PhD thesis

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Mortality in patients coinfected with HIV and viral hepatitis B and C in Denmark.

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Omland LH, Jepsen P, Weis N, Christensen PB, Laursen AL, Nielsen H, Krarup H, Sørensen HT, Obel N. Mortality in HIV-infected injection drug users with active versus cleared HCV-infection: A population-based cohort study. Journal of Viral Hepatitis, 2010; 17: 261-268.

CONTENTS

1. PREFACE

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2. ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
CCI	Charlson comorbidity index
CRS	Civil Registration System
DHCS	Danish HIV Cohort Study
DNPR	Danish National Patient Registry
HAART	Highly active antiretroviral treatment
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICD	International Classification of Diseases
IDA	The Integrated Database for Labour Market Research
IDU	Injection drug use
MRR	Mortality rate ratio
PH	Proportional hazard
SVR	Sustained virologic response

3. INTRODUCTION

This section briefly discusses the background for this thesis. Initially the concept of prognosis is discussed. Second a discussion of the cohort study follows with a special focus of why cohort studies with mortality as an outcome are feasible in Denmark. The final part of this section is a discussion of the existing literature on HIV and viral hepatitis, the limitations of this literature and where this thesis has the potential to provide new knowledge.

3.1 PROGNOSIS

Prognosis is the prediction of the future course of a disease following its onset [1]. The value of prognosis research is a matter of ongoing debate [2], but affected individuals and families have a genuine interest in knowing what to expect. Prognosis research could have different outcomes, but ultimately patients diagnosed with a disease want to know their risk of dying within a specified time range [1]. Doctors need prognosis research in order to guide patients, asking this particular question. With improvements in treatment, existing prognosis research might become outdated [2]. Infection with human immunodeficiency virus (HIV) is a disease, for which prognosis has changed markedly since the introduction of effective antiretroviral treatment [3, 4].

3.2 COHORT STUDIES

Cohort studies can be defined as studies following groups of individuals over a period of time [5] with the purpose of measuring the rate of an outcome (disease, complication to a disease or death) between individuals with a specified exposure compared with those without this exposure. Compared with the other major type of observational study (the case control study), the cohort study offers some advantages;

- it allows for a temporal relationship between exposure and outcome [5, 6],
- the measure of association (relative risk) has a meaningful interpretation [7],
- it is suitable for rare exposures [6] and
- selection bias is not a threat to the validity of cohort studies to the same degree as it is to the validity of case control studies [6, 8].

Further, two of the more pronounced disadvantages of cohort studies do apply in Denmark as much as in other places of the world:

- Whereas price is an issue of cohort studies in most of the world, Denmark offers the potential of register based studies minimising costs [9-11]. Although the main data source used in this thesis was a clinical database (the Danish HIV Cohort Study [DHCS], please see description below) [12], we used several national registries to supplement the information from this registry. Thereby the price of the thesis has been minimized.
- A major threat to the validity of cohort studies is the bias introduced by differential loss to follow up, which means that loss to follow up is associated with both exposure and outcome [5, 7, 13]. This problem is nearly nonexistent when studying mortality as an outcome (as in this thesis) due to the extreme completeness of the Civil Registration Systems registration of vital status (as discussed below) [9, 10, 14].

3.3 COINFECTION WITH HIV AND VIRAL HEPATITIS

Acquired immunodeficiency syndrome (AIDS) was discovered in the beginning of the 1980's and HIV as the causative agent shortly thereafter [15, 16]. With the introduction of antiretroviral therapy and subsequently highly active antiretroviral treatment (HAART), survival in HIV-infected patients has increased substantially [3, 4]. However, mortality in HIV-infected patients continues to exceed that of the general population [3, 17-19]. Therefore, consistent attention has been focused on identifying prognostic factors (for death) in HIV-infected patients on HAART. Except from side-effect of specific HAART regiments [20], comorbidity [21], and smoking [22], attention has centred on coinfection with other pathogens, such as hepatitis B virus (HBV) [23-26] and hepatitis C virus (HCV) [23, 27-29]. There are many reasons why research has been focused on coinfection with HIV and viral hepatitis. Due to shared routes of infection, infection with one of these viruses (HIV, HBV and HCV) is more common in individuals infected with another of these viruses than in the general population [30]. Further, infection with one of these viruses is believed to worsen the prognosis of infection with another one of these viruses [24, 29-31]. And finally, effective treatment exists for all three viruses that can either eradicate or suppress the virus [32-34].

HBV-coinfection has been associated with increased mortality in most studies, mainly through an increase in liver-related mortality [24, 35], but some studies have had insufficient size to render firm conclusions [23, 25]. Conversely, HIV-infection increases the risk of cirrhosis in patients infected with HBV [36-40]. This adverse synergistic effect of HIV and HBV underpins the importance of investigating the prognostic impact of HBV-coinfection in HIV-infected patients. No previous studies have been conducted in population-based, nationwide settings, and therefore selection bias could limit these studies [41].

Parallel to the wish to analyse how viral coinfection with hepatitis virus affects prognosis of HIV-infected individuals, the opposite question is just as relevant; how will HIV-coinfection affect mortality in patients infected with viral hepatitis? Especially HCV-infected patients are at an increased risk of death compared with the general population [42], although recent and future treatment developments give hope for an improved prognosis [43, 44]. Whether HIV-infection increases the risk of death in HCV-infected patients remains poorly understood. In one study on HCV-infected patients with decompensated cirrhosis, HIV-coinfection shortened survival [31], but whether this applies more broadly in HCV-infected patients is unknown.

Besides from HBV-coinfection, also HCV-coinfection has been associated with increased mortality in HIV-infected patients, although results have been conflicting [23, 27-29, 45, 46]. In a paper from DHCS, HCV-coinfection was associated with a 2.4-fold increased risk of death compared with HCV-infection alone [29]. However, further studies in DHCS revealed, that a) siblings of HCV-coinfected patients had a 3-fold increased risk of death

compared with siblings of HIV-monoinfected patients [47] and b) that a predominant cause of death in siblings of HIV/HCV-coinfected patients compared with siblings of HIV-monoinfected patiens was substance abuse and unnatural causes of death [48]. Therefore, whether HCV-infection itself or the often concomitant injection drug use (IDU) causes the increased mortality remains to be elucidated. In HCV-infected patients with advanced fibrosis or cirrhosis, achievement of sustained virologic response (SVR) is associated with an improved chance of survival compared with non-SVR [49-51]. Whether these findings can be applied in HIV/HCV-coinfected patients is unknown, and to what extent chronic HCV viraemia (compared with cleared HCV-infection) contributes to mortality in HIV/HCV-coinfected patients have not yet been described in a nationwide population-based setting.

4. OBJECTIVES

The objectives of this Ph.D. thesis were:

- to analyse the impact of HBV-coinfection on mortality and treatment response in HIV-infected patients on HAART (Study 1; Omland et al., 2008),
- to analyse the impact of HIV-coinfection on mortality in patients infected with HCV (Study 2; Omland et al, 2009), and
- to analyse the impact of having a chronic compared with a cleared HCV-infection in HIV-infected patients (Study 3; Omland et al., 2010).

5. METHODS

5.1 SETTING

All studies took place in Denmark. In the study period, the population in Denmark increased from 5.2 million (1995) to 5.4 million (2006) [52]. HIV-infected patients (including those, who are coinfected with viral hepatitis) are treated in one of eight specialized medical centres, where they are seen on an outpatient basis at intended intervals of 12 weeks [12]. HCV-infected patients are treated in hospital departments that are specialised in infectious diseases, gastroenterology, or hepatology [53]. Medical care, including antiviral treatment, is provided free of charge to all HIV, HBV and HCV-infected patients. During the follow up period (1 January 1995 – 30 November 2006 in Study 1 and 1 January 1995 - 31 December 2006 in Study 2 and Study 3), national criteria for initiation of the HAART regimen were HIV-related disease, acute HIV-infection, pregnancy, CD4 cell count < 300 cells/µl, and until 2001, plasma HIV RNA > 100 000 copies/ml. Although with some uncertainty, it has been estimated that only 2% of the Danish HCV-infected population has been treated with interferon [54]. However, for those HCV-infected that are referred for evaluation in one of the 15 centres specialized in treating viral hepatitis in Denmark, the 5-year probability of being treated with interferon is 33% (95% CI 28–38%) [55].

5.2 DATA SOURCES

For this thesis, the study populations were captured in two clinical databases, which were the DHCS [12] and the DANVIR cohort [56]. The information from these databases was linked to national registries using the unique personal identifier as described below.

