The Road to Success

Long-term prognosis for persons living with HIV in Denmark -time trends and risk factors

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This review is based on the following papers

I. Søgaard OS, **Lohse N**, Østergaard L, Kronborg G, Røge B, Gerstoft J, Sørensen HT, Obel N. *Morbidity and risk of subsequent diagnosis of HIV: a population based case control study identifying indicator diseases for HIV infection.* **PLoS One. 2012**;7(3):e32538. (1)

II. **Lohse N**, Ladefoged K, Obel N. *Implementation and effectiveness of antiretroviral therapy in Greenland.* **Emerg Infect Dis. 2008** Jan;14(1):56-9. (2)

III. **Lohse N**, Obel N, Kronborg G, Laursen A, Pedersen C, Larsen CS, Kvinesdal B, Sørensen HT, Gerstoft J. *Declining risk of triple-class antiretroviral drug failure in Danish HIV-infected individuals*. **AIDS. 2005** May 20;19(8):815-22. (3)

IV. **Lohse N**, Kronborg G, Gerstoft J, Larsen CS, Pedersen G, Pedersen C, Sørensen HT, Obel N. *Virological control during the first 6-18 months after initiating highly active antiretroviral therapy as a predictor for outcome in HIV-infected patients: a Danish, population-based, 6-year follow-up study.* **Clin Infect Dis. 2006** Jan 1;42(1):136-4. (4)

V. Audelin AM, **Lohse N**, Obel N, Gerstoft J Jørgensen LB. *The incidence rate of HIV type-1 drug resistance in patients on antiretroviral therapy: a nationwide population-based Danish cohort study 1999-2005*. **Antivir Ther 2009**; 14(7):995-1000. (5)

VI. **Lohse N**, Obel N, Kronborg G, Jørgensen LB, Pedersen C, Larsen CS, Kvinesdal B, Sørensen HT, Gerstoft J. *Declining prevalence of HIV-infected individuals at risk of transmitting drug-resistant HIV in Denmark during 1997-2004*. **Antivir Ther. 2006**;11(5):591-600. (6)

VII. **Lohse N**, Jørgensen LB, Kronborg G, Møller A, Kvinesdal B, Sørensen HT, Obel N, Gerstoft *Genotypic drug resistance and long-term mortality in patients with triple-class antiretroviral drug failure.* **Antivir Ther. 2007**;12(6):909-17. (7)

VIII. **Lohse N**, Hansen AB, Pedersen G, Kronborg G, Gerstoft J, Sørensen HT, Vaeth M, Obel N. *Survival of persons with and without HIV infection in Denmark, 1995-2005*. **Ann Intern Med. 2007** Jan 16;146(2):87-95. (8)

IX. **Lohse N**, Gerstoft J, Kronborg G, Larsen CS, Pedersen C, Pedersen G, Nielsen L, Sørensen HT, Obel N. *Comorbidity Acquired Before HIV Diagnosis and Mortality in Persons Infected and Uninfected With HIV: A Danish Population-Based Cohort Study*. **J Acquir Immune Defic Syndr. 2011** Aug 1;57(4):334-339. (9)

PAPERS PREVIOUSLY INCLUDED IN ACADEMIC THESES

Papers III, IV, and VI were three of the five papers included in my PhD thesis *HIV in Denmark and Greenland, 1995-2004: The effect of highly active antiretroviral therapy and characteristics of the HIV-infected population: An observational study*, University of Southern Denmark, 2006. Paper V was part of Anne Audelin's PhD thesis *Molecular-epidemiological studies of HIV-1 and antiretroviral resistance in Denmark*, Copenhagen University, 2011. Papers I, II, VII, VIII, and IX have not previously been submitted for obtainment of an academic degree.

1 INTRODUCTION

1.1 THE HIV EPIDEMIC

The HIV epidemic is a marvellous example of a new disease hitting the medical community – and the whole world - by surprise, and then going through the stages from being overwhelming to

gradually becoming a disease, which is largely manageable with regard to both prevention and treatment. The immense progress would not have been possible were it not for a concerted action by patients, civil society groups, doctors, scientists, donors, politicians, the pharmaceutical industry, and many others. Fortunately, the HIV epidemic possessed the right cocktail of scientific challenge, urgency, despair, human discrimination, and geographical distribution to stimulate these various groups.

In 2003, when I started the work providing the basis for this thesis, the global HIV epidemic was out of control, increasing in incidence in most parts of the World(10), with the prevalence being kept down only due to the high death rates. Antiretroviral therapy (ART) combinations showing high efficacy towards HIV had been known for 6-7 years (11), but only a minority of all persons with HIV were getting the full benefit (10). In many places, treatment was not available, people could not afford it, or they did not have access to trained health care professionals. For those who did have access, some were burdened by considerable side effects, or they were infected with virus that had developed drug resistance after previous years' exposure to less effective single drugs or drug combinations. Many found it extremely difficult to adhere to the strict requirements for taking the medication at specific times of the day, and without interruptions – not made easier by the often large pill burden of the drug combinations. Finally, it was unknown how long the drugs could maintain their efficacy in the individual even if administered as intended.

Thus, despite many individual stories of success, there was reasonable doubt as to whether these successes would translate into a positive population effect, and result in decreased morbidity and mortality. On the contrary, there was a fear that the increased drug pressure would increase the prevalence of drug resistance in the population, subsequently leading to transmission of resistant virus from one individual to another, and thereby waning the treatment options available.

Absolute prevention of new infections will always be the key to eradicating this epidemic (12), and for those already infected, finding a cure is the optimal goal(13–18). However, until we have overcome these obstacles, we must optimize infection control and management both in the individual and at the population level. Ideally, an HIV-infected individual should know immediately that he/she is infected, should have access to specialized medical and social support, receive a drug combination which effectively suppresses the virus and has no side effects, and should be without comorbid conditions both before and after he/she gets infected.

As a country with free access to health care including treatment for HIV infection, and a limited number of highly specialized HIV clinics, Denmark is one of few countries providing the basic ingredients for optimal HIV control at the population level (19). Further, the systematized collection of clinical and paraclinical data on all persons with HIV in the Danish HIV Cohort Study (DHCS) (20,21), combined with access to excellent population-based administrative databases that can all be linked to DHCS through a unique person identification number, makes Denmark an ideal place to study the prerequisites for and effects of good population control.

2 AIMS OF THIS THESIS

2.1 SPECIFIC AIMS

The papers on which this thesis is based each aimed to provide new knowledge to different aspects of the above. Accordingly, the aims of the thesis were:

i. To explore the potential for an indicator disease-based HIV testing strategy (paper I).
ii. To compare temporal trends in quality and quantity of ART introduction in countries with optimal and sub-optimal health systems for HIV care (paper II).
iii. To assess temporal trends of virological failure and the importance of virological control at the population level (papers III and IV).
iv. To assess temporal trends of drug resistance development and drug resistance transmission at the population level (papers V and VI).
v. To assess the implications of drug resistance at the population level (paper VII).
vi. To project long-term survival in an HIV population with excellent access to treatment and care (paper VIII).
vii. To assess the impact of non-HIV related morbidity on the prognosis for HIV patients in a health system delivering high-quality HIV care (paper IX).

2.2 SCOPE OF THIS WORK RELATED TO MY PHD THESIS

The work that was part of my PhD thesis (papers III, IV, and VI) was focused primarily on biomarkers, i.e. virological control and virological failure, and associated risk factors and prognosis, and was based on DHCS only. Papers V and VII added resistance data from DHSD, allowing these studies to detail and explore previous findings of time trends and risks by relating these to specific resistance mutations. Papers I, II, VIII, and IX took a much broader view and compared findings from DHCS with other populations. This expansion in scope reflected the evolving focus from the individual with HIV to popuations with HIV. By taking advantage of the unique availability of other databases, the latter papers allowed us to study pertinent questions such as: How do we identify those at increased risk of HIV in a mixed clinical population? (paper I); What is the positive effect of being diagnosed with HIV within a good healthcare system? (paper II): How long can persons with HIV expect to live compared to the general population? (paper VIII); and What would have been the impact of HIV if the comorbidity pattern had been similar to that of the general population? (paper IX).

3 DATA SOURCES

3.1 THE DANISH HIV COHORT STUDY (DHCS)

DHCS is an open, prospective, population-based cohort(20,22), initiated in 1998 as a collaborative effort by Denmark's eight HIV treatment centres(23). Data going back to 1 January 1995 were retrieved from patient files and entered into the database. Hence, the cohort includes all prevalent HIV cases as of 1 January 1995 and all incident cases since then. Types of data collected are comparable to other HIV cohort studies around the world(24–38), namely individual characteristics, biochemical test results, treatment history, and clinical events. DHCS was founded at Aarhus University Hospital. It was later moved to Odense University Hospital and is currently, as of 2014, based at Copenhagen University Hospital Rigshospitalet. Physicians and research nurses collect clinical data at the participating clinics. The individual identity is kept anonymous, but an identification link exists locally at each participating clinic, to detect double counting when a patient moves between clinics. Crosschecking and validation algorithms are incorporated into the database in order to catch data retrieval and typing errors. In addition, 5-10 percent of records are monitored during annual visits to participating clinics. DHCS covers the whole country and is virtually complete.

3.2 DHCS GREENLAND

A database with the same design as DHCS was established in Greenland in 2003(39). To include every HIV-infected individual seen at Greenland's clinics since 1995, personal contact was initiated with all 18 district health clinics, and old patient files were retrieved by searching the archives of the Venereal Disease Clinic at Dronning Ingrid's Hospital in Nuuk. Doctors from this clinic were responsible for HIV treatment and care during the first years of the epidemic(40). The files thus obtained were compared with the records collected by the Chief Medical Officer of Greenland(41–44). This provided presumably complete coverage in the study database of known HIV patients since 1995. Data is now updated through the Department of Internal Medicine at Dronning Ingrid's Hospital, which has assumed responsibility for all HIV treatment in Greenland.

3.3 DANISH NATIONAL PATIENT REGISTRY (DNPR)

DNPR was established in 1977 and covers all Danish hospitals and records all hospital admissions, and diagnoses. Since 1995, all outpatient and emergency visits are registered as well(45). The DNPR covers both private and public hospitals.

3.4 DANISH CIVIL REGISTRATION SYSTEM (DCRS)

DCRS is a national registry of all residents of Denmark and Greenland, containing information on date of birth, sex, immigration, residency, date of migration, and death(46,47). Each individual is assigned a 10-digit personal identification number (CPR number). DCRS is updated within less than a week after a person is born, changes address, dies, or emigrates. We used CPR numbers to link data between the registries.

3.5 DANISH CANCER REGISTRY (DCR)

DCR has recorded all incident cancers in Denmark since 1943, classifying cancers registered after 1977 according to ICD-10(48).

3.6 DANISH HIV SEQUENCE DATABASE (DHSD)

DHSD is a prospective, nationwide, population-based database of all genotypic HIV drug resistance tests performed in Denmark after 31 December 1999.

4 METHODOLOGICAL CONSIDERATIONS

4.1 UTILITY OF THE DHCS COHORT

A cohort is a group of individuals who are followed over a period of time (49). A cohort study may be experimental, for example a randomized clinical trial (RCT), or non-experimental (synonymous with observational study). The Danish HIV Cohort Study (DHCS) is a non-experimental cohort study(50), and it is prospective, because it is assembled in the present and followed into the future(51). Individuals in the cohort compose the *study base*; in DHCS the study base is all HIV-infected persons in Denmark and Greenland(20,22,39). DHCS is open, because new individuals join the cohort over time, and it is population-based, because it aims to include all HIV patients in the geographic area under study (52). Even though RCTs are considered the gold standard for comparing the efficacy(53) of drugs and other treatments, observational studies of HIV confer a number of distinct advantages over RCTs(54,55). They provide information on the clinical history and spectrum of HIV disease, they are useful for exploring patterns of antiretroviral drug use (56) and monitoring the course of side effects (37,57), and they give an opportunity to examine questions as they crop up (58). Further, in contrast to the *efficacy*(53) examined by RCTs, observational studies shed light on the *effectiveness* of treatment. Thus, advantages of DHCS include the ability to study population-based prevalences and incidences, as well as population trends over time (papers II, III, V, and VI). Furthermore, the unique personal identifier enables linkage to numerous Danish registries (papers I, VIII, IX) (59). The size of DHCS limits studies of rare events or subgroups with rare characteristics; and results obtained in Denmark may not be generalizable to other countries because of regional differences in the composition of study populations(60,61). Data in one cohort may be compared with data in another cohort in a *double-cohort study* (62). Papers I, II, VIII, and IX used a double-cohort study design to compare the outcome of interest in people who were "exposed" (infected with HIV) with mortality in people who were "unexposed" (the general population). Papers III, IV, V, VI, and VII were single-cohort studies based on DHCS, with papers V and VII expanding the available information by including resistance mutation data from DHSD. An overview of data sources and study design is shown in Table 1.

