51-T519
Other substances	<i>remaining codes</i>	<i>remaining codes</i>
Ear, nose, and throat diseases	38000-38999, 46000-46599, 50000-50999	H60-H959, J00-J069, J30-J399
Acute pharyngitis and sinusitis	46100-46299	J01-J029
Acute tonsillitis	46300-46399	J03-J039
Other acute upper resp. tract infections	46000-46099, 46400-46599	J00-J009, J04-J069
Chronic pharyngitis and sinusitis	50200-50399	J31-J329
Chronic disease of tonsils and adenoids	50000-50099	J35-J359

Peritonsillar abscess	50100-50199	J36-J369
Other chronic upper respiratory tract disorders	50400-50999	J30-J309, J33-J349, J37-J399
Diseases of external ear	38000-38099	H60-H629
Diseases of middle ear and mastoid	38100-38399, 38700-38799	H65-H759
Diseases of inner ear	38400-38699	H80-H839
Other ear disorders	38800-38999	H90-H959
Skin diseases	69000-69539, 69550-70999	L10-L999
<i>Subcategory</i>		
Atopic dermatitis	69100-69199	L20-L209
Seborrhoeic dermatitis	69000-69099	L21-L219
Other dermatitis and eczema	69200-69299	L22-L309
Papulosquamous disorder	69600-69799	L40-L459
Urticaria and erythema	69500-69539, 69550-69559, 70800-70899	L50-L549
Other skin diseases	<i>remaining codes</i>	<i>remaining codes</i>
Gastrointestinal diseases	52009-57192, 57194-57799	K00-K929, K931-K939
<i>Subcategory</i>		
Disorder of jaws, teeth and supporting structures	52009-52699	K00-K109
Disease of salivary glands, oral mucosa, tongue and lips	52700-52999	K11-K149
Disease of esophagus	53000-53099	K20-K239
Gastric, duodenal, peptic, and gastro-jejunal ulcer	53100-53499	K25-K289
Gastritis and duodenitis	53500-53599	K29-K299
Dyspepsia	53600-53699	K30-K309
Appendicitis	54000-54299	K35-K379
Hernia	54400-55399	K40-K469
Non-infective enteritis and colitis	56100-56199	K50-K529
Fissure/abscess of anal and rectal regions	56500-56699	K60-K619
Other disease of intestines and peritoneum	56200-56499, 56700-56999	K55-K599, K62-K679
Liver disease	57000-57192, 57194-57399	K70-K779
Disorder of gallbladder and biliary tract	57400-57699	K80-K839
Pancreatitis	57700-57719	K85-K862
Other gastrointestinal disease	<i>remaining codes</i>	<i>remaining codes</i>
Eye diseases	36000-37999	B30-B309, H00-H279, H281-H359, H361-H599
<i>Subcategory</i>		
Disorder of eyelid, lacrimal system, and orbit	36100-36299, 36800-36899	H00-H069
Conjunctivitis	36100-36199	H10-H109
Disorder of sclera, cornea, iris, and ciliary body	36300-36599	H15-H229
Disorders of lens	37400-37499	H25-H279, H281-H289
Other eye disease	<i>remaining codes</i>	<i>remaining codes</i>
Lung diseases	49000-49999, 51000-51999	J40-J850, J852-J999
<i>Subcategory</i>		
Chronic bronchitis	49000-49199	J40-J429
COPD		J44-J449
Asthma	49300-49399	J45-J469
Pneumothorax	51200-51299	J93-J939