5.2.1 Civil Registration System (CRS)

A unique feature of Denmark is the establishment of the CRS in 1968 and the creation of the personal identifier (the CPR-number), which is used by all Danish national registries. By use of this unique CPR-number, accurate linkage of all Danish registries is made possible [9, 10, 14, 56], something that is expensive in most countries in the world [10]. The CRS also stores information on vital status, enabling accurate follow up in all three studies [14]. Therefore, we used the unique CPR-number to link the databases described below:

5.2.2 The Danish HIV Cohort Study (DHCS)

DHCS is a population-based prospective nationwide cohort study of all HIV-infected individuals over the age of 15 at diagnosis, treated at Danish HIV centres after 1 January 1995 [12]. Patients are consecutively enrolled and the cohort is ongoing. Important cohort parameters are dates of first positive HIV test and start of HAART (a regimen consisting of at least 3 antiretroviral drugs, including either abacavir, a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor or a combination of efavirenz and lopinavir/ritonavir), route of infection, all CD4 cell counts and HIV RNA viral load measurements, most recent prothrombin time (PT) and data on HBV- and HCV status including dates and results of HCV RNA measurements [12, 29, 57]. In the study period HCV RNA was quantified using a PCR-based method as previously described [58]. As of 31st December 2006, DHCS included 4720 individuals with 31 029 person-years of follow up, of whom 3543 were males. Men who had sex with men was reported as the route of infection in 2129 cases and 1778 persons were infected heterosexually. The majority of patients are treated in the two major HIV centres located in Copenhagen (Rigshospitalet and Hvidovre Hospital) [12].

5.2.3 DANVIR

DANVIR is a prospective research cohort consisting of all patients tested for HBV- and HCV-infection in 14 of the 18 Danish laboratories that perform such testing [56, 59-61]. DANVIR is designed to study the clinical course of chronic viral hepatitis, and its data includes results and dates of HCV antibody tests (from 1991 onward) and HCV RNA tests (from 1995 onward) with most HCV RNA measurements performed at one centre. As no clinical data are collected in DANVIR except from testing site, clinical information is obtained through linkage to national registries [56]. When the DANVIR cohort was established, it was estimated to include more than 90% of all Danish patients tested for HCV RNA and the majority of patients tested for HCV antibodies. A formal assessment of the coverage of tests performed in the DANVIR cohort is in progress.

5.2.4 Danish National Patient Registry (DNPR)

DNPR was established in 1977 and collects information on all non-psychiatric hospital admissions in Denmark. Data from outpatient and emergency department visits have been included since 1995. For each contact, the DNPR records dates of admission and discharge and up to 20 discharge diagnoses, assigned by physicians and coded according to the International Classification of Dis-

eases, 8th revision (ICD-8) through 1993 and the 10th version (ICD-10) from 1994 onward [62].

5.3 STUDY DESIGNS AND STUDY PARTICIPANTS

All 3 studies included in this thesis were cohort studies studying the prognosis of a group of patients having one parameter in common (HIV-infection in Study 1, HCV-infection in Study 2 and HIV/HCV-coinfection in Study 3) comparing prognosis of those with a particular prognostic factor (HBV-coinfection is Study 1, HIV-infection in Study 2 and HCV viraemia in Study 3) with that of those without that prognostic factor (Figure 1).

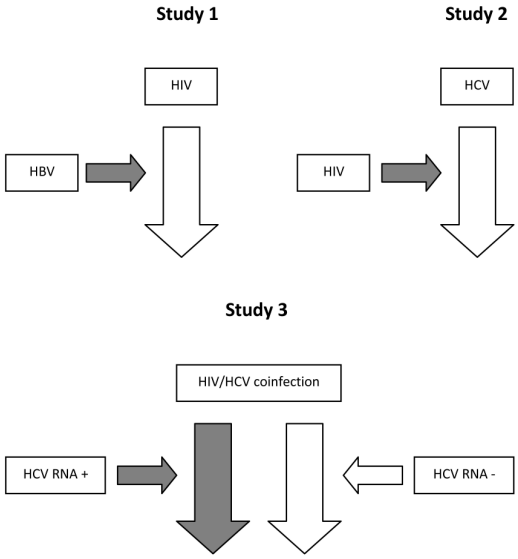


Figure 1
Graphical presentation of study designs of Study 1-3.

In Study 1 the study participants were all HIV-infected patients in DHCS above age 15 years starting HAART before 1st December 2006. The patients included were then categorised according to whether or not they were HBV-coinfected at time of HAART initiation, and patients with unknown HBV status were excluded from the study [57]. HBV-coinfection (chronic HBV) was defined as having two or more positive tests for HBsAg 6 months apart or at least one positive test for HBsAg on routine testing. Patients without HBV-confection was defined as those, who were tested for HBV-infection and not fulfilling the criteria for chronic HBV. Some additional internal comparisons were performed among HIV/HBV-coinfected patients; patients with HBeAg positivity compared with patients with no HBeAg positivity and patients with anti-HBV active drugs (tenofovir and emtricitabine/lamivudine) [37] in the initial HAART regiment compared with patients with no anti-HBV active drugs in the initial HAART regimen. In Study 2 the study participants were all patients in DANVIR diagnosed with HCV subsequent to an HIV diagnosis (as specified in DHCS) and then sampled from DANVIR a comparison cohort of four HCV-infected individuals without HIV-infection per coinfected patient, who were matched on age, gender and year of diagnosis [59]. In this study, HCV-infection was defined as a positive test for HCV antibodies or HCV RNA. The study participants in Study 3 were all HIV-infected patients in DHCS, who (a) were infected with HIV through IDU, (b) had evidence of HCV exposure (positive test for HCV RNA and/or HCV antibodies), and (c) had an available test for HCV RNA on or after the date on which evidence of both HCV exposure and HIV-infection had been established (HIV–HCV date). Although not included in the published paper (Study 3), we performed all calculations also on patients meeting criteria (b) and (c), who were not infected through IDU. Data from these calculations on non-IDUs are presented in this thesis as well (i.e. previously unpublished results).

5.4 INFORMATION ON STUDY PARTICIPANTS

5.4.1 Characteristics of the HIV-infected patients

In Study 1 and Study 3 all patients included were HIV-infected, and in Study 2 20% were HIV-infected. These patients were characterised according to the progression of their HIV-infection; the level of HIV RNA and CD4 cell count at study inclusion as well as to what extent patients were on HAART, whether or not patients had developed AIDS, the most likely route of infection, year of first HIV-diagnosis and race. In Study 1, response to HAART was a study outcome, and therefore we assessed the proportion of patients with HIV RNA < 500 copies/ml and increases in CD4 cell count. This was done in 12 weeks intervals as described previously [63]. If more than one value of the parameter was available for the period, the mean of the log transformed value was calculated. If no CD4 cell count or viral load was available for a 12 weeks interval, the missing parameter was replaced by the value from the previous period (i.e. the principle of 'last value carried forward'). A viral load of < 500 copies/mL was considered undetectable, because this value represented the highest level of sensitivity for all the test systems used in the observation period. Missing viral loads were regarded as detectable (> 500 copies/mL); however, when the viral load just before and after a missing viral load was undetectable, then the missing viral load was considered undetectable.

5.4.2 The Charlson Comorbidity Index (CCI)

The CCI was developed in New York, USA, in response to restrictive eligibility criteria employed by investigators of prospective studies [64]. These studies eliminated comorbid individuals from the study population in order to limit confounding and to increase efficacy of the trial, but the price was limited generalizability and difficulty in recruiting a sufficient number of eligible patients. The intention with the CCI was to develop a prognostic score based on comorbid conditions, which could predict (short term) mortality in longitudinal studies [64]. This scoring system assigns between 1 and 6 points to a range of diseases, and the sum of points serves as a measure of the burden of comorbidity (Figure 2). The score proved capable of also predicting long-term mortality in a validation cohort [64], and it has been validated a number of times since then [65-67]. Coding algorithms for diagnosis codes in healthcare registries have been developed and validated [66, 67]. However, since the CCIs development, advances in therapy for (and thereby improvement in prognosis of) some of the diseases included have not led to a change in score weights given for these specific diseases in the CCI. This has led to a need for reappraisal

for weighted scores especially for AIDS [68], which except from metastatic solid tumor is the only condition given the (top-) score of 6 (Figure 2) [64].

Table 3. Weighted index of comorbidity

Assigned weights for diseases	Conditions
1	Myocardial infarct
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Ulcer disease
	Mild liver disease
	Diabetes
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end organ damage
	Any tumor
	Leukemia
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS

Assigned weights for each condition that a patient has. The total equals the score. Example: chronic pulmonary (1) and lymphoma (2) = total score (3).

Figure 2
The weighted index of comorbidity from the paper by Charlson et al., 1987 [64]. Reprinted with permission from Elsevier.

We did not include AIDS (or liver diseases) in the comorbidity score in our studies, as these conditions were considered being on the causal pathway [69]. Therefore we possibly avoided one of the most pronounced problems with the CCI [68]. We used the ICD-10 codes provided by Quan et al., matching ICD-8 codes to ICD-10 codes as closely as possible [66]. The CCI was used in Study 2 and Study 3, but not Study 1 as we did not have access to DNPR in this study.