Many HIV cohorts are *prevalent cohorts*, in which patients are included at some time point after the initiating event(63,64). In an *inception cohort*, all individuals are followed from the time of an initiating event, (e.g., the date of infection with HIV) (49,65).

DHCS may be considered both an inception and a prevalence cohort. If the initiating event is defined as initiation of combination ART, DHCS is an inception cohort for HIV patients initiating ART in Denmark. If the initiating event is defined as diagnosis of HIV, DHCS comes close to being an inception cohort for patients diagnosed since 1995. If the initiating event is defined as HIV transmission, DHCS is a prevalent cohort.

Table 1

Data sources and study design for each of the nine papers.

Data sources and study design

Paper	I	II	III	IV	V	VI	VII	VIII	IX
Publication year	2012	2008	2005	2006	2009	2006	2007	2007	2011
Study base									
Danish HIV Cohort Study (DHCS)									
Incident cases of HIV diagnosis	•								•
Incident cases of ART initiation			•	•	•	•	•		
All persons in the cohort		•						•	
Other data sources									
DHCS Greenland		•							
Danish National Patient Registry	•								•
Danish Civil Registration System	•							•	•
Danish Cancer Registry	•								
Danish HIV Sequence Database					•		•		
Study type									
Descriptive		•	•		•	•			
Analytic	•		•	•			•	•	•
Double-cohort study	•	•						•	•

4.2 OUTCOMES

The events of primary interest in clinical epidemiology are health outcomes, for example death, disease, abnormal laboratory tests, or discomfort(51). Some outcomes are surrogate measures of the outcome of interest; low CD4+ cell count and high viral load are surrogate measures of clinical disease progression(66), and high viral load is also a surrogate measure of increased infectivity (67–70). Use of surrogate outcome measures saves time and money, but to have validity they must be strongly associated with the main health outcome of interest. CD4+ cell count and viral load are long-established measures of disease progression to AIDS or death. (66).

4.3 DESCRIPTIVE AND ANALYTIC STUDIES

Observational studies can be descriptive or analytic, or both. *A descriptive study* examines patterns of health conditions in persons, places, and over time. Papers II, III, V, and VI provided descriptive information on temporal trends in health outcomes. *Analytic studies* test one or more specific hypotheses, typically whether exposure to a given factor is a *risk factor* for a health outcome. Papers I, IV, VII, VIII, and IX were mainly analytic studies. The distinction between descriptive and analytic studies is one of intent, objective, and approach, rather than one of design. Data obtained in an analytic study may be explored in a descriptive mode, and data obtained in a descriptive study can be analyzed to test hypotheses. For example in paper VI, a primarily descriptive study, we applied an analytic approach to examine causes of the observed temporal trends in the prevalence of drug resistance carriers; and in paper III we described temporal trends in triple class virological failure and performed a multivariable analysis to identify risk factors for virological failure.

4.4 MEASURES OF FREQUENCY AND EFFECT

In an epidemiological study, the key clinically relevant measures of event frequency are incidence and prevalence (51). *Incidence* is defined as the fraction of a group that develops a condition (an outcome) over a given time period. Incidence is often reported per unit of time, as an incidence rate (IR). *Prevalence* is the fraction of a group possessing a condition at a given point in time. The prevalence depends on both the incidence and the duration of the condition. In a steady state, prevalence equals "IR x duration". *Risk* is the probability that an event will occur in an individual during the observation period (100). *Incidence proportion* (used in paper IX) is the equivalent measure for a population and approximates "IR x time". Measures of frequency – most commonly the risk and the incidence rate – can be compared to assess the effect of an exposure. The *absolute effect* is measured as the *risk difference*, i.e., the difference in risk between the exposed and unexposed groups. The incidence rate difference can be calculated in a similar fashion (used in paper VIII). The *relative effect* is measured as a *relative risk*, an *incidence rate ratio* (used in papers II, III, IV, VII, and VIII), or – when the frequency measure is prevalence – as a *prevalence ratio* or *odds ratio* (used in paper I).

4.5 BIAS AND CONFOUNDING

An observed outcome may be affected by random error or systematic error (bias)(49). Random error is due to chance, and its estimated magnitude is presented as confidence intervals and p-values in the statistical analysis. Bias can arise from the way people are selected into a study (selection bias), the way the variables are measured (information bias), or from an uncontrolled confounder (confounding). Observational studies are particularly prone to bias and confounding, and rigorous assessment and control of these is imperative.

4.5.1 Selection bias

Selection bias may occur if groups of subjects characterized by an unusual and unequal relationship between exposure and outcome are selectively recruited into the study, or drop out before completion. Selection bias has to be dealt with at the design stage, for example by selecting only incident cases, restricting inclusion to a geographical area, minimizing the number lost to follow up or implementing a procedure to track those who drop out. Selection bias in papers I-IX was dealt with by all of the above. Many HIV observational cohorts recruit from only one or a few HIV clinic(s) where the clientele may be self-selected, may be predominantly patients with complicated or advanced disease referred from general practitioners, or may be lost to follow-up. A patient who does not keep a regular visit at the HIV clinic, and is therefore considered lost to follow up, may not have moved from the area; rather, the patient may be hospitalised elsewhere for a non-HIV- related condition or may have died. This type of selection bias, in which censoring is associated with the outcome (e.g.,

death), is called informative censoring in survival analysis. In some cohorts, requirements for informed consent may lead to selective recruitment, and persons may later withdraw their consent, leading to selective dropout.

4.5.2 Information bias

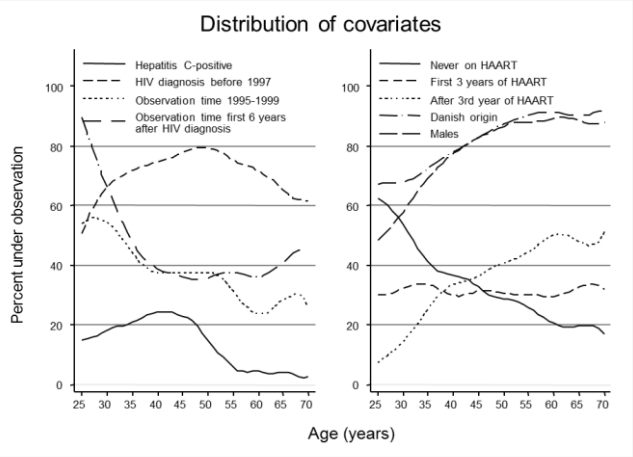
Information bias may occur if the methods of measurements are consistently dissimilar in different groups of patients(51). The study design is crucial for minimizing information bias, for example by ensuring a standardized measurement process, and by using objective, pre-defined criteria for exposure and outcome. Most HIV observational cohorts, including DHCS, retrieve information from patient files, and many exposures and outcomes (e.g., AIDS-defining events, deaths, and laboratory test results) are defined from objective criteria, all of which will tend to minimize information bias. Some data depend on the patients' own information and are more prone to cause information bias, e.g., information on alcohol use or mode of HIV transmission.

4.5.3 Confounding

To be a potential confounder, a variable has to be an independent risk factor for the outcome of interest, it must be associated with the exposure, and it must not be an intermediate variable. Several variables are related to health outcomes and therefore commonly act as confounders in HIV cohort studies.

Figure 1

Potential *confounders in DHCS and their variation over time. X-axis: observation year, time scale = age. Y-axis: prevalence of covariates at each observation time point.*



These include for example AIDS, mode of infection, coinfection with hepatitis C virus (HCV), age, time on ART, time since HIV diagnosis, and observation year. Figure 1 shows an analysis of the cohort used in paper VIII and depicts how the prevalence of confounders in DHCS vary according to age, for all persons observed during 1995-2006. It draws attention to the complexity of clinical epidemiological studies of HIV. The fatal natural history counteracts with the continuous emergence of improved treatment options, rendering it highly important for researchers to know the details of their cohort. Incidence rates may change considerably when analyses are stratified by the observations' position on different time scales (papers III and VIII).

Confounding control can take place both at the design stage or analytical stage, using tools such as randomization, matching, exclusion, restriction in design, restriction in analysis, standardization, stratification, and multivariable analysis and modelling(71). With the exception of randomization, all of the above methods were used in papers I-IX.

4.5.4 Bias in prevalent cohorts

Some types of bias relate specifically to prevalent cohorts. *Length-biased sampling* (49,51) may occur because patients at increased risk of death will have shorter disease duration between HIV infection and death and therefore be underrepresented in the prevalent sample. *Differential length-biased sampling* (63,64) may occur if the risk of death increases (or decreases) with the duration of the infection. Patients with a covariate that increases the risk of death (e.g., HCV coinfection) tend to have a shorter prior duration of infection than patients without the covariate. Low-risk patients thus will be infected for a longer time, causing them to have more advanced disease and therefore an increased risk of death. These countervailing factors reduce the disparity in risk between the two groups, biasing the relative risk estimate towards 1.0. In contrast, if the risk of death decreases with the duration of the infection, the relative risk estimate will be biased away from 1.0 (72). Another type of bias, *onset confounding* arises when a covariate is associated with the initiating event. If a covariate is associated with earlier infection dates (e.g., being a male homosexual), individuals with this covariate will have longer infection times, causing the covariate to appear associated with any outcome dependent on time from infection (e.g., the risk of dying). Results may be biased in both directions depending on the direction of the effect of the covariate. To avoid bias related to prevalent cohorts, we restricted our study populations to either incident cases of HIV diagnosis (papers I and IX) or incident cases of ART initiation (papers III-VII).

4.6 STATISTICAL ANALYSES

4.6.1 Comparing individual characteristics

Individual characteristics between study groups were compared using the *chi-square test* for categorical variables, and the *Student's t-test* or *one-way analysis of variance* for continuous variables.

4.6.2 Comparing outcomes

Time-to-event analyses were used to estimate incidence rates of TCF, mortality rates, and cumulative incidence proportions (papers III, IV, VII, VIII, and IX), using the Cox proportional hazards regression and log-rank test to compare outcomes between groups. A time-to-event model with left truncation was used to estimate incidence rates on two different timelines (papers III and VIII). *Logistic regression* was used to compare proportions with undetectable viral load (paper IV), and *conditional logistic regres-*

sion was used in a matched case control design to compare the odds of subsequent HIV diagnosis (paper I). Trends over time in incidence rates and prevalence were estimated with *Poisson regression* (papers II, III, V, and VI), and changes over time in CD4+ cell count were estimated in a *linear regression* model (paper IV). *Population attributable risk* was used to estimate the proportion of deaths attributable to comorbidity acquired before HIV diagnosis, and *interaction risk* was used to estimate the interaction between the effects of HIV and comorbidity on mortality (paper IX).

4.7 DATA SAFETY END ETHICS

Establishment of DHCS and the linkage to other registries were approved by the Danish Data Protection Agency (journal number 2012-41-0005). As none of the studies included direct patient contact, approval from the national or regional committees on health research ethics were not required. Data were handled and protected in compliance with Danish law (73).

5 EARLY DETECTION

5.1 BACKGROUND

Early detection is one of the cornerstones of optimal HIV management both at the individual and on the population level(74). Detecting persons with HIV as early as possible will allow for timely initiation of ART and lower the risk of disease progression in the individual(74,75). Persons initiating ART at very low CD4+ cell counts are at higher risk of death(76,77) and take longer to experience good immune reconstitution(78–80) than those commencing therapy with higher CD4+ cell counts. Most current guidelines, including those published by the World Health Organization (WHO), recommend ART initiation when the CD4+ cell count falls below 350 cells/mcl (81,82), Further, timely and adequate prevention efforts require knowledge of where the next new infection is most likely to be (83–85). As local HIV epidemics change over time, early detection is an important tool in mapping this. Finally, with recent evidence that ART can effectively reduce the risk of HIV transmission(86), there are speculations that bringing down the population viral load by comprehensive treatment of all persons infected will lead to fewer new infections and thereby have a positive effect on the HIV incidence (87–90). Whether such a "treatment as prevention" strategy is feasible(91), cost-effective (92,93), and ethically acceptable(94,95), and in which populations and areas it might be recommended (96,97), is still up for discussion(98–102). Also not known is the coverage level required, and the potential added impact on HIV-associated comorbidities such as tuberculosis (103,104). Numerous modelling exercises are being conducted, and at least three cluster-randomized trials are underway to give answers to some of the above-mentioned questions (97,105–111).