Lung abscess/empyema without pneumonia	51000-51099, 51300-51399	J850, J852-J869
Respiratory disease principally affecting the interstitium	51400-51499, 51700-51799, 51900-51919	J80-J849
Other lung disease	<i>remaining codes</i>	<i>remaining codes</i>
Kidney diseases	58000-58499, 59109-59409, 59510-59609, 59800-59999	N00-N088, N13-N298, N31-N338, N342-N389
<i>Subcategory</i>		
Glomerular disease	58000-58499	N00-N088
Acute, chronic and unspecified renal failure	59310-59329	N17-N199
Urolithiasis	59200-59299, 59400-59499	N20-N239
Other kidney diseases	<i>remaining codes</i>	<i>remaining codes</i>
Non-IHD cardiovascular diseases	39000-40499, 42000-42009, 42200-44599, 44700-45899	I00-I159, I26-I328, I34-I379, I40-I879, I890, I892-I999, G45-G459
<i>Subcategory</i>		
Hypertension	40000-40499	I10-I159
Pulmonary heart disease	42600-42699	I26-I289
Peri- and myocarditis	42000-42009, 42200-42299	I30-I309, I40-I419
Cardiomyopathy	42500-42599	I42-I429
Arrhythmia	42740-42799	I44-I499
Heart failure	42700-42719	I50-I509
Heart valve disease	39400-39709, 42400-42499	I34-I379
Ischaemic cerebral event	43200-43599	G45-G459, I63-I639
Subarachnoidal/cerebral haemorrhage	43000-43199	I60-I629
Other cerebral vascular diseases	43600-43899	I64-I699
Arterial and capillary diseases	44000-44599, 44700-44899	I70-I799
Thrombophlebitis	45100-45199	I80-I809
Varicose veins of lower extremities	45400-45499	I83-I839
Hemorrhoids	45500-45599	I84-I849
Other non-IHD vascular diseases	<i>remaining codes</i>	<i>remaining codes</i>
Ischaemic heart disease (IHD)	41000-41499	I20-I259
<i>Subcategory</i>		
Angina pectoris	41300-41399	I20-I209
Myocardial infarction	41000-41099	I21-I239
Other IHDs	41100-41299, 41400-41499	I24-I259
Neurological diseases	33000-35809, 73300-73319	G10-G449, G46-G999
<i>Subcategory</i>		
Hereditary, atrophic, extrapyramidal, and degenerative CNS disease	33000-33399	G10-G329
Multiple sclerosis and other demyelinating CNS disease	34000-34099	G35-G379
Epilepsy, migraine and other episodic CNS disorder	34500-34709	G40-G449, G46-G479
Facial nerve disorder	35000-35099	G51-G519
Other nerve, nerve root, plexus disorder	35100-35399, 35600-35799	G50-G509, G52-G599
Polyneuropathy	35400-35499	G60-G649
Neuromuscular, muscular, and other neurological diseases	<i>remaining codes</i>	<i>remaining codes</i>
Trauma	80000-95999, 99000-99699	S00-T357, T66-T758
<i>Subcategory</i>		
<i>Injuries to</i>		

Head	80000-80499, 83000-83099, 85000-85999, 87000-87399, 91000-91099, 92000-92199	S00-S099
Neck	80500-80619, 87400-87499	S10-S199
Thorax	80700-80799, 80900-80999, 86000-86299, 87500-87699, 91100-91199, 92200-92299	S20-S299
Abdomen, lower back, lumbar spine, pelvis	80620-80699, 80800-80899, 84600-84799, 86300-86999, 87700-87899	S30-S399
Shoulder and upper arm	81000-81299, 83100-83199, 84000-84099, 88000-88099, 91200-91299, 92300-92399	S40-S499
Elbow and forearm	81300-81399, 83200-83299, 84100-84199, 88100-88199, 91300-91399, 92400-92499	S50-S599
Wrist and hand	81400-81799, 83300-83499, 84200-84299, 88200-88399, 88500-88699, 91400-91599, 92500-92699	S60-S699
Hip and thigh	82000-82199, 83500-83599, 84300-84399, 89000-89099	S70-S799
Knee and lower leg	82200-82399, 83600-83699, 84400-84499, 89100-89199	S80-S899
Ankle and foot	82400-82699, 83700-83899, 84500-84599, 89200-89399, 89500-89699, 91700-91799, 92800-92899	S90-S999
Multiple body regions or unspecified part of trunk, limb or body region	82700-82999, 81800-81999, 83900-83999, 84800-84899, 87900-87999, 88400-88499, 88700-88799, 89400-89499, 89700-89799, 90000-90999, 91600-91699, 91800-91899, 92700-92799, 92900-92999	T00-S149
Effects of foreign body entering through natural orifice	93000-93999	T15-T199
Burns, corrosions, and frostbites	94000-94999, 99100-99199	T20-T357
Other/unspecified effects of external cause	99000-99099, 99200-99699	T66-T758
Other injuries	<i>remaining codes</i>	<i>remaining codes</i>
Rheumatological diseases	44600-44699, 69549, 71000- 73299, 73320-73809	M00-M999
<i>Subcategory</i>		
Infectious arthropathy	71000-71199, 71490	M00-M039
Inflammatory arthropathy	71200-71299	M05-M149
Arthrosis		M15-M199
Other joint disorders	71300-71489, 71500-71599	M20-M259
Systemic connective tissue disorders	71600-71699, 73400-73499, 44600-44699	M30-M369
Dorsopathy	72500-72699, 72800-72899, 73500-73599	M40-M549
Disorder of muscle, synovium, tendon	73100-73399	M60-M689
Disorders of bone density and structure	72300-72309	M80-M859
Other rheumatological diseases	<i>remaining codes</i>	<i>remaining codes</i>