5.4.3 Alcohol abuse

Alcohol abuse is associated with increased mortality [70], and alcohol consumption in Denmark is among the highest in the world [71]. In Study 2 and Study 3 we captured alcohol abuse in DNPR. This was defined as receipt of one or more of the following diagnoses prior to inclusion in the study: ICD-8: 291, 57109, 57110 and 303 (except for 30390), and ICD-10: K70.0–K70.9, F10.2–F10.9 and G31.2. In Study 1, we did not include alcohol abuse in the analysis, but rather estimated the risk of dying with a known alcohol abuse as an indirect measure of alcohol abuse. It is important to underscore that the diagnoses listed above indicate a rather severe alcohol abuse. Light and moderate alcohol abuse is unlikely to be captured using data from DNPR.

5.4.4 Cirrhosis

Cirrhosis was defined as receipt of one or more of the following diagnoses prior to inclusion in the study: ICD8: 57109, 57192, 57199; and ICD10: K70.3, K74.6.

5.4.5 Cause of death

In Study 1 and Study 3, we studied causes of death with the focus on deaths related to HIV-infection and deaths related to liver disease. Whenever a patient dies, physicians in DHCS code the death as being AIDS-related or not. By examining patient charts, we further categorised deaths as being liver-related or not. In this way, more than one cause of death was allowed per patient in Study 1. This approach has also been used by others [24]. In Study 3, causes of death were mutually exclusive and coded into one of six categories: AIDS-related, liver-related, infection-related, cancer death (excluding AIDS defining cancers and hepatocellular carcinoma), unnatural causes of death (overdose, accidents, suicide and murder) and other/unspecified causes of death.

5.5 STATISTICAL ANALYSES

In all 3 studies the main outcome was time to death. Start of observation differed according to study objectives. In Study 1 we wished to determine the impact of HBV-coinfection on response to HAART, and hence the start of observation time was date of HAART initiation. In Study 2, the start of observation was date of HCV-infection, whereas in Study 3, start of observation was first date of HCV RNA assessment following HIV-infection and testing positive for HCV antibodies. Patients were followed until death, emigration or some specified time of censoring. Using time since study inclusion as the time scale, all three studies used the Kaplan-Meier technique to construct survival curves and Cox regression to compute mortality rate ratios (MRRs) as a measure of the relative risk of death.

5.5.1 The Cox regression model

The Cox regression model is a popular mathematical model for analyzing individual level data on survival [72, 73]. The model has many synonyms (The Cox proportional hazards regression model [72], The Cox proportional hazards model [73] or simply the Cox's method [74]), but in this thesis it is referred to as the Cox regression model. The Cox regression model has the following formula:

$$h(t, \boldsymbol{X}) = h_0(t) e^{\sum_{i=1}^{p} \beta_i X_i}$$

, with X = (X1, X2, ..., Xp) serving as explanatory variables. The Cox regression model describes the hazard rate ($h(t, \boldsymbol{X})$) of some outcome (death) at time t, which depends on two principal different components; the first part = the baseline hazard rate ($h_0(t)$) and then the second part ($e^{\sum_{i=1}^{p} \beta_i X_i}$). Although the shape of the baseline hazard rate can be estimated and described [72], one of the main reasons why the Cox regression model has gained such popularity is, that in general the baseline hazard rate is left unspecified and regarded as a nuisance parameter [72, 73]. Estimation of the second part of the equation (especially the regression parameters (β1, β2 ,..,. βp)) is the main reason for performing the Cox regression analysis. For instance, consider the simple situation where just one explanatory variable (such as sex) is introduced in the model. This could be written as follows:

$$h_1(t, \boldsymbol{X}) = h_0(t)e^{\beta_1 X_1}$$

, where Xi is 0 if i is a female and 1 if i is a male. Then the hazard for person i would be $h_0(t)e^{\beta_1 0} = h_0(t)$, if i is a female and $h_0(t)e^{\beta_1 1} = h_0(t)e^{\beta_1}$, if i is a male. The hazrad ratio (or, as in this thesis where death is the outcome, the mortality rate ratio [MRR]) for males compared with females can then be estimated as:

$$MRR = \frac{h_0(t)e^{\beta_1}}{h_0(t)} = e^{\beta_1}$$

So the main reason for performing the Cox regression analysis is to obtain hazard ratios of some specified outcome (death) between individuals with different characteristics (males versus females, HBV-coinfected versus non-HBV-coinfected, patients with HIV-infection versus patients without HIV-infection etc.). There are some aspects of the Cox regression analysis that deserve further attention, as they apply to this thesis:

- The Cox regression model was developed in order to deal with survival time following medical treatment [74]. Because of this and because some statistical software packages (such as SPSS) do not allow other time scales in the model, time since study inclusion is the most widely used time scale when performing Cox regression analysis. However, the model allows for the usage of other time scales, such as age or calendar time [74]. In contrast to using time since study inclusion as the time scale, where the risk set (those at risk of death) decreases as time advances, using age or calendar time as the time scale may result in an increasing risk set as time advances [74]. Several software packages, including R [75], allow flexibility in the choice of time scale, which should be the time scale with strongest relationship to failure rate [74]. Although the main analyses for this thesis used time since study inclusion as the time scale (adjusting for age in Study 1 and Study 3), the analyses were repeated using age as time scale to test the robustness of the models.
- The Cox regression model does not treat the explanatory variables and confounders differently [76]. To accommodate confounding, we included different variables recorded at start of observation in the Cox regression model. The choice of variables included was a balance between the relatively few deaths in the studies (limiting the amount of variables, which could reasonably be included in the Cox regression), the variables available at time of performing the calculations for the study (for instance, comorbidity was not available for the Study 1) and variables that were known to be of prognostic importance (for instance whether or not patients became immune suppressed, defined as reaching a CD4 cell count < 300 cells/µL in Study 2 or HAART in Study 3). Accordingly, some variables were forced into the models on account of prior knowledge of the prognostic impact of such variables, whereas others were included according to the change in estimate method [77].
- One key assumption of the Cox regression model is the proportional hazards (PH) assumption stating that effects of the explanatory parameters (X = (X1, X2, ..., Xp)) on mortality are independent of time [72-74]. However, if the PH assumption is violated, the Cox regression model allows for time dependent variables [72, 78]. This was used in Study 2 in terms of a variable describing whether or not HIV-infected patients had a CD4 cell count < 300 cells/µL (as a marker of immune deficiency). This variable was introduced in the model as a time dependent variable resulting in two different MRRs for HIV/HCV-coinfected patients (compared with patients infected with HCV alone): an MRR before immune deficiency and an MRR after immune deficiency. In the same manner, HAART was introduced as a time dependent variable in Study 3.

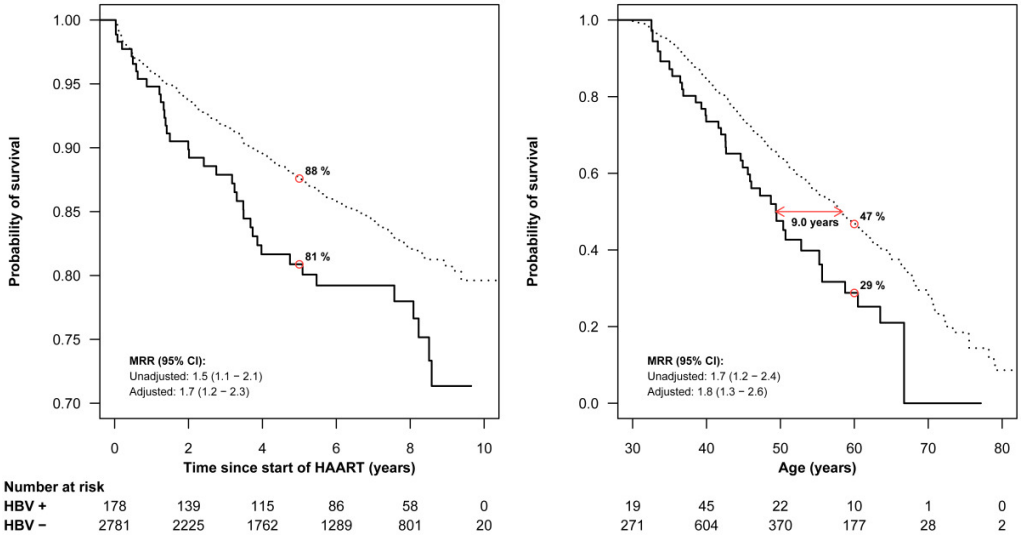
5.5.2 Kaplan-Meier survival analysis

The Kaplan-Meier formula is based on conditional probability (i.e. survival) terms. Each term in the product is the probability of surviving a specific (ordered) failure time provided that the individual survives up to that failure time [79]. The Kaplan-Meier formula can handle typical survival data with right censoring, like the data in this thesis. Right censoring means that for a proportion of the individuals studied, we have not observed them until death, but only up to some point in time (where they were still alive) [79, 80]. Thus, the objective of performing a Kaplan-Meier survival analysis is to estimate the probability of surviving up to some specified time, based on data with right censoring. For the survival estimates of the Kaplan-Meier survival analysis to be valid, it is of importance that censoring is non-informative (the independent-censoring assumption), that is, that the probability of being censored at time t is not associated with the risk of death at time t [24]. Substantial loss to follow-up can threat the validity of a cohort study [11] and definitely could pose a threat to the independent-censoring assumption. As with the Cox regression model, the Kaplan-Meier analysis allows for other time scales than time since study inclusion. Using time since study inclusion as the time scale (which is the most common) allow researchers to address questions like: “What is the chance of surviving 5 years from study inclusion”? Using age as the time scale allow researchers to address questions like: “What is the chance of surviving until age 70 if the subject studied is 30 years at study inclusion”? The main analyses for this thesis used time since study inclusion as the time scale, but the Kaplan-Meier analyses were repeated using age as time scale to obtain survival estimates from age 30.