5.2 TRENDS IN LATE DIAGNOSIS AND LATE PRESENTATION

5.2.1 Epidemiology

A considerable barrier to optimal HIV care in both high-income countries (HIC) and low- and middle-income countries (LMIC) are the many *late presenters* (112–117), defined as presenting to HIV care with a CD4+ cell count below 350 cells/mL or with an AIDS-defining event (74,118,119). These are either diagnosed late (120–124), or the time from diagnosis until they reach clinical care is long. Although improvements are observed in some countries (112,114,121,125), recent reports estimate late diagnosis and/or late presentation to occur in 35-60% of newly diagnosed (112,126,127), similar to 2005 figures for Denmark (128).

5.2.2 Risk factors

Those who are diagnosed late are more often males, older, with low education level and low socioeconomic status, and belong to marginalized groups such as immigrants (115,120,121). They often do not perceive themselves at risk of infection or have not gone for testing due to fear of the disease itself and of stigmatization(90,115), and they have not routinely been offered HIV testing(121). In addition, many do not have easy access to HIV testing facilities. Timely diagnosis, on the other hand, has been associated with belonging to a known risk group such as men who have sex with men (MSM) or injecting drug users (IDUs) (120,129), and perceived effectiveness of treatment (115).

Those who are late presenters will naturally share the risk factors of those who are diagnosed late (121). Specific additional conditions associated with longer time from diagnosis until care are IDU (129), lack of disclosure of HIV status to spouse or partner, and being unmarried (130). Associated with early presentation are current pregnancy, having young children, and consuming alcohol in the previous year (130)

5.2.3 Clinical and economic consequences:

The consequences of late presentation are grave (131). Late presenters have higher rates of morbidity (132) and mortality (75,133–135), and they are more likely to be admitted to the Intensive Care Unit (123). They have higher likelihood of poor adherence, exacerbated by the same factors that contribute to their late diagnosis such as lack of knowledge on HIV and the benefits of highly active antiretroviral therapy (74,116). They are also more likely to transmit HIV, not only because of the high viral load when not on ART (68,136), but also because they have low general awareness of the risk of transmission (137). Finally, these medical conditions translate into higher medical costs (138–140).

5.3 BOOSTING EARLY DIAGNOSIS AND PRESENTATION FOR CARE (PAPER I)

5.3.1 Testing strategies

More than 30% of persons with HIV in Europe are estimated to be undiagnosed(141). To turn the epidemic, we need to diagnose more persons earlier and make sure they present to clinical care without undue delay. The optimal screening strategy will depend on the nature of the local epidemic: transmission patterns, risk

groups, healthcare system, and cultural norms. Client-initiated screening (opt-in) voluntary counselling and testing has been the dominant form of testing for many years. However, due to the often disappointingly low uptake of testing by this strategy, provider-initiated "opt-out" counselling and testing (142,143) is now being widely introduced in various forms(144).

A number strategies that could permit earlier testing are currently being recommended or used in low-prevalence countries(90,143,145,146). These include screening of high-risk groups such as MSM, IDUs, and sex workers; universal screening in selected healthcare facilities such as patients in sexually transmitted disease (STD) clinics(147), pregnant women in antenatal care facilities, and persons newly-diagnosed with viral hepatitis or tuberculosis(121); and symptom-guided screening in all healthcare facilities based on selected indicator conditions associated with high risk of HIV infection (87,148,149). Further, newer self-testing technologies recently being approved in the United States(150–153) might be able to reach populations who would not reach a medical facility for testing, or be used more frequent than facility-based services and thereby lead to earlier detection of persons with HIV (154). To have the desired effect, however, emphasis must be on linking the self-test to timely HIV care.

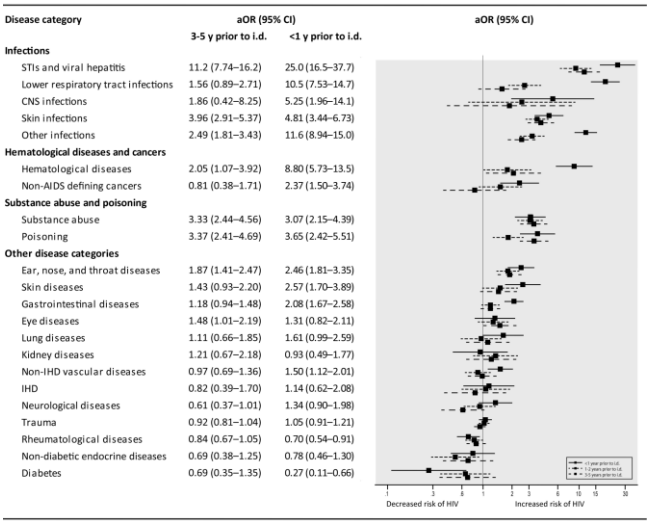
5.3.2 Indicator condition-based HIV testing

Conditions and diseases that should lead to HIV testing fall into three basic categories: conditions for which, in case the presence of HIV infection is identified, their clinical management can have deleterious consequences for the individual; conditions that are AIDS defining in persons with HIV; and conditions that are otherwise associated with high prevalence of undiagnosed HIV. The latter two categories are called indicator conditions. As the prevalence threshold above which testing has been shown to be cost-effective in high-income settings is 0.1% (155–157), this has become the target prevalence in studies of new indicator conditions. With the greatly varying economic status and HIV prevalence in countries affected by HIV, the set of indicator conditions that should lead to an offer of HIV testing will naturally be different from one setting to another. Apart from AIDS-defining illnesses, some of the conditions first shown to be associated with HIV prevalence higher than 0.1% were Guillain Barré syndrome / acute inflammatory demyelinating polyneuropathy (158,159), unexplained fever (160), visceral leishmaniasis (161,162), candidaemia (163), community-acquired pneumonia (164) mononucleosis-like illness(165–167), HCV infection (168,169), anal or cervical cancer or dysplasia(170–173), herpes zoster (174,175), malignant lymphoma (176), and psoriasis (177). As the population effect of modern ART kicked in during the first decade of this millennium, HIV and public health experts and advocates expressed several calls for action to identify and implement better strategies for early detection (178,179).

With access to complete diagnostic history for in-patients in Danish hospitals since 1977, we used a case-control design to study the association between potential indicator conditions and HIV diagnosis one, three, and five years later (paper I). We identified a broad range of conditions with an adjusted odds ratio (aOR) of being diagnosed with HIV at between 3.0 and 94.7. With the controls in our study population identified by *incidence density sampling*, the OR was a direct estimate of the *relative risk* of HIV. We confirmed already known associations between HIV and polyneuropathy (aOR=4.52), candida infection (aOR=25.5), lower respiratory tract infections (aOR=3.98), mononucleosis (aOR=8.64), hepatitis B and C (aOR=23.6), herpes zoster (aOR=33.7), and lymphoma (aOR=5.83). Other broader disease groups which we identified as having an increased risk of HIV were "STIs and viral hepatitis" (aOR=12.3), "CNS infections" (aOR=3.44), "skin infections" (aOR=3.05), "other infections" (aOR=4.64), and "haematological diseases" (OR=4.28). Detailing the above disease groups, we identified a number of specific potential indicator conditions who all had adjusted ORs above 10: opioid abuse (aOR=43.5), hepatitis A (aOR=41.6), thrombocytopenia (aOR=24.0), endocarditis (aOR=23.2), bacterial meningitis (aOR=14.7), seborrheic dermatitis (aOR=11.8), and drug poisoning (aOR=11.2). Our data allowed us to look at future HIV risk at various distances in time from the occurrence of the indicator condition (Figure 2). Thrombocytopenia, seborrhoeic dermatitis, and bacterial infections are manifestations of the HIV infection and were highly associated with being diagnosed with HIV during the coming year and less so during the 3 to 5-year period. Substance abuse, hepatitis A, and drug poisoning, on the other hand, were associated with an almost constant 5-year long increased risk of HIV diagnosis. These conditions share behavioural risk factors with HIV and are therefore indicators of not only current HIV but also of future HIV acquisition.

Figure 2

Forest plot of selected indicator diseases showing how some risk estimates may vary depending on time to future HIV diagnosis. (Source: paper I)



Disease category	aOR (95% CI) 3-5 y prior to i.d.	aOR (95% CI) <1 y prior to i.d.
Infections		
STIs and viral hepatitis	11.2 (7.74–16.2)	25.0 (16.5–37.7)
Lower respiratory tract infections	1.56 (0.89–2.71)	10.5 (7.53–14.7)
CNS infections	1.86 (0.42–8.25)	5.25 (1.96–14.1)
Skin infections	3.96 (2.91–5.37)	4.81 (3.44–6.73)
Other infections	2.49 (1.81–3.43)	11.6 (8.94–15.0)
Hematological diseases and cancers		
Hematological diseases	2.05 (1.07–3.92)	8.80 (5.73–13.5)
Non-AIDS defining cancers	0.81 (0.38–1.71)	2.37 (1.50–3.74)
Substance abuse and poisoning		
Substance abuse	3.33 (2.44–4.56)	3.07 (2.15–4.39)
Poisoning	3.37 (2.41–4.69)	3.65 (2.42–5.51)
Other disease categories		
Ear, nose, and throat diseases	1.87 (1.41–2.47)	2.46 (1.81–3.35)
Skin diseases	1.43 (0.93–2.20)	2.57 (1.70–3.89)
Gastrointestinal diseases	1.18 (0.94–1.48)	2.08 (1.67–2.58)
Eye diseases	1.48 (1.01–2.19)	1.31 (0.82–2.11)
Lung diseases	1.11 (0.66–1.85)	1.61 (0.99–2.59)
Kidney diseases	1.21 (0.67–2.18)	0.93 (0.49–1.77)
Non-IHD vascular diseases	0.97 (0.69–1.36)	1.50 (1.12–2.01)
IHD	0.82 (0.39–1.70)	1.14 (0.62–2.08)
Neurological diseases	0.61 (0.37–1.01)	1.34 (0.90–1.98)
Trauma	0.92 (0.81–1.04)	1.05 (0.91–1.21)
Rheumatological diseases	0.84 (0.67–1.05)	0.70 (0.54–0.91)
Non-diabetic endocrine diseases	0.69 (0.38–1.25)	0.78 (0.46–1.30)
Diabetes	0.69 (0.35–1.35)	0.27 (0.11–0.66)

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 the index date; 1–2 years prior to the index date; 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 collums. aOR, adjusted odds ratio; CI, confidence interval; i.d., index date; STIs, sexually transmitted infections; IHD, ischaemic heart disease.

As a response to the urgent need for guidance, the HIV in Europe

Initiative, with contributions from the European Center for Disease Control and the World Health Organization published in late 2012 a guidance for indicator-based HIV testing (180). While there is evidence of undiagnosed HIV prevalence of >0.1% for some of the recommended indicator conditions, many of the indicators are included based on the opinion of experts who consider them likely to be associated with an HIV prevalence of >0.1%. The document acknowledges the paucity of evidence to robustly identify indicator conditions, and the document is likely to be modified during the coming years as we gain more knowledge.

Published in 2013, a case-control study using the UK-based general practice database THIN (The Health Improvement Network) tested the 37 indicator conditions recommended in the UK National Guidelines for HIV testing 2008 (178). and found 12 of these to be associated with HIV infection (181). Another recent study from England and Wales found an HIV prevalence of 2.4% among persons with invasive pneumococcal disease (182), while a small Spanish study tested a strategy of four indicator diseases and found an HIV prevalence of 4.7% (95% CI 1.3%-11.6), corresponding to a cost per new diagnosis of only €129 (183).

The HIV in Europe Initiative (149) is currently running the HIV Indicator Diseases across Europe Study (HIDES), which aims to identify indicator diseases and develop a model for implementation of targeted HIV testing in clinical settings. Eight conditions tested in HIDES I were all found to be associated with an HIV prevalence of >0.1% (148). These included STIs, malignant lymphoma, cervical dysplasia or anal cancer, herpes zoster, hepatitis B or C, ongoing mononucleosis-like illness, unexplained leukocytopenia/thrombocytopenia, and seborrhoeic dermatitis/exanthema. HIDES II is now expanding to >50 sites across Europe and will include, in addition, the diseases hospitalized pneumonia, unexplained lymphadenopathy, peripheral neuropathy, lung cancer, and recalcitrant psoriasis (184).