Non-diabetic endocrine diseases	24000-24609, 25100-27909	E00-E079, E15-E909
<i>Subcategory</i>		
Thyroid diseases	24000-24609	E00-E079
Obesity	27700-27799	E65-E689
Metabolic disorder	27000-27699, 27800-27909	E70-E909
Other endocrine disorder	<i>remaining codes</i>	<i>remaining codes</i>
Diabetes mellitus (DM)	24900-25099	E10-E149, G590, G632, H280, H360, M142, N083
<i>Subcategory</i>		
DM insulin dependent	24900-24999	E10-E109
DM insulin independent	25000-25099	E11-E119
Unspecified DM		E12-E149, G590, G632, H280, H360, M142, N083

Supplementary Table 2. Supplementary Table 2 (section 1 to 22) contains information and risk estimates on subcategorized disease groups for each of the 22 major disease categories. First-time diagnoses within each disease group were recorded if occurring less than 5 years prior to index date. Unadjusted odds ratio [OR] and adjusted odds ratio [aOR] for all other variables within the same disease category are shown with 95% confidence intervals [95% CI]. The number of persons in the analyses were: Cases (n=2,036) and controls (n=35,718)

Section 1: Sexually transmitted infections (STIs) and viral hepatitis

Disease	Hospital contacts		OR (95% CI)	aOR (95% CI)
	Cases	Controls		
Syphilis	15	2	135 (30.8 to 590)	94.7 (20.9 to 429)
Condyloma	55	95	9.92 (7.09 to 13.9)	8.99 (6.32 to 12.8)
Anogenital herpes simplex	7	10	11.9 (4.52 to 31.2)	12.7 (4.65 to 34.8)
Hepatitis A	14	4	62.1 (20.4 to 189)	41.6 (11.7 to 148)
Non "A" viral hepatitis	77	55	25.1 (17.7 to 35.7)	23.6 (16.5 to 33.7)
Other STIs	18	12	26.1 (12.6 to 54.2)	14.8 (6.35 to 34.6)

Section 2: Lower respiratory tract infections (LRTIs)

Disease	Hospital contacts		OR (95% CI)	aOR (95% CI)
	Cases	Controls		
Bronchitis and non-specific LRTIs	8	55	2.62 (1.24 to 5.54)	1.47 (0.66 to 3.28)
Influenza and viral pneumonia	9	43	3.69 (1.79 to 7.61)	3.21 (1.51 to 6.81)
Pneumococcal pneumonia	9	14	11.0 (4.75 to 25.4)	4.33 (1.63 to 11.5)
Other bacterial pneumonia	17	42	7.40 (4.20 to 13.0)	2.79 (1.44 to 5.40)
Unspecified pneumonia	126	290	8.47 (6.81 to 10.5)	7.56 (6.03 to 9.48)

Section 3: CNS infections

Disease	Hospital contacts		OR (95% CI)	aOR (95% CI)
	Cases	Controls		
Bacterial meningitis	5	9	9.53 (3.19 to 28.5)	5.51 (1.60 to 19.0)
Viral meningitis and encephalitis	9	25	6.64 (3.08 to 14.3)	6.33 (2.90 to 13.8)
Other CNS infections	9	10	17.0 (6.74 to 43.1)	14.7 (5.63 to 38.1)