5.5.3 The cumulative incidence function

In the presence of competing risks, the Kaplan-Meier cannot be used to estimate the risk of some event, as this will result in too high risk estimates. Rather, methods have been developed, that take into account the informative nature of the competing risk [81]. The cumulative incidence function is a non parametric method for estimating the risk of some event in the presence of competing risks, and this function has been available in R statistical software [81-83]. We used the cumulative incidence function to estimate 5- and 10 year risks of specific causes of death treating other causes of deaths as competing risks.

Figure 3
Kaplan-Meier survival curves following HAART initiation by HBV status. Broken lines: HBV – group, solid line: HBV + group. The figure to the left illustrates survival with time since start of HAART as the time scale, whereas the figure to the right illustrates survival with age as the time scale (restricted to patients aged 30 years or more during follow up).



5.5.4 Other analyses

In Study 1, we also analyses the proportion of patients with an undetectable HIV RNA (HIV RNA < 500 copies/ml) in 12 weeks intervals as well as the median increase in CD4 cell count as a study outcome. This was simply done by plotting the dependent variable (viral suppression and median increase in CD4 cell count) according to time after HAART initiation (in 12 weeks intervals).

6. RESULTS

6.1 STUDY 1.

3180 patients commenced HAART in DHCS in the period 1 January 1995 to 1 December 2006. Of these, 221 had an unknown HBV status at time of HAART initiation, and they were excluded for further analyses. Of the remaining 2959 individuals included in the study, 178 were categorized as having chronic HBV (HBV + group) whereas 2778 were categorized as not having chronic HBV (HBV - group). These patients differed according to some characteristics recorded at time of HAART; age, race and CD4 cell count, whereas no substantial difference existed regarding other characteristics: HCV-coinfection, sex, route of infection, time of diagnosis, time from HIV-diagnosis to start of HAART, (HIV-) viral load, treatment naivety at start of HAART and inclusion of HBV active drugs in initial HAART regiment.

6.1.1 Overall mortality

413 patients died during follow up. The 5-year survival was 81% (95% CI: 75% - 87%) in the HBV + group and 88 % (95% CI: 86% - 89%) in the HBV – group. The 9.5-year survival was 71% (95% CI:

Figure 4
Cumulative incidence function illustrating AIDS-related (left), non-AIDS-related mortality (right). Broken lines: HBV – group, solid line: HBV + group.

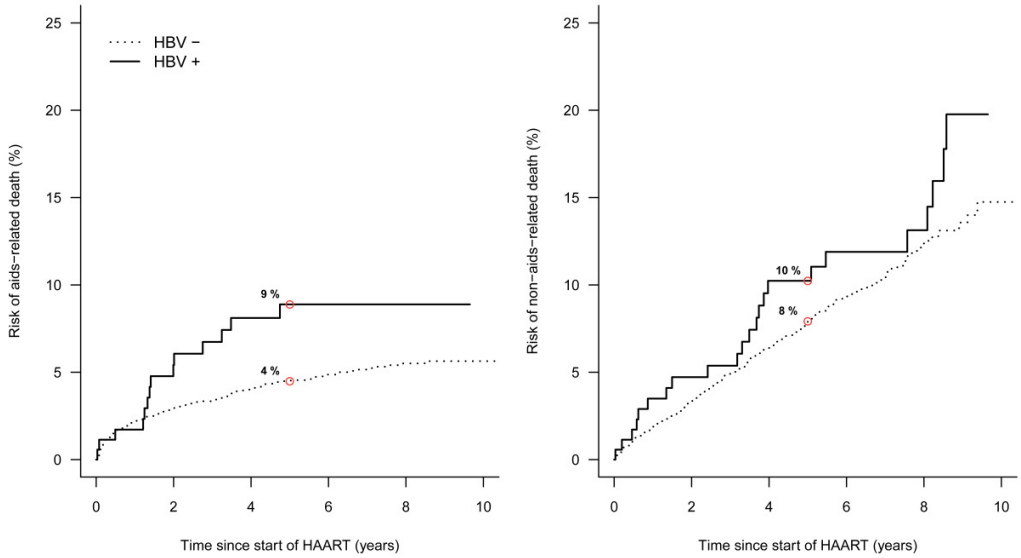
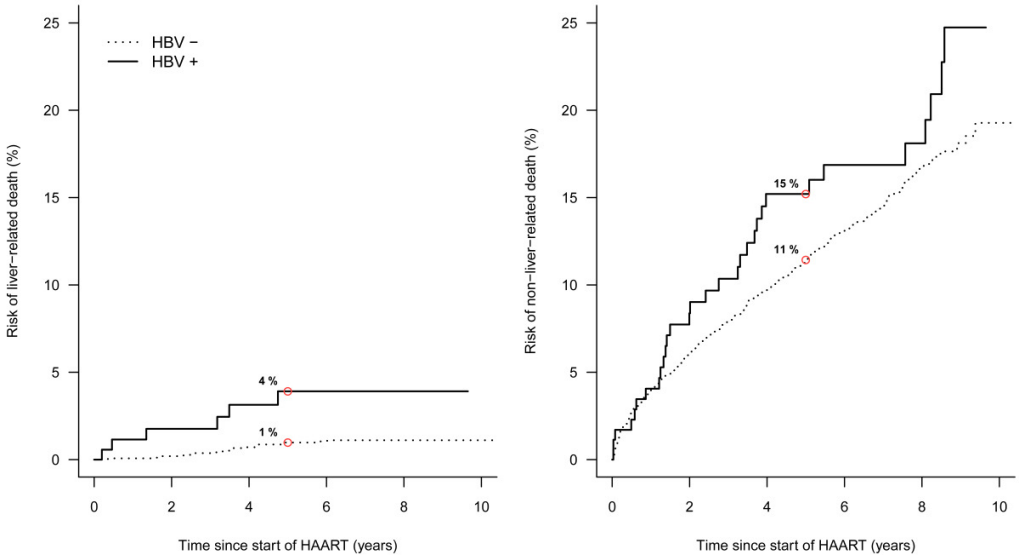


Figure 5
Cumulative incidence function illustrating liver-related (left) and non-liver-related mortality (right). Broken lines: HBV – group, solid line: HBV + group.



63% - 81%) in the HBV + group and 79 % (95% CI: 77% - 82%) in the HBV – group (we did not have follow up for 10 years in the HBV + group). The corresponding MRR was 1.5 (95% CI: 1.1 – 2.1) in the unadjusted analysis and 1.7 (95% CI: 1.2 – 2.3) in the analysis adjusted for route of infection and race (Figure 3). Using age as time scale revealed nearly the same association between HIV/HBV-coinfection and mortality, and from this analysis we estimated a median loss of time lived of 9 years (Figure 3). Initially we analysed of HBeAg negative and HBeAg positive individuals in the HBV + group separately. As we observed not substantial difference in mortality between these two groups, and as they were too small to be reasonably analysed separately, the two groups were pooled for further analyses. We reanalysed mortality in individuals not infected by IDU, which did not change the association between HBV + and mortality. Among HIV/HBV-coinfected patients, the choice of initial HAART regimen (+/- anti-HBV active drugs) did not affect mortality.

6.1.2 Specific causes of death

The primary categorisation of causes of death in DHCS is in AIDS-related death and deaths not related to AIDS. The result of this categorisation is illustrated in Figure 4. HIV/HBV-coinfection was associated with an increased risk of AIDS-related death with a 5-year risk of AIDS-related death of 9 % (95% CI: 5% - 14%) in HIV/HBV-coinfected patients and of 4% (95% CI: 4% - 5%) in HIV-infected patients, corresponding to an adjusted MRR of 1.9 (95% CI: 1.1 – 3.3). We also categorised deaths as being liver-related or not (Figure 5). Two deaths were categorised as both liver-related and AIDS-related (and thereby both depicted as AIDS-related deaths in Figure 4 and liver-related deaths in Figure 5): One pa-

Figure 6
Kaplan-Meier survival curves following HCV diagnosis by HIV status. Broken lines: HCV-monoinfected patients, solid line: HIV/HCV-coinfected patients. The figure to the left illustrates survival with time since HCV diagnosis as the time scale, whereas the figure to the right illustrates survival with age as the time scale (restricted to patients aged 30 years or more during follow up).