5.4 CONCLUSION

Late diagnosis and late presentation to clinical care continue to be major barriers to improved HIV management, and we need to find ways to identify those who are not yet diagnosed. New testing strategies must be tailored to the settings in which they are to be used to ensure they are feasible and cost-effective. The body of knowledge on indicator conditions is increasing rapidly, and studies confirming previous findings and adding new pieces to the puzzle continue to improve our knowledge on where and when indicator condition-based testing can be applied and have a positive effect. Thus, indicator condition-based testing may turn out to be a valuable addition to the existing practice in many settings.

6 ACCESS TO GOOD HEALTH CARE

6.1 BACKGROUND

Before a person with HIV can get the life-saving medication, the drugs need to be available, accessible, and affordable. While this is the case in most high-income countries, successful roll-out of antiretroviral therapy (ART) furthermore requires a functional health care system with trained medical staff (185,186). Some evidence suggests that personal support from friends, family and peers improves drug effectiveness even further (187). Suboptimal health care systems are most prevalent in poorer parts of the world (188), but they also exist in wealthy countries. Washington DC has recently been portrayed as an example of a city with poor access to care for many of its HIV-infected population (189). The causes of poor ART uptake are often complex and not immediately visible, and there is an increasing need to identify these barriers.

6.2 UPTAKE OF ANTIRETROVIRAL THERAPY (PAPER II)

6.2.1 Factors associated with ART uptake

Uptake of ART is influenced by individual as well as health system-related factors. Characteristics such as sex (being male), age (being younger), and employment status (being unemployed) and homelessness are associated with lower ART uptake (190–192), but also less visible, psycho-socio-cultural issues such as illness ideology, unfamiliarity with chronic disease management, depression, interpersonal challenges, stigma, and values of church or marriage have been shown to provide barriers to ART initiation (192,193). System-related factors include distance to the nearest clinic (191), waiting times for medical care (194–196) poor linkage between HIV testing and HIV care and treatment services, and shortage of HIV/AIDS specialists (197). While psycho-socio-cultural barriers are found in both LMIC and HIC, the economic and health system barriers are predominantly described in LMIC (198).

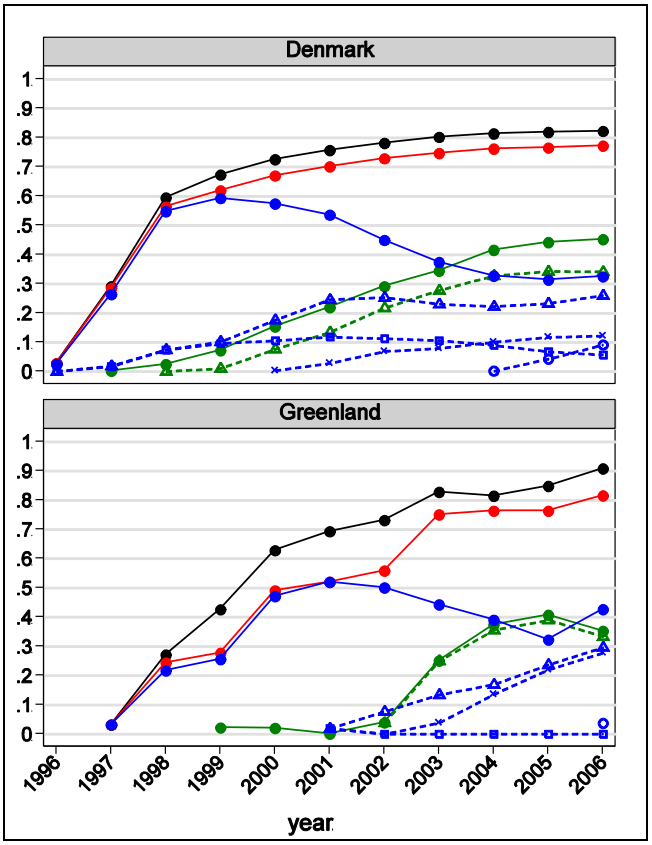
6.2.2 ART uptake in Greenland

The health care system in Greenland is well funded, public, and with free access for all citizens (39). Health care provision, however, is challenged by the vast geography and staffing issues. Fifty-six thousand people live in 74 towns and settlements between which transportation is only possible by air or sea, making them frequently inaccessible due to bad weather; only 18 of these have facilities with permanent physician staffing, and frequent use of locums impedes the consistency of care for patients with chronic conditions. We compared the uptake of ART and changes in HIV mortality over time in Greenland with Denmark, its former colonial power (paper II). Both are high-income countries with public health care offered free of charge, and the Greenland health care system is staffed with physicians trained in Denmark. We found that ART introduction had been delayed in Greenland, with the total coverage level among persons with HIV only catching up in 2003, and with newer combination regimens such as those including ritonavir-boosted protease inhibitors reaching levels in Denmark only in 2006 (Figure 3). These patterns were also found among the proportion with suppressed viral load, and reflected in the mortality rates that dropped dramatically in Denmark in years 1998-2000 to 29/1,000 per year, and although steadily declining in Greenland were still 59/1,000 per year in

2004-2006. A later study found a slight further decline in mortality until 2011 of 53.4/1,000 per year (199).

Figure 3

ART introduction in Denmark and Greenland 1996-2006. Numerator, proportion of patients who were receiving antiretroviral therapy as part of a highly effective ART regimen on Jan 1st each year. Denominator, all patients under observation. NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor. (Source: paper II)



6.3 CONCLUSION

Despite similar levels of health worker education and economic resources, ART implementation and mortality decline in Greenland lacked several years behind Denmark. Geography, lack of consistency in clinic staffing, and difficult infrastructure with less access to advanced laboratories, hospital care, and HIV specialist clinics most likely bear part of the cause. Furthermore, the HIV epidemic in Greenland is characterized by a mainly middle-aged, heterosexually transmitted population with low socio-economic status, and these issues related to the individual might have further challenged timely and effective introduction of new treatments. While we were not able to single out the main reason for the observed differences, the study reminded us that although economy may be a prerequisite for implementing an effective HIV care system, it is certainly not all it takes.

7 VIROLOGICAL CONTROL

7.1 BACKGROUND

The goal of modern antiretroviral therapy is continuous suppression of HIV replication in the body, so-called virological control. This will delay the HIV-induced deterioration of the immune system (81) and postpone or even avoid immune-deficiency-related morbidity and eventually death. Assessing the drug efficacy in persons on ART is done by regular measurements of the amount of virus (HIV RNA) in the blood (viral load), which serves as a proxy measure for HIV replication in the cells.

Obtaining and sustaining virological control can be challenging. Primarily, the prescribed drugs must be efficacious and able to suppress HIV replication, but HIV is a chronic disease, and the drugs must remain effective and acceptable to the patient also after long-term use. Factors that determine long-term effectiveness include properties of the ART combination used, the genotype and phenotype of the dominant HIV strain in the individual, and the person´s ability to adhere to the prescribed treatment. Some drugs have lower efficacy and are less forgiving if one or several doses are missed, some are more likely to cause side effects, and some should be taken twice or even three times daily. Some viral strains are resistant to the most commonly used drugs, and some patients are highly burdened by side effects, find it very difficult to take medication at designated hours, or find that psychosocial aspects of their life keep them from adhering to a rigorous treatment scheme.

7.2 ART COMBINATIONS

The first ART combinations that were able to induce virological control for more than a few months consisted of a PI and two nucleoside reverse transcriptase inhibitors (NRTIs)(11), so-called PI-based regimens. Later came regimens based on NNRTIs or ritonavir-boosted PIs (200–202), and more recently we have seen the advent of the newer drug classes (203) such as fusion inhibitors (204), integrase inhibitors (205–209) and entry inhibitors(210,211). Each new drug or drug combination has offered improvements in terms of fewer side effects, lower long-term drug toxicity, lower pill burden, or more forgivingness to inconsistent adherence with lower risk of drug-induced resistance

development (212–216). Other new drugs have found their place in "salvage therapy" to persons who harbour multi-drug resistant virus, often due to a long and complex treatment history (217,218).

7.3 TRIPLE-CLASS VIROLOGICAL FAILURE (PAPER III)

Along with the advent of efficacious drug combinations around the millennium came a decrease in mortality (77,219–221), but also a concern about how long the effect would last. When people failed their first regimen, they had to start so-called second-line or third-line therapy because their virus had become drug-resistant and thereby rendered previously administered ART combinations ineffective. Experts were uncertain as to whether this evolvement would be avoidable even in the individual with perfect treatment adherence, and whether the invention of new antiretroviral drugs could keep up with the rate of resistance development and drug failure in the population. Early studies showed multi-drug class failure to be associated with poor prognosis (222), but only little was known about the incidence and prevalence of virological failure (223).

In paper III, we estimated time trends in both incidence and prevalence of drug failure towards three drug classes, so-called triple-class failure (TCF). Many studies of time trends in failure up to 2005 had been rather pessimistic with regard to failure rates and prevalence at the population level (224,225), but most of these studies had been prone to bias because their design was cross-sectional and based on observations from a single clinic. These cohorts are often ill suited for measuring temporal trends because they have a higher accumulation of difficult cases. DHCS, with its nation-wide design, is much less prone to this type of bias. In paper III, we found a declining population incidence of TCF during the years 1997-2003. When looking at incidence rates according to *time since ART initiation*, the incidence of TCF was declining from the 4th year onwards. Later studies have come to similar conclusions. The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) Group found a rising TCF incidence until 2005, followed by a decline during the subsequent 4 years until 2009. In another large study containing almost 46,000 observation years, the same group found the cumulative incidence of TCF to be 3.4% at 5 years and 8.6% at 9 years after starting ART, and a study from the UK Collaborative HIV Cohort (UK CHIC) containing >27,000 observation years found a 9.2% risk of TCF after 10 years of ART (226). These results correspond well to the cumulative incidence of 7.0% after 7 years of ART that we found in paper III (227). Of note, DHCS is part of COHERE but contributes less than 10% of total patient years, so this cohort overlap has only contributed marginally to the similar findings in the two studies.

7.4 CONSEQUENCES OF SUBOPTIMAL VIROLOGICAL CONTROL (PAPER IV)

The risk of virological failure in HIV populations with access to well-functioning health care is now quite low (paper III), but a proportion does not obtain full virological control (228–230). Getting full control requires a tailored ART combination that suits the individual in terms of virus susceptibility, side effects, and pill burden. Despite such "technical optimization" with regard to efficacy, however, some individuals experience temporary or permanent viraemia.

We do not always know the causes of these single or repeated episodes of detectable viral load, but we need to know their clinical relevance and role as predictors of long-term effectiveness. Many other predictors of poor outcome are present before starting therapy and include both biological and biochemical markers such as low CD4+ cell count, high viral load, malnutrition, and anaemia (77,219,231–233); and social determinants such as substance use (234), low socioeconomic status (235), mental disorders, and distress (236,237). Once a person has started ART, additional and valuable information is obtained from the virological response during the first 6 months, where increased viral load is associated with higher risk of death (238,239).

In paper IV, we went one step further and looked at whether virological control during the post-primary treatment period (7-18 months after ART initiation) was related to long-term clinical and paraclinical outcome. We found a clear difference in prognosis between persons with virological suppression 100% of the time (Group 1), persons with virological suppression part of the time (Group 2), and persons with no virological suppression at all during the 12-month period (Group 3). Whereas 89% of persons in Group 1 would be alive and virologically suppressed 6 years later (7.5 years after starting ART), this would be true for just 71% in Group 2 and 43% on Group 3 (Table 2).

Even the subgroup with virological suppression 75-99% of the time had a 2.17 times higher risk of death than the fully suppressed Group 1 (95% confidence interval 1.31-3.61). In all three groups, CD4+ cell counts continued to rise for 7.5 years, mostly so in Group 1. Later published studies similarly found that the number of episodes with viral rebound >500 copies/mL was inversely related to CD4+ cell count increase (240), and that the percentage of time with virological suppression was inversely related to future risk of virological failure (241).