Section 4: Skin infections

Disease	Hospital contacts		OR (95% CI)	aOR (95% CI)
	Cases	Controls		
Erysipelas	25	76	5.82 (3.69 to 9.17)	3.92 (2.39 to 6.45)
Pilonidal cyst	8	85	1.58 (0.76 to 3.27)	1.26 (0.60 to 2.66)
Abscess, furuncle, and carbuncle	137	409	6.22 (5.10 to 7.59)	5.15 (4.17 to 6.35)
Fungal skin infections	3	11	4.80 (1.34 to 17.2)	4.41 (1.18 to 16.5)
Other skin infections	45	95	8.80 (6.12 to 12.7)	5.29 (3.56 to 7.86)

Section 5: Other infections

Disease	Hospital contacts		OR (95% CI)	aOR (95% CI)
	Cases	Controls		
Infectious gastroenteritis	50	216	4.15 (3.03 to 5.68)	3.48 (2.49 to 4.87)
Malaria	10	12	14.5 (6.28 to 33.7)	9.53 (3.86 to 23.5)
Mononucleosis	11	19	9.49 (4.51 to 20.0)	8.64 (4.04 to 18.5)
Candida infection	40	22	33.8 (19.9 to 57.3)	25.5 (14.6 to 44.6)
Herpes zoster	22	8	49.2 (21.9 to 110)	33.7 (14.3 to 79.6)
Sepsis	23	34	12.1 (7.12 to 20.7)	4.90 (2.52 to 9.52)
Pyelonephritis	12	40	5.23 (2.74 to 9.97)	2.63 (1.25 to 5.51)
Cystitis	29	136	3.85 (2.57 to 5.78)	2.45 (1.55 to 3.87)
Endocarditis	11	7	27.0 (10.4 to 69.6)	23.2 (8.71 to 61.9)
Mycobacterial infections including tuberculosis	24	21	20.2 (11.3 to 36.4)	15.2 (7.99 to 29.1)

Lymphangitis	5	8	10.6 (3.46 to 32.5)	7.88 (2.40 to 25.9)
Unspecified viral illness	23	44	9.18 (5.53 to 15.2)	7.87 (4.56 to 13.6)
Other types of infection	67	182	6.73 (5.06 to 8.95)	4.77 (3.46 to 6.56)

Section 6: Haematological diseases

Disease	Hospital contacts		OR (95% CI)	aOR (95% CI)
	Cases	Controls		
Nutrition deficiency anaemia	7	27	4.61 (2.01 to 10.6)	3.44 (1.42 to 8.30)
Hemolytic anaemia	2	7	5.06 (1.05 to 24.4)	2.70 (0.47 to 15.5)
Unspecified anaemia	24	44	10.3 (6.24 to 17.2)	7.26 (4.19 to 12.6)
Aplastic and other specified anaemias	7	17	7.28 (3.02 to 17.6)	3.11 (1.11 to 8.70)
Coagulation defect, purpura and non-thrombocytopenic haemorrhagic dis.	5	23	3.83 (1.45 to 10.1)	1.35 (0.38 to 4.84)
Thrombocytopenia	15	10	26.7 (12.0 to 59.6)	24.0 (10.5 to 54.7)
Lymphadenitis	13	42	5.56 (2.97 to 10.4)	4.58 (2.38 to 8.79)
Lymphoma	18	43	7.70 (4.41 to 13.4)	5.83 (3.22 to 10.5)
Other haematological diseases	5	18	5.02 (1.86 to 13.5)	4.30 (1.54 to 12.0)