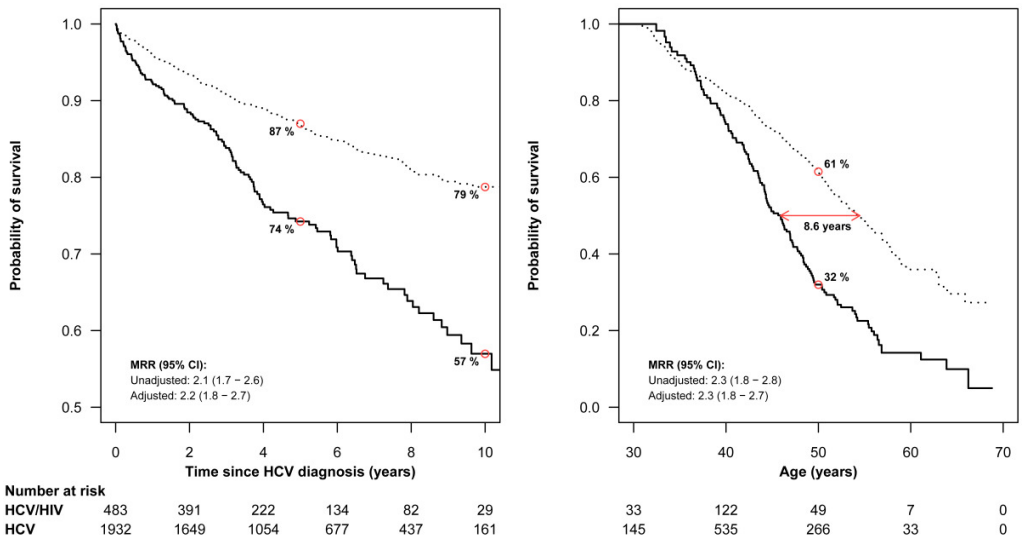
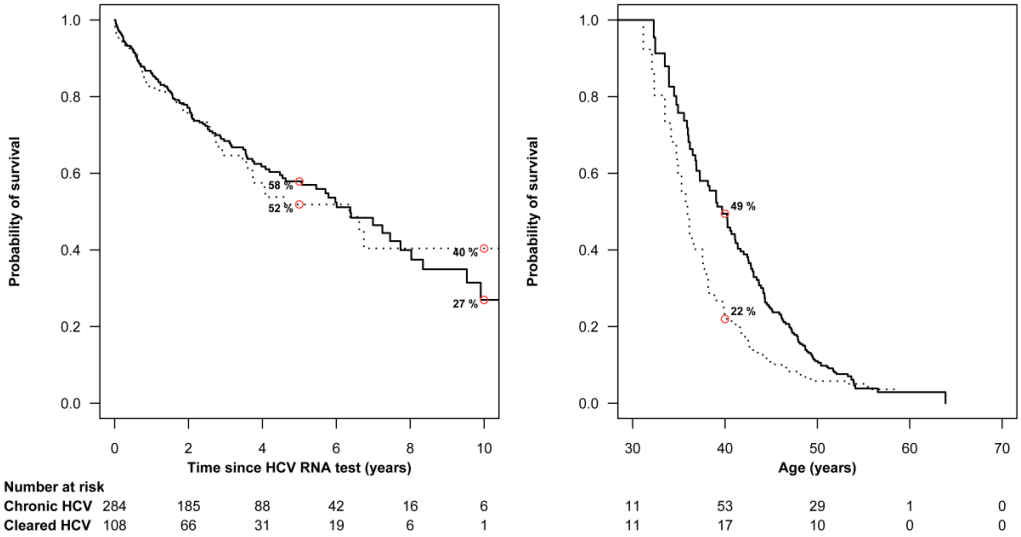


Figure 7
Kaplan-Meier survival curves following HCV RNA test by HCV status in HIV-infected IDUs. Broken lines: Cleared HCV, solid line: Chronic HCV. The figure to the left illustrates survival with time since HCV RNA test as the time scale, whereas the figure to the right illustrates survival with age as the time scale (restricted to patients aged 30 years or more during follow up).



tient was admitted prior to death with a CD4 cell count of 70 cells/µL, severe cachexia and esophageal candidiasis but also with jaundice and enlargement of the liver. The other patient was admitted prior to death with a CD4 cell count of 16 cells/µL, a solid process of the liver and what appeared to be retroperitoneal lymphomas. HIV/HBV-coinfection was associated with an increased risk of liver-related death with a 5-year risk of liver-related death of 4 % (95% CI: 2% - 8%) in HIV/HBV-coinfected patients and of 1% (95% CI: 1% - 1%) in HIV-infected patients, corresponding to an adjusted MRR of 4.9 (95% CI: 2.0 – 12.1).

6.2 STUDY 2

We identified 483 patients in DANVIR, who were diagnosed with HIV-infection prior to a diagnosis of HCV with a median age of 40 years and with the majority being male. We identified 4 HCV-monoinfected patients, matched on age and sex in DANVIR per HIV/HCV-coinfected patient comprising a cohort of 1932 patients.

Table 1
Mortality rate ratios (MRR) in HIV/HCV-coinfected patients compared with HCV-monoinfected patients (reference) estimated by Cox Regression analysis.

	Unadjusted MRR* (95% CI)	Adjusted MRR§ (95% CI)
HIV/HCV group	2.1 (1.7 – 2.6)	2.2 (1.8 – 2.7)
HIV/HCV group# Time *before* first measurement of a CD4 cell count < 300 cells/µL	0.7 (0.4 – 1.3)	0.9 (0.5 – 1.5)
HIV/HCV group# Time *after* first measurement of a CD4 cell count < 300 cells/µL	3.5 (1.9 – 6.3)	3.0 (1.7 – 5.5)

*: Estimated from Cox regression analysis including HIV status as binary variable.
§: Estimated from Cox regression analysis adjusting for potential confounders (age, gender, presence of drug abuse, alcohol abuse and comorbidity).
#: Estimated from Cox regression analysis by including the date of first CD4 cell count < 300 cells/µL as a time-updated parameter.

6.2.1 Overall mortality

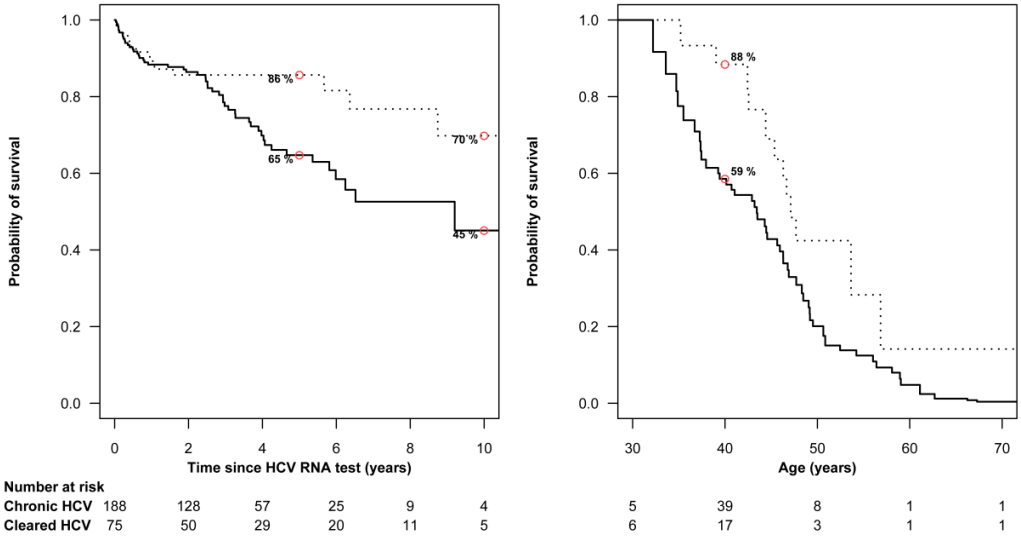
400 patients died during 12 085 person years of follow up. 10 years survival in HIV/HCV-coinfected patients was 57% (95% CI: 50% - 65%) compared with a 10 years survival of 79% (95% CI: 76% - 81%) in HCV-infected patients without HIV-infection. This corresponds to a 2-fold increased risk of death in HIV/HCV-coinfected patients, irrespective of whether time since HCV diagnosis or age was used as time scale (Figure 6 and Table 1). Importantly, the increased risk of death in HIV/HCV-coinfected patients was confined to time after a first time experience of immunosuppression (defined as a CD4 cell count < 300 cells/µL), whereas coinfection before immunosuppression did not increase the risk of death (Table 1). For patients aged 30 years, median survival was until age 45.9 years in HIV/HCV-coinfected patients compared with age 54.5 years in HCV-monoinfected patients, corresponding to a median loss of lived years of 8.6 years (Figure 6).