Table 2

6-year prognosis from 1.5 to 7.5 years after ART initiation, according to level of viral suppression during the preceding 12-months. Group 1=fully suppressed, Group 2=partly suppressed, Group 3=not suppressed. (Source: paper IV)

Survival and viral suppression 72 months after baseline (7½ years after HAART initiation)					
Group	Cumulative survival from 0 to 72 months after baseline (percent) †	95% CI	Percent with VL<400 copies/ml 72 months after baseline	Percent alive and with VL<400 copies/ml 72 months after baseline	95% CI
1	93	(90 - 94)	96	89	(87 - 90) ††
2	86	(82 - 89)	83	71	(68 - 74) ††
3	76	(71 - 81)	57	43	(40 - 46) ††

Baseline: 18 months after HAART initiation
VL: viral load
†: Kaplan-Meier survival estimates
††: 95% CI estimated as [95% CI for survival] * [percent undetectable at 72 months]

7.5 CONCLUSION

Fortunately, the prevalence of TCF seems to have stabilized in Denmark (paper III) and in other settings (242). Hence, the concerns expressed 10 years ago that the majority of persons with HIV might exhaust their treatment options due to accumulation of multi-drug class failure have been somewhat allayed, but the risk remains relevant in many settings (243). With an estimated annual risk of TCF of 0.5-1.5% (227,242), the cumulative risk in children (244) and other HIV-infected persons with a long life ahead of them is far from negligible. Further, we must be aware that measured prevalences can be influenced downward by newly infected persons entering the population, i.e. increasing the denominator, and by increased mortality in persons with TCF, i.e. decreasing the numerator (paper VI) (226,245). Not only is comprehensive virological failure associated with increased risk of death (paper VI), a worsened long-time prognosis is also seen even after modest viraemia (paper IV). Many persons experience viraemia because they find it hard to adhere to treatment, and they often require more intensive support from the health care system or from peer groups, family or friends (187). Teams providing care for persons with HIV should keep in mind that "partial virological responders" compose a group at high risk of future failure and death and who should be given increased attention and support. Despite the positive trends, continued investments in development of new antiretroviral drugs will be required to ensure future treatment options for all persons with HIV.

8 DRUG RESISTANCE

8.1 BACKGROUND

8.1.1 Emergence of drug resistance

HIV mutates heavily, and thus has the potential to mutate into new strains that are resistant towards ART. The wild type virus phenotype is the most fit and will therefore remain the dominant sub type in persons who are infected with this type, as long as they are not exposed to antiretroviral drugs. When treating with ART, though, the virus can escape pressure from the antiretroviral drugs by emergence and proliferation of new mutations that are resistant towards the given treatment (246). It is therefore ultimately important to suppress viral replication completely (81), thereby avoiding the vicious cycle of ongoing replication and subsequent emergence of drug-resistant virus.

8.1.2 Relation between ART and drug resistance

Whether an ART combination is effective in the individual depends on both behavioural and biological factors. A multitude of factors influence adherence in the individual (195,237,247–250), and each drug has specific pharmacokinetic and pharmacodynamic properties (214,251–253). Each drug selects for up to several specific mutations (252), and some mutations confer cross-class resistance (254) to other drugs within the same class. Even though it is possible to fully suppress viral load for years and thereby avoid emergence of drug resistance, longer time on ART is invariably associated with increased risk of drug resistance both in the individual (255) and at the population level (5,256)(paper V). The clinical implications of individual mutations vary (257,258), but the accumulation of multiple resistance mutations towards several drugs and drug classes is associated with poor prognosis (7,259–262) (paper VII).

8.1.3 Relation between viral load and HIV transmission

Whether exposure to HIV results in HIV transmission depends on factors such as properties of the virus, properties of the recipient's immune system, genetics (e.g., the CCR5Δ32 mutation) (263), mode of exposure, and the amount of virus that enters the recipient (264). Evidence from early observational studies supported the theory that transmission was markedly diminished with low viral load (67,70,265,266), but only recently has it been confirmed in randomized trials that the risk of sexual HIV transmission from partners on ART with fully suppressed viral load is extremely low, both through heterosexual (86) and homosexual (267,268) intercourse.

8.1.4 Public debate

Before these game-changing RCTs, it was vividly discussed which kind of advice should be given to discordant couples comprising an HIV-infected person and an HIV-negative partner. In the so-called "Swiss Statement" from 2008 (269,270), the Swiss public health authorities publicly stated: "HIV positive individuals do not risk transmitting HIV to an HIV negative partner if the person has had undetectable HIV in the blood for at least 6 months has adhered strictly to his/her antiretroviral regimen, and is free of any other sexually transmitted infections". The statement was heavily criticized by a range of international bodies (271) for being overconcluding on available evidence.

While the above dispute predominantly concerned the transmission risk from individual to individual and the associated advice on HIV prevention, experts also discussed and studied the potential population effect of more and more persons being on ART, and the associated lower viral load in the population. The number of persons diagnosed with HIV was increasing as a result of rising or stable incidence combined with longer survival. Could it be, though, that the positive effect of better treatment coverage would counterweight this trend and thereby would result in lower population viral load, ultimately reducing transmission?

8.2 TIME TRENDS IN DRUG RESISTANCE DEVELOPMENT (PAPER V)

With an ever-larger cumulated time on ART in the population, and an increasing number of persons no longer on first-line treatment, there was fear that this would translate into an increasing incidence of new resistance mutations (272). On the other hand, the continuous advent of new drugs less likely to induce resistance could pull the trends in the other direction, as could a natural "saturation" of mutations occurring in the individ-

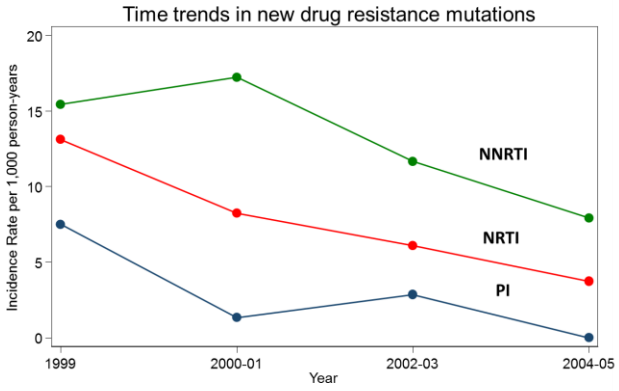
ual during the first months or years of treatment. Many studies reported scaringly high prevalences of drug resistance (273–276) and increasing time trends (277), but these studies were often cross-sectional in design and based on data collected from convenience-sampling. Thus, drawing conclusions on the incidence of new mutations was not possible.

As HIV genotyping started to become a more frequent procedure, large resistance databases became a valuable tool to estimate not just prevalence, but also incidence of new mutations. We used DHCS and DHSD to create a nationwide, Danish data set where genotypic test results were combined with clinical and paraclinical data. By applying strict criteria to when a new mutation was detected in an individual, related to when this individual had experienced virological failure, and with which ART regimen, we were able to estimate time trends in the incidence of new mutations (paper V).

We found decreasing population-based incidence rates of drug resistance acquisition during 1999-2005 for all three drug classes (Figure 4). Later studies from Italy and Switzerland have reported a decline in the prevalence of resistance-conferring mutations (215,278–280), and a very recent pan-European analysis found not only a moderate decline in the prevalence of resistance, but also a steep drop from 31% in 2000 to 1% in 2008 of persons who had exhausted available drug options (281). Even though most studies report declining trends, there may be geographical areas and subgroups in which the forecast is less optimistic. A recent Spainsh study in children with HIV reported rising prevalence of resistance mutations for all three major drug classes (282), while a study from the United Kingdom found a 17% 8-year cumulative risk of any mutation, although the cumulative risk of a PI mutation among those who started ART with a ritonavir-boosted PI regimen was only 7% (283).

Figure 4

Declining incidence rates of new drug resistance mutations from 1999 to 2005 for the three major drug classes. PI=protease inhibitor. NRTI=nucleoside reverse transcriptase inhibitor. NNRTI=non-NRTI. (Adapted from paper V)

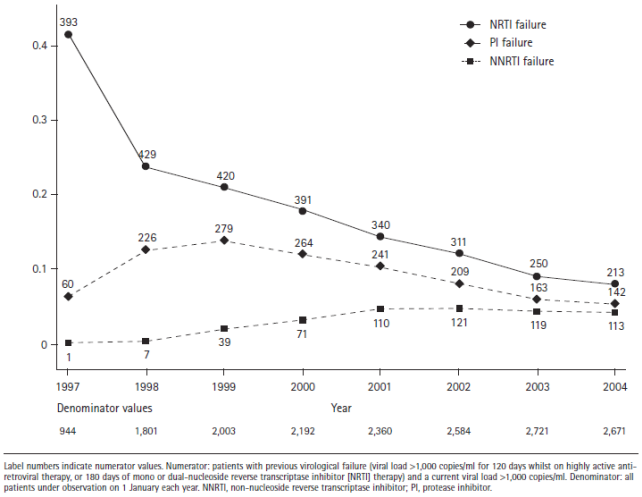


8.3 TIME TRENDS IN TRANSMISSION OF DRUG-RESISTANT HIV (PAPER VI)

A worst-case scenario of the population effect of introducing ART would be if drug resistance induced by antiretroviral drug pressure was widely transmitted from person to person and thereby increasing the proportion of persons newly infected with HIV who had limited treatment options already from the beginning. This concern grew along with the wide expansion of ART availability, changing thresholds for ART initiation putting more people on therapy, and the longer cumulated time on ART in the populations. Indeed, early studies found higher than 20% prevalence of transmitted drug resistance (TDR) on both sides of the Atlantic Ocean (284–288), increasing over time, and with multidrug-resistance prevalence up to 10.2% (289). Another issue adding further concern were reports of changes in risk behaviour: the general opinion that HIV was becoming a treatable disease meant that persons without HIV were less worried about protecting themselves; and the improved health among persons with HIV was leading to a more active life and sex life (290). Pulling in the other direction, towards less transmission of drug-resistant virus, was the growing scientific evidence that persons with fully suppressed HIV replication are de facto non-transmitters (67,265,266), and the fact that drug-resistant viral strains are less fit and therefore possibly less likely to be transmitted(246,261,291,292). Indeed, a number of studies reporting declining or stable levels of TDR were published in the early 2000s (293–297).

Figure 5

Prevalence of persons in DHCS at risk of transmitting drug-resistant HIV during 1997-2004. (Source: paper VI)



Based on the availability of comprehensive data on ART regimens and viral load in our cohort of Danish persons with HIV we were able to estimate temporal changes in the prevalence of persons with HIV who could potentially transmit drug-resistant virus (paper VI). We found a decrease from 1997 to 2004 in the prevalence of potential transmitters of drug-resistant HIV (Figure 5), brought

about by successful re-suppression of viral load in potential transmitters as well as a decline in the incidence of drug re sistance.

Later studies from different parts of the world have expressed diverging trends: a decline and stabilisation of TDR (298,299) and a projected stabilisation of persons with extensive triple-class failure and viral load >50 copies/mL (300) in the UK, stable TDR in France (301), and an increase in TDR in Canada (302) driven by NRTI and NNRTI resistance. Recent reports from Sub-Saharan Africa, the Dominican Republic, and other part of Latin America (303–306) indicate emergence of TDR in locations where viral load testing and resistance monitoring are not routine practices.

8.4 CONSEQUENCES OF HARBOURING DRUG RESISTANCE MUTATIONS (PAPER VII)

Virological failure, drug resistance, and mortality are intertwined. Virological failure increases the emergence of drug-resistant mutations, mutations decrease the chance of virological re-suppression (307–311) and immunological recovery (312), and the result of this vicious cycle is increased risk of death (222,259,260,262,313).

Our results should be interpreted together with a range of related findings: increased mortality in patients with multidrug-resistance (314–316); specific individual mutations related to the prognosis (317); and the link between viral load suppression, increased CD4+ cell count (318) and reduced clinical progression (319) after TCF. The prognosis after TCF has improved during later years, and recent studies point towards the introduction of new antiretroviral drugs having been the prime driver (245,320).If a patient experiences virological failure, a resistance test is used to guide the clinician in choosing a different and efficacious drug regimen. If no drug resistance is found, the clinical team will have confidence in attempting to improve adherence on the current treatment regimen. Such a drug-conservation strategy is often preferred, because a regimen change could mean one less treatment option for future use, and because second-line regimens are often more costly than first-line combinations. Unfortunately, in areas with no easy access to drug resistance tests, the clinical decision has to be made as a qualified guess, predominantly based on HIV RNA measurements. Testing for drug resistance was not yet routine in the early years of combination ART (and still is not in most low- and middle-income countries). More knowledge was therefore needed concerning the association between observed virological failure and existence of drug resistance, and on the association between drug resistance and death in persons with virological failure.