Section 7: Non-AIDS defining cancers

Disease	Hospital contacts		OR (95% CI)	aOR (95% CI)
	Cases	Controls		
Digestive tract cancer	7	54	2.44 (1.11 to 5.37)	1.76 (0.76 to 4.11)
Respiratory tract cancer	4	24	3.11 (1.08 to 8.97)	2.10 (0.70 to 6.31)
Malignant skin cancer	18	117	2.85 (1.72 to 4.71)	2.77 (1.67 to 4.60)
Secondary and unspecified malignant neoplasm of lymph nodes	11	22	9.10 (4.41 to 18.8)	6.74 (3.14 to 14.5)
Genital cancer	6	83	1.32 (0.57 to 3.03)	1.02 (0.43 to 2.43)
Other cancer types	18	111	3.02 (1.82 to 4.99)	2.28 (1.33 to 3.92)

Section 8: Substance abuse

Disease	Hospital contacts		OR (95% CI)	aOR (95% CI)
	Cases	Controls		
Substance abuse alcohol	97	520	3.45 (2.76 to 4.32)	2.31 (1.79 to 2.98)
Substance abuse opioids	69	17	73.9 (42.9 to 127)	43.5 (24.6 to 76.8)
Substance abuse other	51	55	16.4 (11.2 to 24.1)	6.54 (4.07 to 10.5)

Section 9: Poisoning

Disease	Hospital contacts		OR (95% CI)	aOR (95% CI)
	Cases	Controls		
<i>Poisoning by</i>				
Narcotics and hallucinogens	47	43	18.8 (12.4 to 28.5)	11.2 (7.08 to 17.8)
Other psychotropic drugs	19	51	6.55 (3.85 to 11.1)	2.39 (1.20 to 4.75)
Nonopioid analgesics, antipyretics and antirheumatics	12	60	3.41 (1.83 to 6.36)	1.10 (0.50 to 2.43)
Antiepileptic, sedative-hypnotic and antiparkinsonism drugs	14	29	8.38 (4.42 to 15.9)	1.68 (0.71 to 3.98)
Systemic antibiotics, other systemic anti-infectives and antiparasitics	15	51	5.07 (2.85 to 9.03)	1.90 (0.91 to 3.96)
Alcohol	9	37	4.28 (2.06 to 8.86)	1.74 (0.71 to 4.27)
Other substances	70	358	3.50 (2.70 to 4.55)	2.34 (1.74 to 3.16)

Section 10: Ear, nose, and throat diseases

Disease	Hospital contacts		OR (95% CI)	aOR (95% CI)
	Cases	Controls		
Acute pharyngitis and sinusitis	7	44	2.75 (1.23 to 6.14)	2.45 (1.08 to 5.57)
Acute tonsillitis	16	89	3.01 (1.76 to 5.16)	1.99 (1.12 to 3.54)

Other acute upper respiratory tract infections	10	30	5.91 (2.87 to 12.2)	5.02 (2.38 to 10.6)
Chronic pharyngitis and sinusitis	8	53	2.68 (1.27 to 5.66)	1.95 (0.89 to 4.30)
Chronic disease of tonsils and adenoids	43	129	5.68 (4.01 to 8.05)	4.95 (3.45 to 7.09)
Peritonsillar abscess	13	68	3.28 (1.81 to 5.94)	2.44 (1.30 to 4.56)
Other chronic upper respiratory tract disorders	28	372	1.32 (0.90 to 1.95)	1.04 (0.70 to 1.56)
Diseases of external ear	9	65	2.43 (1.21 to 4.88)	1.89 (0.92 to 3.89)
Diseases of middle ear and mastoid	31	154	3.56 (2.41 to 5.25)	2.88 (1.91 to 4.34)
Diseases of inner ear	14	229	1.13 (0.65 to 1.94)	0.98 (0.55 to 1.73)
Other ear disorders	28	398	1.30 (0.88 to 1.92)	1.15 (0.76 to 1.74)

Section 11: Skin diseases

Disease	Hospital contacts		OR (95% CI)	aOR (95% CI)
	Cases	Controls		
Atopic dermatitis	4	28	2.43 (0.85 to 6.94)	1.40 (0.46 to 4.26)
Seborrhoeic dermatitis	9	8	20.3 (7.83 to 52.6)	11.8 (4.30 to 32.6)
Other dermatitis and eczema	25	120	3.73 (2.42 to 5.76)	2.83 (1.78 to 4.50)
Papulo-squamous disorder	11	68	2.93 (1.54 to 5.57)	1.68 (0.83 to 3.40)
Urticaria and erythema	11	72	2.69 (1.43 to 5.08)	2.21 (1.14 to 4.29)
Other skin diseases	44	314	2.50 (1.82 to 3.44)	2.11 (1.51 to 2.95)