6.3 STUDY 3

6.3.1 Overall mortality

Of the 392 HIV-infected IDUs included in Study 3, 157 died during follow up. Chronic HCV-infection compared with cleared HCV-infection was not associated with mortality. The unadjusted and adjusted Cox regression model rendered MRRs close to - and confidence intervals crossing 1. This was also the case in a series of subanalyses, where we restricted the study population according to patient characteristics (gender, time of HIV diagnosis [<1997 versus ≥1997], age [<40 versus ≥ 40 years] and previous AIDS-defining events) and when follow up was censored at initiation of interferon treatment. From the cumulative survival illustrated in Figure 7, the lack of association between HCV status (chronic versus cleared) and mortality is evident. Figure 7 further demonstrates the very sinister prognosis for this group of patients with a 10-year survival of approximately 1/3 and a very small chance of surviving until the age 50 for a 30-year old patient. Although not published in the paper [84], we also analysed the association between HCV status (chronic versus cleared) in HIV-infected patients not known to be infected via IDU (n=263). These

Figure 8
Kaplan-Meier survival curves following HCV RNA test by HCV status in HIV-infected non-IDUs. Broken lines: Cleared HCV, solid line: Chronic HCV. The figure to the left illustrates survival with time since HCV RNA test as the time scale, whereas the figure to the right illustrates survival with age as time (restricted to patients aged 30 years or more during follow up).



patients had a better prognosis but still suffered from substantial mortality (Figure 8). Further, in these patients, cleared compared with chronic HCV-infection was associated with some improvement in prognosis. The 5-year survival was 86% and 65% in patients with cleared and chronic HCV-infection, respectively (Figure 8). In the unadjusted Cox regression analysis, chronic HCV-infection was associated with 1.8 increased risk of death (95% CI: 1.0 – 3.4). However, the Kaplan Meier plot as well as the plot of Schoenfeld residuals suggested a possible violation of the proportional hazards assumption. Therefore we introduced a time dependency in the Cox regression analysis. In this way we analysed the following 2 time periods separately: the first 2 years of follow up and the third year and onwards, respectively. In the first 2 years of follow up, chronic compared with cleared HCV-infection was not associated with increased mortality ($MRR_{0\text{-}2\ years}$ of 1.0 (95% CI: 0.5 – 2.0) in the unadjusted analyses and of 0.9 (95% CI: 0.4 – 2.0), when adjusting for age, sex and CD4 cell count [<200 cells/µL versus >= 200 cells/µL]), whereas chronic compared with cleared HCV-infection increased the risk of death from 2 years of follow up and onwards ($MRR_{2+\ years}$ of 5.1 (95% CI: 1.5 – 17.1) in the unadjusted analysis and of 4.3 (95% CI: 1.3 – 14.3) in the analysis adjusted for age, sex and CD4 cell count [<200 cells/µL versus >= 200 cells/µL]).

6.3.2 Specific causes of death

Specific causes of death are illustrated in Figure 9 in patients infected via IDU, whereas cause of death in patients infected via other routes are illustrated in Figure 10.

7. DISCUSSION

This Ph.D. thesis concerns prognosis in patients infected with HIV, HBV and HCV and examines the impact of being coinfected with more than one of these viruses. This section contains a discussion of our findings in the context of existing literature and the perspectives of this thesis. Each study will be discussed separately. Further a general discussion of the strengths and limitations of the methodology is provided.

7.1 STUDY 1

The prevalence of HIV-infected patients with chronic HBV-infection in Denmark was 6% - a percentage higher than in the general Danish population, probably because risk factors for chronic HBV in low endemic countries (like Denmark) are somewhat the same as risk factors for HIV (IDU, sexually transmitted diseases and number of sexual partners) [85-87]. The prevalence is lower than in the EuroSIDA cohort and in HIV-infected patients in most of Africa and Asia [24, 88], which probably reflects the higher prevalence in the general population in these countries [89].

The main finding of our study was the 50 – 70% increased mortality among HIV-infected patients chronically infected with HBV compared with HIV-infected patients without HBV-infection. This finding accords with the 53% increased risk of all cause mortality in the EuroSIDA study [24]. Further, the 4-fold increased risk of liver-related mortality corresponds with the EuroSIDA [24] and MACS [35] studies. However, even when censoring patients in case of a liver-related death, we still observed an increased overall mortality, which points towards other contributing factors. Coinfection with HBV did not affect the response to HAART in terms of viral load suppression or immune system recovery, but there was an increased risk of both AIDS-related and liver-related mortality. Therefore, although HBV coinfected patients predominantly are at increased risk of liver-related mortality, our data suggest other causes might contribute to the increase in overall mortality. Whether the possible effect on AIDS-related mortality is caused by adverse viral effect of HBV on HIV progression or whether the association is caused by some unknown confounder (such as socioeconomic risk factors) are unknown. Interestingly, like in our study, a more recent MACS paper also demonstrated an increased AIDS-related mortality in HIV-infected patients with chronic HBV-infection although these patients had the same viral suppression and CD4 cell count rise, as HIV-infected patients

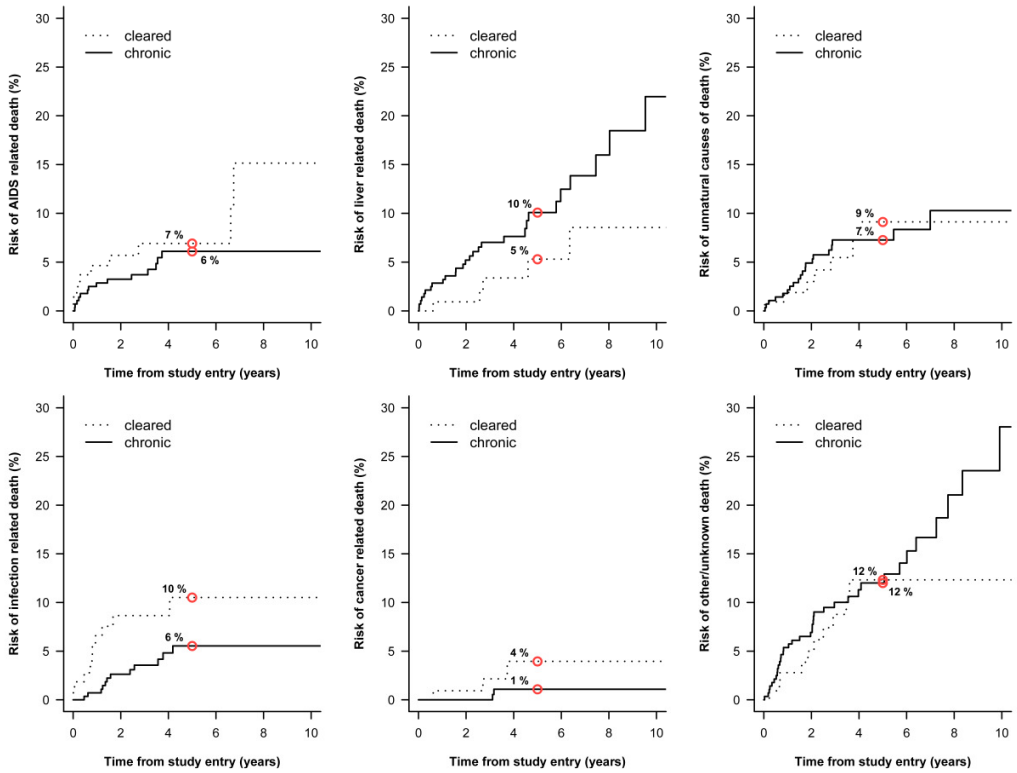
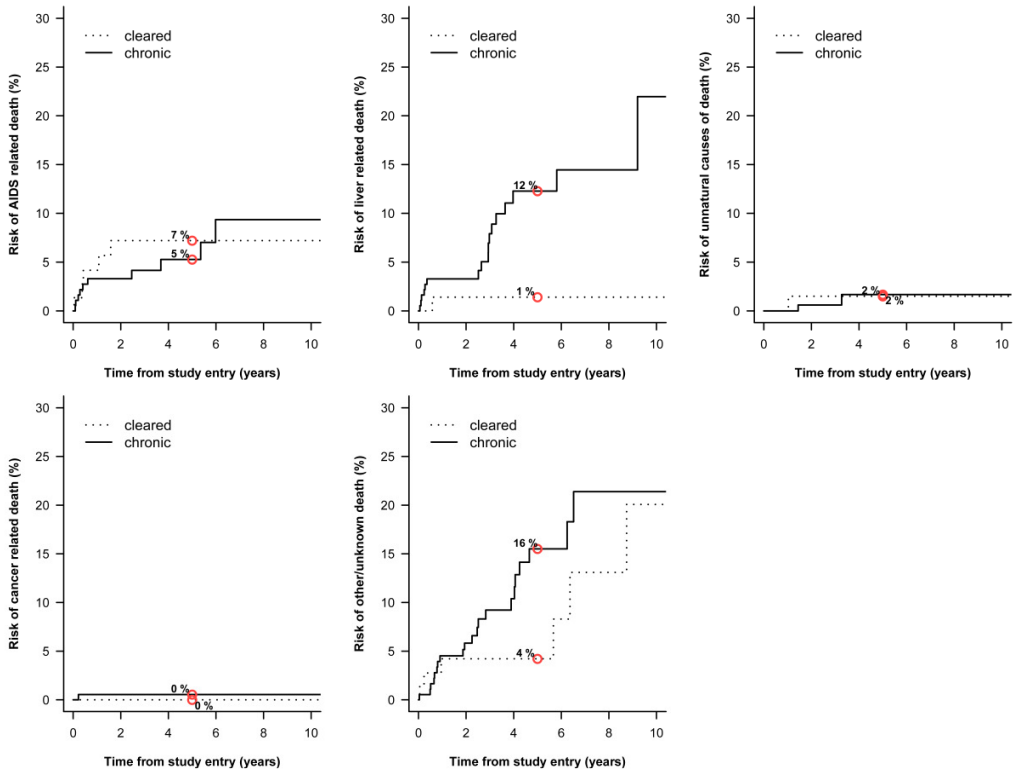