In Denmark, drug resistance testing had long been routine every time a patient experienced virological failure, so the testing pattern was less influenced by convenience sampling seen in many previous studies. Combined with the nationwide nature of the cohort, DHCS therefore provided a very good setting for assessing both the prevalence of resistance mutations in patients with virological failure, as well as the influence of these on mortality (paper VII). In our population of persons with triple-class virological failure, 88% had resistance mutations towards at least one drug class, and 61% had resistance mutations towards all three major drug classes. A high overall number of mutations as well as three individual mutations, one from each drug class, were independent predictors of death. The relationship between resistance mutations and death seemed to be mediated by low CD4+ cell count (Table 3).

Table 3

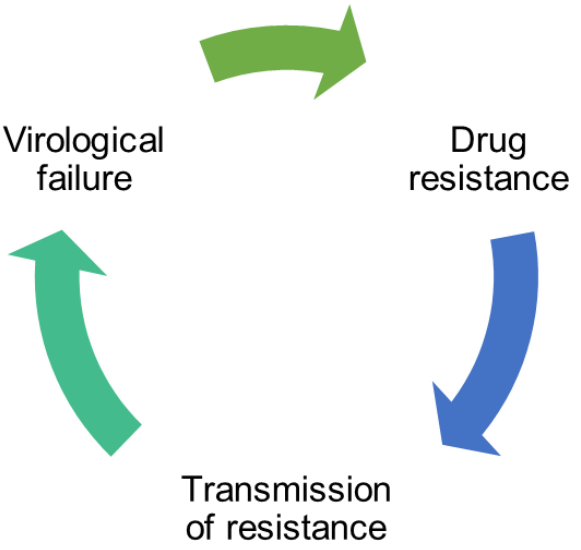
Mortality after triple-class virological failure according to number and pattern of drug-resistance mutations. (Adapted from paper VII)

Mortality after TCF												
	Adjusted for CD4 cell count at baseline*			Adjusted for time-updated CD4 cell count*			Adjusted for [illegible] CD4 cell count at baseline and influential individual [illegible]			Adjusted for time-updated CD4 cell count and influential individual mutations*		
	MRR	95% CI	P	MRR	95% CI	P	MRR	95% CI	P	MRR	95% CI	P
Number of mutations												
<=8	1.0	-	-	1.0	-	-	1.0	-	-	1.0	-	-
>=9	2.3	1.1-4.8	0.020	1.4	0.7-2.9	0.348	0.9	0.4-2.3	0.896	0.8	0.3-1.9	0.556
CD4 count at baseline												
>200	1.0	-	-	-	-	-	1.0	-	-	-	-	-
50-200	3.6	1.5-8.8	0.005	-	-	-	3.4	1.4-8.4	0.008	-	-	-
<50	8.6	3.0-24.7	<0.001	-	-	-	10.5	3.6-30.5	<0.001	-	-	-
CD4 count, time-updated												
>200	-	-	-	1.0	-	-	-	-	-	1.0	-	-
50-200	-	-	-	3.1	1.2-8.0	0.020	-	-	-	3.0	1.1-7.9	0.026
<50	-	-	-	9.9	3.9-25.4	<0.001	-	-	-	9.6	3.7-25.1	<0.001
T215Y	-	-	-	-	-	-	3.0	1.3-7.4	0.014	3.0	1.2-7.0	0.014
G190A/S	-	-	-	-	-	-	2.7	1.2-6.4	0.023	1.7	0.7-3.9	0.228
V82F/A/T/S	-	-	-	-	-	-	1.1	0.5-2.7	0.760	0.8	0.4-1.9	0.656

Cox regression analysis of time to all-cause death after triple-class virological failure (TCF). *Further adjusted for log(10) viral load (VL) and age at baseline, gender, year of TCF, and being antiretroviral therapy (ART)-naive at initiation of highly active ART. CI, confidence interval; MRR, mortality rate ratio.

8.5 CONCLUSION

The fear of a vicious cycle of virological failure → drug resistance → transmission of resistance → virological failure remains relevant in 2014. Local epidemics are not yet under control (321), and while the positive reports are examples of what can be achieved in privileged settings; the negative reports remind us of how much needs to be done to get every corner of the epidemic under control. Our findings in papers V and VI underline the crucial importance of always having an effective treatment option available for the patient with drug-resistant virus. Access to viral load testing and resistance monitoring needs to be expanded to allow every person with HIV initiate ART with an efficacious drug combination, detect virological failure in time, and change to the best possible second or third line regimens when needed.



9 LIFE EXPECTANCY

9.1 BACKGROUND

9.1.1 Improved HIV management

The decade around the millennium saw a tremendous improvement in HIV management. Drugs and drug regimens became more efficacious and effective, they were less likely to induce resistance if a pill or two were forgotten, they had fewer side effects, and one tablet a day drug combinations became available (200,202,203,213,216). Overall, it was becoming easier to live with HIV, in particular for those who were not infected with drug-resistant virus and who were to receive ART for the first time. Not only had the drugs become better, medical staff was also learning how best to use the available drugs and monitoring tests. Further, being an HIV patient in a state-of-the-art clinic meant access to psychosocial support such as counselling and peer groups, important ingredients in the package offered to persons with HIV (187).

9.1.2 Reduced mortality

Positive reports were emerging, comparing mortality rates in successfully treated HIV-infected persons with those of the general population. Mortality rate ratios were as low as 3-10 and thus approaching those of other chronic diseases (39,219,322,323), and in a subgroup of the Swiss HIV Cohort Study the excess mortality rate was found to be below just 5 deaths per 1,000 persons per year (324). A computer model estimated that patients in the Collaborations in HIV Outcomes Research/US (CHORUS) cohort had a median survival from diagnosis to death of 20.4 years (325), about twice as long as in untreated patients.

9.1.3 The need to plan for the future

As persons with HIV were now clearly surviving longer in countries where HIV treatment was available (220), affordable and accessible, many started to ask the question of how long they might expect to live. Many persons with HIV were banned from privileges which most persons take for granted such as obtaining mortgage, life insurance or even health insurance, because HIV was still largely seen as a disease which would only allow you few years of survival. Other important decisions such as having a child or saving up for retirement pension might also become relevant and necessary if death was no longer near coming.

There was a strong desire among persons with HIV to know their life expectancy, but many experts considered available knowledge too uncertain to try to answer this question. The first highly effective ART combination regimens had been introduced in 1996-1997 (11), so any predictions would be based on less than 10 years of experience. There were many unanswered questions: How long would people be able to adhere to treatment? Would any effective treatment eventually lead to virological failure? Would mutations emerge, either being a result of the failing treatment or even be the primary cause of failure? Would the speed of new and more effective drugs arriving on the market be able to keep up with the accumulation of drug mutations in the population? While it was likely that we would continue to see individual success stories, might one dare hope that this would translate into substantial improvement on the population level?

9.2 LONG-TERM SURVIVAL (PAPER VIII)

9.2.1 Measuring survival

Whatever method used to estimate survival in a population, it has shortcomings. A *cohort life table* created from direct observation of mortality in a very large cohort followed for a very long time will allow for accurate estimates of both median survival time (the time until half of the studied population has died) and life expectancy (the arithmetic mean of the survival times (326)) in that cohort. Due to the many years of data collection involved in this approach, the measurements would likely be outdated and therefore not useful to predict survival in a current cohort. Another approach is to use a *period life table,* whereby age-specific mortality observed in a cohort over a shorter period of time is assumed to apply to an individual over a life span (327). The clear disadvantage of this approach when studying the effect of ART on population survival is that we estimate survival way beyond the current maximum experience with ART. A third approach is to use *mathematical computer models*. These models, based on cohort data, can apply different assumptions to the effect of uncertain and potentially influential factors such as future effectiveness of ART and drug-resistance development, but their reliability is highly dependent on the quality of the data that are driving the assumptions that go into the model.

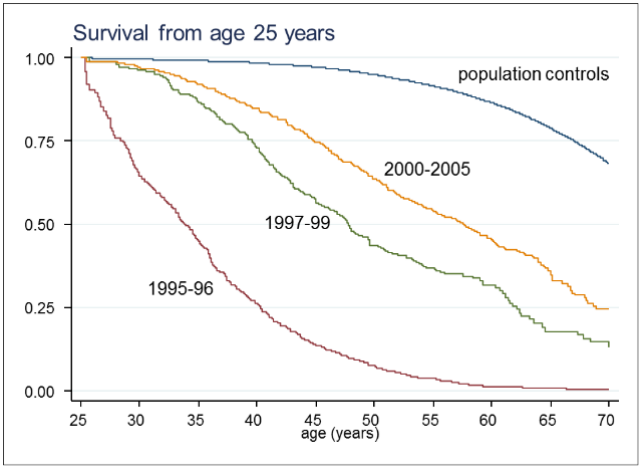
9.2.2 Survival in persons with and without HIV

In Paper VIII, we used *period life table* methods to estimate age-specific mortality rates and median survival for the entire DHCS cohort in different time periods, compared with a cohort from the general population. The previously described advantages of DHCS being nationwide and with very few persons lost to follow-up

allowed us to interpret the results as a largely unbiased picture of the impact of a cross-healthcare system effort to manage HIV. We found a clear improvement in survival over time from the period before availability of highly effective combination ART (1995-1996), to the period immediately thereafter (1997-1999), with further improvements to the period after 2000 when highly effective ART had become established across the health care system. Most importantly, we estimated that a 25-year old person with HIV had a 50 percent chance of surviving another 32.5 years (Figure 6) if he/she was under care in the period 2000-2005.

Figure 6

Cumulative survival curve for persons with HIV and persons from the general population. Persons with HIV infection are divided into 3 calendar periods of observation. (Adapted from paper VIII)



In DHCS, HCV coinfection is correlated to injecting drug use (IDU) and is a marker of family-related increased risk of death (328,329). During the period 2000-2005, persons with HCV represented 16% of the cohort. The median survival for a 25-year old HIV/HCV coinfected person was just 20 years (Table 4), whereas for a person with HIV but without HCV infection the median survival was 39 years, only 12.2 years less than in the matched general population cohort. We saw no signs of increased mortality with increasing years on ART, nor with increasing time after diagnosis. Thus, although we had less than 10 years observation of any individual, we carefully assumed that our results were a valid estimate of long-term survival.

9.2.3 Current status

Not surprisingly, studies estimating life expectancy and mortality have been booming in later years. The gap between persons with HIV and the general population is consistently reported to have declined over time, shown in single- and multi-cohort studies from China (330), the United States (76), and across Europe(76,331). The difference in life expectancy between persons with HIV and the general population reported in recent studies range from 7 to 18 years (332–337). In selected subpopulations for example non-IDUs or persons with good CD4+ cell response to ART or high CD4+ cell count at ART initiation, life expectancy approaches (338), equals(333,339–342) or in some cases even exceeds (332) that of the general population. Recent review studies come to the conclusion that the life expectancy for persons with HIV equals that of the general population "under ideal circumstances" (343–346). A recent Australian study showed no signs of increasing standardized mortality ratios (SMRs) in persons who had been on ART for up to 15 years (347), compared to the general population. Further, in those countries most affected by HIV, we are even beginning to see the overall population impact. In Kwazulu-Natal in South Africa, life expectancy increased from 49.2 years in 2003 to 60.1 years in 2011, predominantly due to the introduction and expansion of ART (348).