Section 12: Gastrointestinal diseases

Disease	Hospital contacts		OR (95% CI)	aOR (95% CI)
	Cases	Controls		
Disorder of jaws, teeth and supporting structures	33	224	2.59 (1.79 to 3.74)	2.25 (1.54 to 3.28)
Disease of salivary glands, oral mucosa, tongue and lips	15	58	4.57 (2.59 to 8.07)	4.06 (2.27 to 7.25)
Disease of esophagus	31	269	2.09 (1.44 to 3.05)	1.55 (1.04 to 2.32)
Gastric, duodenal, peptic, and gastro-jejunal ulcer	25	193	2.36 (1.55 to 3.58)	1.43 (0.91 to 2.26)
Gastritis and duodenitis	39	211	3.36 (2.38 to 4.74)	2.33 (1.60 to 3.38)
Dyspepsia	19	183	1.86 (1.16 to 2.99)	1.48 (0.90 to 2.41)
Appendicitis	14	234	1.03 (0.60 to 1.77)	1.00 (0.58 to 1.72)
Hernia	38	690	0.99 (0.71 to 1.38)	0.82 (0.58 to 1.15)
Non-infective enteritis and colitis	28	209	2.40 (1.62 to 3.57)	1.75 (1.14 to 2.67)
Fissure/abscess of anal and rectal regions	50	202	4.41 (3.23 to 6.04)	3.97 (2.88 to 5.48)
Other disease of intestines and peritoneum	42	431	1.76 (1.27 to 2.42)	1.12 (0.80 to 1.59)
Liver diseases	31	103	5.42 (3.62 to 8.10)	4.35 (2.87 to 6.61)
Disorder of gallbladder and biliary tract	27	248	1.97 (1.32 to 2.95)	1.53 (1.01 to 2.33)
Pancreatitis	15	93	2.89 (1.67 to 5.00)	1.64 (0.92 to 2.94)
Other gastrointestinal diseases	22	118	3.39 (2.14 to 5.36)	1.80 (1.09 to 2.97)

Section 13: Eye disease

Disease	Hospital contacts		OR (95% CI)	aOR (95% CI)
	Cases	Controls		
Disorder of eyelid, lacrimal system, orbit	11	102	1.91 (1.02 to 3.58)	1.80 (0.96 to 3.39)
Conjunctivitis	36	291	2.20 (1.55 to 3.13)	2.13 (1.50 to 3.04)
Disorders of sclera, cornea, iris, and ciliary body	12	119	1.76 (0.97 to 3.19)	1.51 (0.82 to 2.77)
Disorders of lens	6	137	0.80 (0.35 to 1.82)	0.69 (0.30 to 1.60)
Other eye diseases	28	399	1.26 (0.85 to 1.85)	1.20 (0.81 to 1.78)

Section 14: Lung diseases

Disease	Hospital contacts		OR (95% CI)	aOR (95% CI)
	Cases	Controls		
Chronic bronchitis	5	62	1.48 (0.59 to 3.69)	0.72 (0.27 to 1.92)
COPD	18	109	3.19 (1.91 to 5.31)	2.69 (1.56 to 4.67)
Asthma	25	272	1.62 (1.07 to 2.45)	1.33 (0.86 to 2.05)
Pneumothorax	8	40	3.56 (1.66 to 7.62)	3.00 (1.37 to 6.55)

Lung abscess/empyema without pneumonia	5	11	8.00 (2.77 to 23.1)	6.42 (2.16 to 19.1)
Respiratory disease principally affecting the interstitium	7	13	9.60 (3.83 to 24.1)	9.22 (3.63 to 23.4)
Other lung diseases	21	95	4.03 (2.50 to 6.49)	3.25 (1.98 to 5.35)