Figure 9
Cumulative incidence function following HCV RNA test by HCV status in HIV-infected IDUs illustrating AIDS-related (top left), non-AIDS-related mortality (top right), liver-related (bottom left) and non-liver-related mortality (bottom right). Broken lines: Cleared HCV, solid line: Chronic HCV.

without chronic HBV-infection [90]. Also like in our study, patients with chronic HBV-infection did start HAART at a lower CD4 cell count [90], and although both studies included CD4 cell counts at start of HAART in the adjusted models, a compelling theory is that HIV-infected patients with chronic HBV-infection die from AIDS at a higher rate partly because they start off at a lower set point.
In HIV/HBV-coinfected patients where treatment for both viruses is indicated, it is recommended to include the combination of tenofovir and emtricitabine (or tenofovir and lamivudine) in the initial HAART regimen, as these drugs have anti-HBV activity [37]. Our study was not designed or powered to address the issue of which drugs to include in HAART in HIV/HBV-coinfected patients. However, during the prepublication process, it was requested that this issue was addressed. The finding that the choice of HAART regiment (i.e. +/- HBV active drugs) did not affect mortality or virological/immunological response to HAART among HIV/HBV-coinfected patients therefore should be interpreted with caution and decisions regarding this issue should be based on properly conducted trials of sufficient size.
The perspectives of Study 1 are first and foremost, that HIV-infected patients chronically infected with HBV deserves extra attention as they are at an increased risk of death compared with HIV-infected patients in general. As management of HBV-infection evolves, hopefully liver-related mortality will decrease. Recognizing that patients coinfected with HBV generally start HAART at an advanced stage of HIV-infection is important, as extra support and encouragement in relation to HAART compliance is warranted. However, HAART is encouraged also in coinfected patients, as response to HAART in terms of virological and immunological parameters is good.

7.2 STUDY 2
The 2-fold increased risk of death in HIV/HCV-infected patients in Study 2 extends findings from Spain demonstrating an increased mortality associated with HIV-infection in HCV-infected patients with decompensated cirrhosis [31]. Di Martino et al reported an increase in cirrhosis-related mortality associated with HIV-induced immunosuppression among HCV-infected patients [91]. This corresponds with our findings, that the increase in mortality in HIV-infected patients was confined to the time after first having had a CD4 cell count < 300 cells/µL. However, the study by Di Martino et al. was from the pre-HAART era and we extent their findings by providing data from the HAART period. In our study, we had no data on fibrosis or causes of death – therefore, we were not able to determine how immunosuppression led to increased mortality. Smit et al. demonstrated an increased all cause and liver-related mortality in HIV/HCV-coinfected IDUs compared with HCV-infected IDUs (without HIV-infection) [92]. This study did not examine the effect of immunosuppression on these risks directly, but it analysed the pre-HAART and HAART period separately as proxy for immunosuppression. This comparison among HIV/HCV-coinfected IDUs demonstrated that the risk of AIDS/HIV-related mortality decreased when HAART was introduced [92]. The risk of liver-related deaths also decreased in the HAART era, but not to the same degree, and this association was not statistical significant [92]. However, when comparing HIV/HCV-coinfected IDUs with HCV-infected IDUs (without HIV-infection) in the HAART era, there was still a substantially increased risk of liver-related, non-natural and natural mortality as well as for death due to unknown causes [92]. Kramer et al. found that HIV-infection in general did not adversely impact the clinical progression of HCV-infection in terms of cirrhosis or hepatocellular carci-

Figure 10
Cumulative incidence function following HCV RNA test by HCV status in HIV-infected non-IDUs illustrating AIDS-related (top left), non-AIDS-related mortality (top right), liver-related (bottom left) and non-liver-related mortality (bottom right). Broken lines: Cleared HCV, solid line: Chronic HCV.



noma. However, studying the pre-HAART era separately demonstrated an increased risk of progression to cirrhosis [93]. Other studies have indicated that HIV-infection is associated with increased HCV RNA levels, increased risk of liver fibrosis and hepatocellular carcinoma and lower chance of achieving sustained virological response [91, 94, 95]. To summarize on these findings, the increased mortality observed in our study among HIV/HCV-coinfected patients with immunosuppression compared with HCV-infected patients is probably conveyed in part by accelerated progression of liver disease and in part by HIV-related complications.

The perspectives of Study 2 (together with the supporting literature) are clear: The risk benefit ratio is in favor of treating HIV/HCV-coinfected patients with HAART in order to prevent immunosuppression. However, HIV/HCV-coinfected patients do not have the same response to HAART (in terms of viral suppression and immune reconstitution) as HIV-infected without HCV-infection [29], probably due to compliance problems. Therefore coinfected patients are in need of extra support in order to improve their prognosis.

7.3 STUDY 3

The main finding in Study 3 was, that in HIV-infected IDUs, chronic compared with cleared HCV-infection did not affect long-term mortality. In HIV-infected patients not known to be IDUs, however, there was an increased risk of death in those with chronic (compared with cleared) HCV-infection, especially from after 2 years of follow up and onwards. Results on the impact of chronic compared with cleared HCV-infection are conflicting [84, 96-98]. A study from Japan in patients without HIV-infection demonstrated a 53% increased mortality in chronic compared with cleared HCV-infection [98]. This paper provided no information on the proportion of IDUs, but there was no mortality due to drug-related causes and only 30/231 deaths from unknown causes. Therefore probably relatively few patients from this cohort were IDUs. A study from Denmark, also in patients without HIV-infection, demonstrated an increased mortality of 55% in patients with chronic compared with cleared HCV-infection, with a smaller impact of chronic compared with cleared HCV-infection in those patients with concurring factors (alcohol abuse, IDU or comorbidity) [84]. In HIV-infected patients in the EuroSIDA study as well as in the Trent study (with 74% IDUs and 51% “ever heavy drinkers”), mortality in HIV-infected patients did not differ according to the result of HCV PCR test at baseline [96, 97]. Therefore the overall picture is, the more cofactors (alcohol abuse, IDU and comorbidity), the smaller is the impact of chronic compared with cleared HCV-infection.

The other main finding from Study 3 was the sinister prognosis for the patients included; all groups but the 75 non-IDUs with cleared HCV-infection had a 10-year survival below 50%.

The observational design of the study prohibits any firm conclusions in regards to treatments recommendations – however, an implication of Study 3 is, that healthcare in HIV/HCV-coinfected IDUs should primarily focus on preventing and managing comorbidity and the concurrent risk factors. Without achieving these goals, the risk benefit ratio of an attempt to eradicate the HCV virus might not be in favor of current treatment regimens, which are associated with severe side effects [43].

7.4 STRENGTHS

Major strengths of all 3 studies are the population-based, nationwide design, the long and nearly complete follow up and the

ability to determine the main predictor status in almost all study participants. The main advantage of the population-based design is the reduced risk of selection bias due to non-responders when using primary data [41]. Strengths (of studies 2 and 3) also include the use of the CRS as the source of information on vital status, which is very accurately recorded [9, 14]. One key assumption in the survival analyses used in this thesis is that censoring is non-informative (the independent-censoring assumption) [83, 99]. Due to the extremely few losses to follow up in the CRS, the survival estimates are probably more valid than comparable estimates from cohorts with more loss to follow up [11].
Finally, from a clinical point of view, studies 1-3 as well as the supplementary analyses provided in this Ph.D. thesis provide useful information regarding prognosis, as 5- and 10 year risk estimates of death are easily extracted from the Kaplan Meier survival analyses. Whereas relative risk estimates (which are also provided) are useful in hypothesis testing, they are difficult to interpret for the patients. On the contrary, patients are more interested in their chance of surviving a given period of time [1]. Therefore study strengths include the absolute survival estimates, both from time of inclusion and from age 30 years.