Table 4

Mortality rates and median survival at age 25 years for persons in DHCS, stratified according to "time on ART", "time after diagnosis", "observation period", and HCV status. (Adapted from paper VIII)

Median survival and mortality rates starting at age 25 years

	Persons with HIV				Persons with HIV observed 2000-2005 only			
	PYR	events	MR per 1000 PYR (95% CI)	Median survival after age 25 years (95% CI), years	PYR	events	MR per 1000 PYR (95% CI)	Median survival after age 25 years (95% CI), years
All	22744	970	43(40-45)		13644	346	25(23-28)	
HAART period								
No HAART	8271	537	65(60-71)		2946	66	22(18-29)	
1st year of HAART	2605	124	48(40-57)		1073	46	43(32-57)	
2nd-3rd year of HAART	4534	121	27(22-32)		2464	57	23(18-30)	
4th-5th year of HAART	3570	92	26(21-32)		3398	81	24(19-30)	
6th year of HAART onwards	3764	96	26(21-31)		3763	96	26(21-31)	
Time since diagnosis								
1st-2nd years after diagnosis	3436	159	46(40-54)		1875	48	26(19-34)	
3rd-4th years after diagnosis	3419	133	39(33-46)		1901	32	17(12-24)	
5th-6th years after diagnosis	3136	116	37(31-44)		1786	32	18(13-25)	
7th-8th years after diagnosis	2799	117	42(35-50)		1630	34	21(15-29)	
9th-10th years after diagnosis	2614	129	49(42-59)		1439	24	17(11-25)	
Hepatitis C status								
HCV-positive	4149	246	59(52-67)	17.5(15.0-19.6)	2245	127	57(48-67)	19.6(16.1-21.9)
HCV-negative	18595	724	39(36-42)	21.0(19.3-23.2)	11399	219	19(17-22)	38.9(35.4-40.1)
Observation period								
Observed 95-96	3242	402	124(112-137)	7.6(4.8-9.6)				
Observed 97-99	5857	222	38(33-43)	22.5(20.0-24.5)				
Observed 00-05	13644	346	25(23-28)	32.5(29.4-34.7)				

HIV: human immunodeficiency virus, PYR: person-years at risk, MR: mortality rate, HCV: hepatitis C virus, HAART: highly active antiretroviral therapy

9.3 CONCLUSION

The uncertainness and fear about the durability of the HIV response at the population level is gradually changing towards a positive feeling for the future. Our study (paper VIII) was one of the first to put an age to the life expectancy, and with several subsequent, similar reports from other corners of the world, it has become evident that the overall prognosis for persons with HIV is moving rapidly in the right direction.

10 COMORBIDITY

10.1 BACKGROUND

10.1.1 AIDS-related comorbidity

Comorbidity in persons with HIV has always been in focus, simply because the clinical manifestation of HIV infection occurs through emergence of infections and other diseases as the virus gradually breaks down the immune system. Unusually high prevalence of Pneumocystis Carinii pneumonia and Kaposi Sarcoma (349,350) were some of the first observations which lead to characterization of AIDS (351) and later discovery of human immunodeficiency-related virus (HIV) (352). As most AIDS-defining conditions are

associated with different levels of immune deterioration, the pattern of comorbidity changes when the CD4+ cell count decreases (353). ART-induced immune recovery not only lowers the incidence of AIDS, it also results in many of the AIDS-defining conditions waning or disappearing as the CD4+ cell count restores; this has been observed even for the malignancy Kaposi sarcoma (354–357).

10.1.2 Non-AIDS related comorbidity

The pattern of non-AIDS comorbidity is equally complex; the epidemiology of the comorbidity is far from fully explored and understood, and the pattern of comorbidity changes from one cohort to another. Some comorbid conditions are present before the person acquires HIV, and some diseases emerge after the HIV infection. In scientific studies, diseases and conditions occurring after the person has been diagnosed with HIV are sometimes called "non-AIDS events". These events can be related to HIV, or they might be no different from those observed in a similar non-HIV population with regard to aetiology and incidence rate.

Several non-AIDS diseases are more common in persons with HIV compared to the general population (358–361). A recent review focusing on anal cancer, Hodgkin's lymphoma, hepatocellular carcinoma, and lung cancer found two-fold increased rates of these four cancer types (362). Highly increased risk of anal cancer was also found in studies from Denmark (363), and the United States (364), the latter additionally finding a 21-fold increased rate of vaginal cancer, as well as moderately increased rates of melanoma, oropharyngeal, colorectal and renal cancer. A meta-analysis studied cancers in 444,172 persons with HIV and performed a similar analysis for 31,977 transplant patients to control for possible confounding by immune suppression. This study found increased standardized incidence ratios for lung cancer, leukaemia, renal cancer, oesophagus cancer and stomach cancer (365). A study among US Veterans showed a doubled risk of end-stage renal disease for HIV-infected compared with uninfected among black persons (366), and other studies have shown increased risk of cardiovascular disease(CVD) (367)(368) and liver disease (369) compared to the general population.

Despite their label, the prevalence of many "non-AIDS" diseases is inversely related to CD4+ cell count. This includes liver diseases (369), non-AIDS malignancies (358,370), renal diseases (358,371), and bacterial non-AIDS infections (372–375). An exception is perhaps CVD (358,376) which doesn't seem to follow this pattern. In some cohorts, non-AIDS morbidity has decreased over time as the CD4+ cell levels in the population has increased (377,378).

10.2 MECHANISMS BY WHICH NON-AIDS CONDITIONS COULD BE RELATED TO HIV

There are numerous possible ways by which non-AIDS related conditions and diseases could be higher in persons with HIV than in persons without HIV (358): *Common risk*: Some comorbidities share risk factors and transmission mode with HIV, for example sexually transmitted diseases, HCV, IDU overdose, and human papilloma virus (HPV)-associated cancers. *Immune activation:* HIV induces alterations in the immune and inflammatory systems and activates the coagulation system (379–383). The immune activation leads to increased lymphocyte turnover which might be linked to cancer (384,385), in particular those types which might be associated with infections (361). These include Chlamydia pneumoniae and lung cancer (386); Helicobacter Pylori and gastric cancer (387); HPV and anal, cervical, and oropharyngeal cancer (388); HBV/HCV and liver cancer (389); and Ebstein-Barr virus and Hodgkin Lymphoma (390). Immune activation might also be related to CVD (391), faster progression of liver disease in persons co-infected with HBV and HCV (392,393), and renal disease such as HIV associated nephropathy (HIVAN) and immune complex glomerulonephritis (394). *Age*: With persons with HIV now living longer, they acquire the same age-related diseases as persons without HIV, for example cancer, neurocognitive impairment, diabetes (395), CVD, and chronic obstructive pulmonary disease. These have to be recognised by the HIV physician, but they also pose new challenges of multi-drug pharmacotherapy and potential drug interactions (396,397). *ART*: Lipodystrophia, hyperlipidemia, CVD, and renal disease are all related to specific antiretroviral drugs (398–407), and antiretroviral therapy might also play a role in the premature frailty observed in persons with HIV(408–410). *Lifestyle and social conditions*: Smoking and rough living conditions are all more common among groups of persons with HIV (411,412), associated with increased risk of for example lung diseases, violent injuries and psychiatric illness (413). *Chronic disease:* As HIV is now a chronic disease, we might see conditions found more frequently among persons with chronic diseases such as depression(414–416).

10.3 COMORBIDITY AND SURVIVAL (PAPER IX)

10.3.1 Measuring comorbidity and causes of death

As mortality has declined towards that of the general population, the pattern of diseases and conditions causing death have changed (221,417–421). Fewer persons with HIV now die from AIDS, and while this has led to an increase in the *relative* contribution of non-AIDS causes of deaths (Paper VIII) (Table 5), several studies report a simultaneous decline in *absolute* mortality from non-AIDS deaths (419,422,423). The association between high CD4+ cell count and lower risk of death also seems consistent across different causes of both AIDS deaths and non-AIDS deaths (358,424,425).

While comorbidity is indeed related to mortality, there is no direct relationship between causes of death and the incidence and prevalence of different comorbidities. Some non-AIDS diseases might not be fatal and therefore never be registered on a death certificate, and others might be overtaken by other non-AIDS events causing immediate death. Thus, diseases associated with shorter time between occurrence and death will more frequently be registered as causes of death, for example in a person with a deadly disease such as cancer who dies from a myocardial infarction. A person might be registered as dying from an acute

event, even if an underlying chronic disease is causing this, for example a person with diabetes who dies from a stroke caused by diabetic angiopathy. Different practices in coding of deaths from one hospital to another might also lead to quite different results, or the validity of causes of death, which are often quickly registered by the physician who happens to be on-call when the person dies, can be rather low. This is of course improved if the standardized coding of deaths (CODE) is used (426,427).

Table 5

Cause-specific mortality in DHCS. (Source: paper VIII)

Mortality rates according to cause of death and calendar period

	Cause of death	PYR	Events	MR per 1000 PYR (95% CI)	Percent of all cause mortality rate	Percent of mortality rate by known causes
Observed 95-96						
	All causes	3243	402	124 (112-137)	100%	
	HIV-related	do	231	71.2 (62.6-81.0)	57%	76%
	Non-HIV related	do	75	23.1 (18.4-29.0)	19%	24%
	Unknown	do	96	29.6 (24.2-36.2)	24%	
Observed 97-99						
	All causes	5857	222	37.9 (33.2-43-2)	100%	
	HIV-related	do	104	17.8 (14.7-21.5)	47%	57%
	Non-HIV related	do	80	13.7 (11.0-17.0)	36%	43%
	Unknown	do	38	6.5 (4.7-8.9)	17%	
Observed 00-05						
	All causes	13644	346	25.4 (22.8-28.2)	100%	
	HIV-related	do	96	7.0 (5.8-8.6)	28%	43%
	Non-HIV related	do	128	9.4 (7.9-11.2)	37%	57%
	Unknown	do	122	8.9 (7.5-10.7)	35%	

The above-mentioned "pitfalls" make analyses of cause-specific survival complicated, because of the many "competing risks" involved. Competing risk statistical models do exist (428), but exploring the relative contribution of comorbidity on mortality is best done by computing relative survival. The relative survival method is a standard approach that can be applied to any disease (429,430). Study groups are stratified into different modes of exposure (disease versus no disease) and all-cause survival and mortality rates are compared between the two groups.

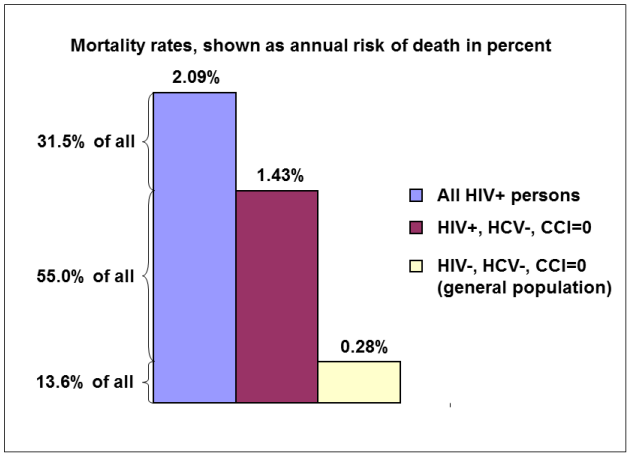
10.3.2 Survival according to comorbidity present before HIV acquisition

In paper IX, we used relative survival methods to explore the impact of comorbidity acquired *before* HIV acquisition on mortality. Access to morbidity records going back 10-20 years before persons in our cohort were diagnosed with HIV enabled us to compare strata with or without comorbidity. Further, access to good survival data in a matched general population enabled us to estimate and adjust for background mortality. We identified comorbidity acquired before HIV as at least one point on the Charlson Comorbidity Index (CCI) score at the time of HIV diagnosis. We found that persons with HIV, compared to the general population, had more CCI comorbidity (11.3% vs 8.0%). All-cause mortality increased with higher CCI score. In an adjusted analysis, having a CCI score of at least one was associated with a 1.84 times increased risk of death, compared a CCI score of zero. We also found that any CCI comorbidity had more impact on mortality in persons with HIV than in persons without HIV, with 34.1%-58.8% of the excess mortality caused by this interaction effect.

Finally, we estimated the size of the proportion of deaths in DHCS could be attributed to comorbidity acquired before HIV or to comorbidity otherwise not on the causal pathway between HIV infection and death. For this analysis, we included background mortality as well as mortality due to CCI score and HCV coinfection. We first calculated the *population attributable risk (PAR)* of comorbidity (HCV and CCI) in our cohort. The *PAR* is the relative reduction in incidence rate (IR) if a given population had been unexposed: PAR = (IR_{pop} - IR_{unexp}) / $IR_{pop.}$ All-cause mortality in the population with HIV was 2.09% per year. Among those persons unexposed to HCV (HCV=0) and other comorbidity (CCI=0), all-cause mortality was 1.43%. This gives a PAR of 0.32 (0.66/2.09). Thus, if all persons with in our HIV cohort had been without HCV and CCI comorbidity, 32% of deaths would have been avoided. We now calculated the *excess risk (ER)* of HIV, compared to the general population, in persons free of HCV and CCI comorbidity. The ER is the difference between the incidence rate in the exposed population, and the incidence rate in the unexposed population: ER = IR_{exp} – $IR_{unexp.}$ All-cause mortality in the population with HIV (HCV=0, CCI=0) was 1.43% per year. Among matched general population controls (HCV=0, CCI=0), all-cause mortality was 0.28%. Thus, the ER of being infected with HIV is 1.15% per year. Our final calculation estimated that 32% of the observed mortality in our cohort was due to HCV and CCI comorbidity, 55% (1.15/2.09) was due to HIV, and the remaining 13% (0.28/2.09) corresponded to the background mortality in the population (Figure 7).