Section 15: Kidney diseases

Disease	Hospital contacts		OR (95% CI)	aOR (95% CI)
	Cases	Controls		
Glomerular disease	6	38	2.78 (1.17 to 6.60)	2.60 (1.03 to 6.54)
Acute, chronic and unspecified renal failure	4	48	1.51 (0.55 to 4.20)	0.96 (0.32 to 2.90)
Urolithiasis	17	196	1.56 (0.95 to 2.57)	1.48 (0.89 to 2.44)
Other kidney diseases	14	124	2.01 (1.15 to 3.49)	1.82 (1.03 to 3.22)

Section 16: Non-IHD cardiovascular diseases

Disease	Hospital contacts		OR (95% CI)	aOR (95% CI)
	Cases	Controls		
Hypertension	19	504	0.69 (0.43 to 1.09)	0.58 (0.36 to 0.93)
Pulmonary heart disease	7	36	3.52 (1.57 to 7.92)	1.60 (0.65 to 3.93)
Peri- and myocarditis	2	35	1.02 (0.24 to 4.26)	0.85 (0.20 to 3.58)
Cardiomyopathy	4	38	1.86 (0.66 to 5.22)	1.03 (0.33 to 3.25)
Arrhythmia	22	328	1.22 (0.79 to 1.89)	1.09 (0.69 to 1.73)
Heart failure	12	85	2.62 (1.42 to 4.83)	2.31 (1.16 to 4.63)
Heart valve diseases	4	62	1.18 (0.43 to 3.24)	0.86 (0.30 to 2.44)
Ischaemic cerebral event	19	143	2.50 (1.54 to 4.06)	2.59 (1.46 to 4.58)
Subarachnoidal/cerebral haemorrhage	2	46	0.78 (0.19 to 3.20)	0.63 (0.15 to 2.67)
Other cerebral vascular diseases	13	158	1.54 (0.87 to 2.73)	0.96 (0.48 to 1.90)
Arterial and capillary diseases	16	176	1.70 (1.01 to 2.85)	1.36 (0.79 to 2.34)
Thrombophlebitis	34	106	5.87 (3.97 to 8.69)	5.29 (3.51 to 7.96)
Varicose veins of lower extremities	15	192	1.41 (0.83 to 2.40)	1.23 (0.72 to 2.12)
Hemorrhoids	19	217	1.57 (0.98 to 2.52)	1.56 (0.97 to 2.50)
Other non-IHD vascular diseases	14	106	2.33 (1.33 to 4.07)	1.77 (0.98 to 3.18)

Section 17: Ischemic heart disease (IHD)

Disease	Hospital contacts		OR (95% CI)	aOR (95% CI)
	Cases	Controls		
Angina pectoris	19	331	1.07 (0.67 to 1.71)	0.97 (0.55 to 1.72)
Myocardial infarction	10	195	0.95 (0.50 to 1.81)	0.81 (0.39 to 1.69)
Other IHDs	16	242	1.24 (0.74 to 2.08)	1.38 (0.71 to 2.66)

Section 18: Neurological diseases

Disease	Hospital contacts		OR (95% CI)	aOR (95% CI)
	Cases	Controls		
Hereditary, atrophic, extrapyramidal, and degenerative CNS disease	6	38	2.83 (1.19 to 6.72)	2.43 (1.00 to 5.93)
Multiple sclerosis and other demyelinating CNS disease	1	49	0.37 (0.05 to 2.67)	0.36 (0.05 to 2.59)
Epilepsy, migraine and other episodic CNS disorder	46	482	1.70 (1.25 to 2.31)	1.64 (1.21 to 2.24)
Facial nerve disorder	8	31	4.53 (2.08 to 9.86)	4.52 (2.07 to 9.85)
Other nerve, nerve root, plexus disorder	13	252	0.93 (0.53 to 1.62)	0.87 (0.50 to 1.54)
Polyneuropathy	9	47	3.49 (1.71 to 7.12)	3.04 (1.46 to 6.35)
Neuromuscular, muscular, and other neurological diseases	6	103	1.03 (0.45 to 2.34)	0.85 (0.37 to 1.96)

Section 19: Trauma

Disease	Hospital contacts		OR (95% CI)	aOR (95% CI)
	Cases	Controls		
<i>Injuries to</i>				