7.5 LIMITATIONS

Given the observational nature of the studies included in this Ph.D. thesis, there are a number of limitations that should be mentioned.
One limitation affecting Study 1 and Study 3 is that the main predictors being studied (i.e. HBV in Study 1 and HCV replication in Study 3) were assessed only once at study inclusion. This approach was necessary from an operational point of view, as the limitations in study sizes prevented more dynamic modelling allowing for changes in the initial categorisation. For instance, in Study 3, HCV-infected patients initially categorised as being chronically HCV-infected could clear the infection subsequently [100], and conversely patients with cleared HCV-infection could be reinfected [101, 102]. If changes in the initial categorisation are common, this could conceal a true effect of HCV replication on mortality. In Study 1, patients initially categorised as not having chronic HBV-infection, could be infected during follow up and thereby change risk category. And conversely, patients with only one positive screening test for HBsAg and no sign of clinical hepatitis (thereby being categorised as having chronic HBV-infection), could in fact clear the virus afterwards. Another related limitation is that due to sample size considerations we have been forced to merge categories. For instance in Study 1, we were not able to differentiate between those without chronic HBV-infection into core only, past infection, vaccinated patients and never infected [90]. Similarly, in Study 2 we did differentiate between HCV RNA positive and HCV antibody positive patients. And in Study 3, HCV replication was treated as a yes/no variable, and we were not able to assess whether there was an effect of increasing HCV viral load. Thereby there is a potential for residual confounding [103]. Residual confounding might also affect the attempt to adjust the MRRs obtained in studies 2 and 3 for comorbidity, as we collapsed high-end categories of comorbidity [104].
Another limitation affecting all 3 studies is lacking information on date of infection. Although seroconversion can be associated with specific clinical syndromes, most infections are initially unrecognised until complications occur. Therefore the associations from these studies reflect the situation at time of diagnosis, not time of infection. From a clinical point of view, this limitation is less relevant, but it is important to remember, that our results do not necessarily apply when describing biological mechanisms.
A third limitation is the reliance on national registries and clinical databases in all 3 studies. We have no access to data of importance for prognosis, such as smoking and socioeconomic factors. Therefore our study might suffer from unmeasured confounding due to lack of information on these important prognostic factors. Further, some confounders might be measured incompletely, such as alcohol and comorbidity in studies 2 and 3 and IDU in Study 3. For instance, probably only more severe cases of alcohol abuse lead to registration in DNHR with one (or more) of the diagnoses used to categorise alcohol abuse in this thesis. Further, comorbidity not leading to hospital contacts will not be registered using DNHR.

8. CONCLUSION

The background for this Ph.D. thesis was the enormous success of HAART on survival in HIV-infected patients, the improvements in treatment of HBV- and HCV-infections and the fact, that HIV, HBV and HCV share routes of infection. In this landscape of treatment improvements, updated information on prognosis was warranted for those infected with more than just one of these 3 viruses. Whereas some issues were already extensively covered, other issues remained poorly elucidated. This Ph.D. thesis demonstrated that

- HBV-coinfection is associated with increased mortality in HIV-infected patients starting HAART,
- HIV-infection increases mortality in HCV-infected patients, but only after immunosuppression has developed and
- HIV-infected IDUs with evidence of HCV exposure have a sinister prognosis that is not influenced by whether the HCV-infection is persistent or if the virus has been cleared.

The perspectives of this Ph.D. thesis studies are, that

- HIV/HBV-coinfected patients should be recognized as a group of individuals with a worsened prognosis, - however HAART should be encouraged in coinfected patients as the virological and immunological response is as good as for HIV-infected patients without HBV-infection,
- HAART should be encourage in HIV/HCV-coinfected patients, as immunosuppression seems to be the source to the increase in mortality compared with HCV-infected patients without HIV-infection and
- in HIV-infected IDUs with evidence of HCV exposure, attention of care should be on concurrent factors, such as alcohol abuse, IDU and comorbidity.

Hopefully these findings will help clinicians and affected patients to understand the prognosis and to identify factors worsening this prognosis. And, if these studies have improved the prognosis for just one patient, the ultimate goal of this Ph.D. thesis has been reached.

9. SUMMARY

Human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) often infect the same individual, as these viruses share routes of infection (sexually and through injection drug use [IDU]). Especially for HIV-infection, prognosis has improved since the introduction of "highly active antiretroviral treatment" (HAART) in the second half of the 1990's, and HIV-infection is no longer considered a lethal illness. As our understanding of these diseases has increased, there is an ongoing demand for accurate estimates of the prognosis for the affected patients. Because coinfection with more than one virus is frequent, particular focus has been on how the prognosis for infection with one virus change, if a person is coinfected with another virus. Especially 3 topics are insufficiently described in the literature, and therefore the aims of this Ph.D. thesis were

- to compare the response to HAART (in terms of CD4 cell count increase, viral suppression and mortality) between HIV/HBV-coinfected patients and patients infected with HIV, but not HCV,
- to compare mortality in HIV/HCV-coinfected patients and patients infected with HCV, but not HIV and
- to compare mortality in HIV-infected IDUs between those with chronic HCV-infection and those, who cleared the virus.

In Study 1 we demonstrated, that HIV/HBV-coinfection had no impact on the increase in CD4 cell count or viral suppression. However, HIV/HBV-coinfection did increase mortality, partly through an increase in liver-related mortality.
In Study 2 we demonstrated, that coinfection with HIV doubled mortality in patients infected with HCV; 10 year survival was 57% for HIV/HCV-coinfected patients and 79 % for HCV monoinfected patients. The increased mortality was restricted to the time after patients experienced a first time event of immunosuppression (CD4 cell count < 300 cells/µL).
In Study 3 we demonstrated, that chronic compared with cleared HCV-infection did not alter prognosis of HIV-infected IDUs, but possibly worsened prognosis for those infected via other routes of infection.
This Ph.D. thesis has contributed to our ability to understand the prognosis of patients infected with HIV, HBV and HCV, and the thesis has some important implications; the increased mortality in HIV/HBV-coinfected patients, which is partly explained through liver-related mortality, suggests a potential benefit of HBV prevention and treatment. The thesis also highlights the importance of avoiding HIV induced immunosuppression in HCV-infected patients by use of HAART. And finally, the fact that chronic compared with cleared HCV-infection did not affect the substantial mortality in HIV-infected injection drugs users underpins, that healthcare in this group should focus on preventing and managing comorbidity and the concurrent risk factors this population faces.

10. DANISH SUMMARY

Human immundefekt virus (HIV), hepatitis B virus (HBV) og hepatitis C virus (HCV) inficerer ofte det samme individ, da disse vira har samme smittemåde(seksuelt og via intravenøst stofmisbrug). Prognosen for især HIV-infektion er bedret væsentligt siden man midt i 1990'erne indførte "highly active antiretroviral treatment" (HAART), og man opfatter ikke længere HIV som en dødelig sygdom. Med den forbedrede sygdomsforståelse og behandlingsmulighed har der været et behov for at få opdateret oplysningerne om disse patienters prognose. Da HIV, HBV og HCV kan smitte samme person har det været særligt vigtigt at afklare, hvordan tilstedeværelsen af et af disse vira ændrer prognosen for patienter inficeret med et andet. Særligt 3 emner er mangelfuldt belyst i litteraturen, hvorfor formålene med denne Ph.D. afhandling var

- at sammenligne responset på HAART (i form af stigningen i CD4 celle niveau, viral suppression og mortalitet) mellem HIV/HBV-coinficerede patienter og patienter alene inficeret med HIV,
- at sammenligne mortaliteten mellem HIV/HCV-coinficerede og patienter alene inficeret med HCV og
- at sammenligne mortaliteten mellem HIV-inficerede patienter med en henholdsvis kronisk og clearet HCV virus infektion.

Studie 1 viste, at HIV/HBV-coinfektion ikke påvirkede responset på HAART i form af stigning i CD4 celle tal eller viral suppression, men medførte en øget risiko for død. Denne overrisiko var delvist, men ikke fuldstændigt forklaret af en øget dødelighed af lever-relaterede dødsfald.
Studie 2 viste, at coinfektion med HIV medførte 2-fold øget risiko for død for HCV-inficerede patienter. 10-års overlevelsen var 57 % for HIV/HCV-coinficerede sammenlignet med 79 % for HCV-monoinficerede patienter. Et væsentligt fund var, at overrisikoen for død blandt de coinficerede patienter alene var begrænset til tiden efter de første gang havde oplevet immunosuppression (dvs. et CD4 celle tal < 300 celler/µL).
Studie 3 viste, at kronisk HCV-infektion (defineret som viral replikation) ikke forværrede prognosen for HIV-inficerede stofmisbrugere sammenlignet med dem, som havde clearet deres HCV-infektion. For patienter med anden smittevej end intravenøst stofmisbrug var der imidlertid tegn til en øget dødelighed blandt dem med kronisk HCV.
Studierne i denne Ph.D. afhandling har været med til at besvare vigtige spørgsmål vedrørende prognosen for patienter inficeret med HIV, HBV og HCV. Den øgede dødelighed blandt HIV/HBV-coinficerede patienter, som delvist er forklaret af lever relateret død, antyder et forebyggelses- og behandlingspotentiale for disse patienter. Afhandlingen understreger også vigtigheden af at forhindre HIV-relateret immunosuppression hos HCV-inficerede patienter vha. HAART. Og endeligt er den manglende betydning af at cleare sin HCV-infektion blandt HIV-inficerede stofmisbrugere vigtigt, idet man som konsekvens heraf bør vægte håndteringen af andre faktorer, såsom comorbitet og det intravenøse stofmisbrug, højt.

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