Figure 7

Visual presentation of the total mortality in persons with HIV and the relative contribution of background mortality (13.6%), HCV coinfection and CCI (31.5%), and HIV (55%). (Source: paper IX)



10.4 CONCLUSION

The results in paper IX can help us focus and set ambition levels for future efforts to reduce mortality in persons with HIV (344,431). Our findings confirm that persons acquiring HIV differ *at large* from the general population, and that we cannot expect overall mortality rates to reach the level of the general population. Instead, we need to identify groups with increased, *preventable* risk of death. The origin, aetiology, and consequences of each comorbid condition should be explored and characterised,

both at the population level and in the individual; including behavioural, social and biological root causes.

11 PERSPECTIVES

11.1 STATUS OF THE EPIDEMIC

This work has given a brief overview of the immense improvements in morbidity and mortality for persons infected with HIV during the first 30 years of the epidemic - with particular focus on how the nine papers included in this thesis might have played a role. The "road to success" for the individual starts with early diagnosis, followed by early enrolment into a health care system that provides high quality HIV care at all levels. Timely initiation of effective ART is essential, and continued monitoring of viral load is the key to avoiding the development of drug resistance and ensuring the shift to appropriate second-line regimens when needed. If the person is fortunate to stay free of other diseases, a successful trip down this road will be rewarded with a life expectancy that is very close to that of a comparable person who is not infected with HIV. This scenario has become reality for many persons in high-income countries, but many groups and individuals have not yet experienced the full benefit (321). Further, although we have also seen immense improvements in countries where the epidemic has hit the hardest (348), only 45% of those living with HIV in sub-Saharan Africa in 2013 knew their status, only 39% received ART, and only 29% had fully suppressed viral load (321).

The good news is that the overall feeling for the future in the HIV community is optimistic. UNAIDS has dared to set ambitious, although not unrealistic targets for the future: a 90% reduction in new infections, a 90% reduction in stigma and discrimination, a 90% reduction in AIDS-related deaths; and an end to the AIDS epidemic as a public health threat by 2030 (321,432). Achieving these goals will require a concerted effort from the HIV community, including targeted research to gain new knowledge as well as a strong focus on scaling up implementation of existing solutions.

11.2 FUTURE OPPORTUNITIES

11.2.1 Integrated solutions

The successful HIV response is causing fewer new infections, lowering mortality, and reducing AIDS-related discrimination, while other diseases are climbing up the ladder as important contributors to the global burden of disease (433,434). The days of *AIDS exceptionalism* are over (435,436), and HIV needs to find its natural place as a chronic disease. More than ever do we need stronger health systems that can provide HIV care and management integrated with that of other diseases in horizontal programmes (437,438). Although the feasibility of integrated care models has been shown in some settings (439–441), more implementation science is required to identify solutions that are scalable and sustainable.

11.2.2 Timely diagnosis

An unacceptably large gap exists between the number of persons living with HIV, and the proportion of those who have yet been diagnosed (321). To fill the gap, countries need detailed knowledge on the demographics of their local epidemic (345). Which groups and geographical areas have high prevalence of persons with HIV, and how can they be reached? "Know your epidemic" was a slogan originally used to describe the need to tailor HIV prevention efforts (83,85), but it is equally relevant (84) when it comes to finding those persons who are unaware of their positive HIV status. Several current initiatives support this challenge: The European HIDES Study aims to develop a model for implementation of targeted HIV testing in clinical settings (149), WHO and UNAIDS have produced guidelines on how countries can use available data for a more effective response to their local HIV epidemic (84), and the systematic collection and compilation of detailed global epidemiological data by UNAIDS provides an invaluable backbone for many of these efforts(442). Ultimately, each country needs to develop its own HIV detection strategy, optimally suited to the local epidemic.

11.2.3 Improved care

Today´s increased life expectancy in persons with HIV calls for improved understanding of aging and comorbidity. There is a growing need for age-specific guidelines (345), for clinicians across specialties who can provide care for an aging population with multiple morbidities (358), and for health systems that can deliver the continuity of care required by older people (443,444). As comorbidity patterns have changed, there is also a growing need to identify groups and individuals with increased, preventable risk of death and disease. We must re-evaluate screening programmes for cancer and other diseases to assess their cost and effectiveness in HIV populations (359,445), and put greater focus on promoting healthy lifestyle (345). Better understanding of the drivers behind non-AIDS comorbidity will allow us to develop and prioritize interventions that are targeted to a specific clinic, cohort, or population.

Despite the undisputable success of ART, a number of questions pertinent to HIV treatment and care remain to be answered. It is currently debated whether individuals will benefit from starting ART at a higher level than the most commonly used CD4+ cell count threshold of 350 cells/µL (89,446). Current evidence is largely based on observational studies (447) and should therefore be interpreted with caution due to the inherent risk of confounding by indication in this type of study. The ongoing Strategic Timing of AntiRetroviral Treatment (START) trial (448) is enrolling study subjects with CD4+ cell count above 500 cells/µL who are randomized to start ART immediately or defer initiation until the CD4+ cell count falls below 350 cells/µL. The START trial should be able to provide new and valuable knowledge on the subject. We also need more knowledge on how to control the chronic immune activation and inflammation which seems to play an important role in the changing patterns of comorbidity (449,450).

Human, technical, and financial resources in health systems are not equally distributed, and many local HIV epidemics are not yet under control (321). Being a key component of effective HIV care, access to viral load testing and drug resistance monitoring needs to be expanded to allow every person with HIV to initiate ART with an efficacious drug combination, detect virological failure in time, and change to the best possible second or third line regimens when needed. If we continue to improve and implement new models of HIV care delivery, mortality can decline even further. These models should be based on an inclusive and individualized approach to patient management, taking into account the biological and psychosocial properties of each person with HIV.

11.2.4 New therapies

The world must not stop investing in the development of new therapies. New antiretroviral drugs will be essential to ensure continued availability of effective treatment options for those who have failed one or more drug combinations and are therefore accumulating multi-drug resistant virus. The scientific community should also continue to look for ultimate solutions such as a preventive vaccine (451) or an HIV cure (15–18). The allogeneic bone marrow transplantation from a donor homozygous for CCR5Δ32 to the so-called "Berlin Patient" was the proof-of-concept that HIV eradication is technically possible (263), and the most promising current methods being investigated are gene therapy (452) or purging of viral reservoirs(453,454).

11.2.5 Prevention

HIV prevention is outside the scope of this thesis, but deserves a few lines due to the recent advances in effective prevention strategies, the dual effect of ART as prevention and treatment at the same time, and the role of prevention as the ultimate goal to eliminate HIV. The immense amount of HIV prevention research has revealed a range of effective behavioural, biomedical, and structural interventions. *Combination prevention* combines these interventions in tailored programmes, and is hoped to have a considerable impact on reducing new infections in the coming years (455,456). More simple in its approach is *treatment as prevention*, which in the most radical version relies on a population-based test-and-treat-all strategy to reduce the population viral load and thereby the incidence of new infections (88,457–459). Upcoming results of cluster-randomized trials will be awaited with excitement (97,105–108,110,111).

12 CONCLUSION

This thesis attempted to map the "road to success", i.e., the road leading to increased survival of individuals and populations with HIV, ultimately to levels approaching those of the general population. Each of the nine studies explored and discussed some of the many bumps and other challenges that one needs to navigate in order to proceed safely down this road. Through a massive global effort for decades, HIV research has taken a giant leap to get this far. The studies in this thesis have each paid their modest contribution to show how crucially important it is to be diagnosed in time, to have access to a well-functioning health system, and to keep free of comorbidity both before and after acquiring HIV. After many years of struggle and despair, the HIV response is on the right track. Thanks to enormous advances in prevention and treatment, we are now looking towards a promising future. With a continued, relentless effort from every corner of the HIV community, we will be able to continue rapid expansion and implementation of current and new knowledge to benefit persons with HIV, persons at risk of acquiring HIV, and global public health.

13 SUMMARY

The work on this thesis began in 2003 when the global HIV epidemic was out of control. A minority of persons with HIV were benefitting fully from the recently introduced highly efficacious antiretroviral therapy (ART) combinations. Among the global challenges were lack of access to good health care, drug toxicity, and emergence of drug-resistant virus. It was unknown how long the drugs could maintain their efficacy in the individual even if administered as intended, and there was a fear that the increased drug pressure would increase the prevalence of drug resistance, subsequently leading to transmission of resistant virus from one individual to another, and thereby waning the treatment options available. Hence, we were far from the ideal conditions where an HIV-infected individual gets to know immediately that he/she is infected, has access to specialized medical and social support, receives a drug combination which effectively suppresses the virus and has no side effects, and is free of comorbid conditions both before and after he/she gets infected. The nine papers on which this thesis is based each aimed to provide new knowledge to aspects of the above.

Late diagnosis and late presentation to clinical care continue to be major barriers to improved HIV management. We used nationwide hospital registries to explore the potential for an indicator disease-based HIV testing strategy. A range of conditions that were manifestations of the HIV infection itself were found to be associated with highly increased risk of HIV diagnosis during the coming year, but less so 3 to 5 years later. Other conditions were associated with an almost constant 5-year long increased risk of being diagnosed with HIV because they share behavioural risk factors with HIV, making them indicators of not only current HIV but also of future HIV acquisition. Hence, indicator condition-based testing should be adapted to the local epidemic and could be a valuable addition to the existing detection practice.

Once diagnosed, getting the full benefit of modern HIV care requires access to a good health care system. We compared temporal trends in quality and quantity of ART introduction in Denmark and Greenland. Despite similar levels of health worker education and economic resources, ART implementation and mortality decline in Greenland lacked several years behind Denmark. The study reminded us that although economy may be a prerequisite for implementing an effective HIV care system, it is certainly not all it takes.

The nationwide nature of the Danish HIV Cohort Study also allowed us to study a number of time trends at the population level. Despite what was feared, we found that the prevalence of triple-drug class virological failure (TCF) seemed to have stabilized after 2000; that the incidence rates of drug resistance acquisition were decreasing during 1999-2005; and that the prevalence of potential transmitters of drug-resistant HIV decreased during 1997-2004. We also looked at some of the consequences of virological failure and drug resistance and found that even modest levels of viraemia were associated with a high risk of future failure and death, and that in persons who have experienced TCF, the number and pattern of resistance mutations were independent predictors of death. Hence, despite the overall positive trends in virological failure and drug-resistance development at the population level, our findings underline the crucial importance of always having an effective treatment option available for the individual patient with drug-resistant virus.

As mortality was declining for persons with access to ART and good HIV care, it became important to know how long persons with HIV could expect to live compared to the general population. We projected long-term survival and found that a 25-year old person with HIV and without hepatitis C virus (HCV) coinfection had a 50 percent chance of surviving another 39 years, only 12.2 years less than a person in a matched general population cohort would survive.
With improved survival and declining HIV-related comorbidity, non-HIV related comorbidity became a more visible contributor to the health status of persons with HIV. We assessed the impact of non-HIV related comorbidity acquired *before* the person became infected with HIV. We found that 32% of the observed mortality in our cohort was due to HCV and comorbidities measured by the Charlson Comorbidity Index, 13% corresponded to the background mortality in the population, and that only 55% of the mortality could be attributed to HIV. Our findings confirmed that persons acquiring HIV differ at large from the general population, and that we should not expect overall mortality rates in populations with HIV to reach the levels in the general population.

This thesis attempted to map some of the many challenges on the road towards increased survival of individuals and populations with HIV up to a level, which today in many settings is close to that of the general population. The studies in this thesis have each paid their modest contribution to show how crucially important it is to be diagnosed in time, to have access to a well-functioning health system, and to keep free of comorbidity both before and after acquiring HIV. After many years of struggle and despair, and thanks to enormous advances in prevention and treatment, we are now looking towards a promising future.

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