Head	286	3,010	1.77 (1.55 to 2.03)	1.68 (1.46 to 1.94)
Neck	24	432	0.95 (0.63 to 1.44)	0.69 (0.45 to 1.06)
Thorax	83	618	2.42 (1.92 to 3.07)	2.01 (1.56 to 2.58)
Abdomen, lower back, lumbar spine, and pelvis	42	404	1.81 (1.31 to 2.50)	1.30 (0.93 to 1.83)
Shoulder and upper arm	58	1,002	1.01 (0.77 to 1.32)	0.79 (0.60 to 1.04)
Elbow and forearm	93	1,131	1.46 (1.17 to 1.81)	1.32 (1.05 to 1.65)
Wrist and hand	240	4,674	0.87 (0.76 to 1.00)	0.78 (0.67 to 0.90)
Hip and thigh	45	366	2.18 (1.59 to 2.98)	1.73 (1.24 to 2.40)
Knee and lower leg	141	2,582	0.94 (0.79 to 1.13)	0.83 (0.69 to 1.00)
Ankle and foot	153	2,905	0.90 (0.75 to 1.06)	0.83 (0.70 to 0.99)
Multiple body regions or unspecified part of trunk, limb or body region	1	42	0.40 (0.05 to 2.91)	0.28 (0.04 to 2.06)
<i>Other traumas</i>				
Effects of foreign body entering through natural orifice	48	1,057	0.78 (0.58 to 1.05)	0.70 (0.52 to 0.94)
Burns, corrosions, and frostbites	22	338	1.12 (0.73 to 1.74)	1.01 (0.65 to 1.57)
Other/unspecified effects of external cause	8	75	1.83 (0.88 to 3.80)	1.58 (0.75 to 3.33)
Other injuries	105	681	2.80 (2.26 to 3.46)	2.48 (1.99 to 3.10)

Section 20: Rheumatological diseases

Disease	Hospital contacts		OR (95% CI)	aOR (95% CI)
	Cases	Controls		
Infectious arthropathy	14	75	3.28 (1.85 to 5.80)	3.18 (1.76 to 5.74)
Inflammatory arthropathy	16	183	1.59 (0.95 to 2.66)	1.36 (0.80 to 2.33)
Arthrosis	17	429	0.72 (0.44 to 1.18)	0.73 (0.44 to 1.20)
Other joint disorders	39	1,096	0.61 (0.44 to 0.85)	0.60 (0.43 to 0.83)
Systemic connective tissue disorders	6	54	1.98 (0.85 to 4.61)	1.81 (0.77 to 4.25)
Dorsopathy	85	1,227	1.25 (1.00 to 1.56)	1.23 (0.98 to 1.55)
Disorder of muscle, synovium, and tendon	51	734	1.22 (0.91 to 1.62)	1.21 (0.90 to 1.62)
Disorders of bone density and structure	8	72	2.01 (0.97 to 4.20)	2.02 (0.97 to 4.24)
Other rheumatological diseases	75	1,297	1.02 (0.81 to 1.30)	1.02 (0.80 to 1.29)

Section 21: Non-diabetic endocrine diseases

Disease	Hospital contacts		OR (95% CI)	aOR (95% CI)
	Cases	Controls		
Thyroid disease	2	166	0.21 (0.05 to 0.87)	0.21 (0.05 to 0.84)
Obesity	8	207	0.69 (0.34 to 1.41)	0.64 (0.31 to 1.31)
Metabolic disorder	31	287	2.02 (1.39 to 2.95)	2.06 (1.41 to 3.01)
Other endocrine disorder	13	149	1.55 (0.87 to 2.73)	1.47 (0.83 to 2.61)

Section 22: Diabetes mellitus (DM)

Disease	Hospital contacts		OR (95% CI)	aOR (95% CI)
	Cases	Controls		
DM insulin dependent	10	244	0.73 (0.39 to 1.38)	0.88 (0.45 to 1.74)
DM insulin independent	9	247	0.67 (0.34 to 1.31)	0.75 (0.38 to 1.51)
Unspecified DM	3	119	0.46 (0.15 to 1.45)	0.55 (0.16 to 1.85)