Anda Karnīte

FACTORS ASSOCIATED WITH OUTCOMES FROM HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Summary of doctoral thesis

Specialization – public health and epidemiology

Riga, 2012

This doctoral thesis was elaborated in the Riga Stradins University (RSU), Department of Public Health and Epidemiology.

Scientific supervisor of the thesis: Prof. **Ģirts Briģis**, RSU Department of Public Health and Epidemiology

Official reviewers:
- Asoc.prof. **Anita Villeruša** (Riga Stradins University)
- Asoc.prof. **Uga Dumpis** (University of Latvia)
- MD, PHD **Kristi Rüütel** (National Institute for Health Development, Estonia)

The defence of the thesis will take place on April 8, 2013 at 15:00 at the open meeting of the Promotion Council of Theoretical Medicine Disciplines of Riga Stradins University in Riga, Dzirciema Street 16, in the Hippocrate lecture-theatre.

The doctoral thesis is available at the RSU library and the RSU website: www.rsu.lv.

Elaboration of the thesis was supported by ESF program „Support for doctoral students in obtaining the scientific degree in Riga Stradins University".

The head of the Promotion Council of Theoretical Medicine Disciplines: Prof. **Jānis Vētra**

Council secretary: Prof. **Līga Aberberga-Augškalne**

TABLE OF CONTENTS

ABBREVIATIONS

AIDS	acquired immune deficiency syndrome
aYPLL	average potential years of life lost
ART	antiretroviral therapy
CDC	Centers for Disease Control and Prevention
CI	confidence interval
EU	European Union
HAART	highly active antiretroviral therapy
HCV	viral hepatitis C
HIV	human immunodeficiency virus
HR	hazard ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th. ed.
ICL	Infectology Center of Latvia
IDU	injecting drug users
ml	milliliter
MRR	mortality rate ratio
MSM	men who have sex with men
n	number of cases / persons
PLHIV	people living with HIV
py	person years
YPLL	years of potential life lost
RNA	ribonucleic acid
SD	standard deviation
SMR	standardized mortality ratio
SPSS	Statistical Package for the Social Sciences
UN	United Nations
USA	United States of America
VL	viral load
WHO	World Health Organization
µl	microliter

1. INTRODUCTION

Objective No 6 of the United Nations (UN) Millennium Declaration is the combatting of HIV/AIDS, malaria and other diseases. Sub-objective 6a calls for a reduction of the spread of HIV in UN countries by 2015 along with an increase in life expectancy for people living with HIV[1].

Target No 7 of the World Health Organization (WHO) policy document for Europe "Health for All in the 21st Century" is the reduction of communicable diseases, including a stable and consistent decrease in the mortality and negative social influence of HIV and AIDS by 2015 in all member states[2].

As little as 30 years ago HIV and its association with AIDS were unknown[3]. At present, however, the infection has become a global phenomena. It has affected all regions of the world and it is estimated that at the end of 2009 about 33 million people were living with HIV and approximately 2 million people annually died of AIDS related causes[4].

Nevertheless, both routine statistics as well as the latest research data show that many countries in Europe and the world have successfully moved toward the UN and WHO objectives due to remarkable advancements in the field of HIV care and treatment during the recent 10 to 15 years. The AIDS incidence and the mortality rates for people living with HIV (PLHIV) have decreased and the life expectancy of HIV infected people has increased. For example, the incidence of AIDS in the European Union (EU) decreased from 2.1 cases/100,000 inhabitants in 2001 to 0.9 cases/100,000 in 2010. The decrease was observed in Denmark, France, Portugal, Spain and other EU countries[5].

Similarly, a decrease in HIV cause specific mortality in the EU is observed - from 1.3 cases/100,000 inhabitants in 2001 to 0.9 cases/100,000 in 2009, with the most significant decreases being observed in the above mentioned countries[6].

Similar conclusions can be drawn from recent results of the D:A:D cohort study (including 21 country in Europe, USA and Australia), showing a reduction in mortality rates in the PLHIV population from 16.9 in 1999/2000 to 9.6 per 1000 person years (py) in 2007/2008[7].

Similarly scientific literature reports that there is a downward trend in deaths due to HIV and causes of death are becoming more similar to those which are seen in the general population in the given age strata[8]. For example, Danish PLHIV cohort study reported a proportional mortality for HIV related causes of death of 76% in 1995/1996, but by 2000 – 2005 this proportion had fallen to 43%[9].

Considering the above mentioned trends, it can be concluded that mortality among PLHIV continues to approach the indicators of the general population. E.g. the multicentre study results published by *Lewden et al.* show that the mortality rate of persons infected through sexual contact and having continuously maintained CD4 cell count above 500/mm^3, was close to the rate among general population with standardized mortality ratio (SMR) 0.9 among men, and 1.1 among women[10].

As it was already mentioned, adequate care and therapy are significant factors in decreasing AIDS incidence and mortality indicators. Although ensuring patients with HIV care and antiretroviral therapy puts an additional strain on the national health care budget, it must be noted that the cost of antiretroviral drugs has decreased significantly in recent years in many countries[11], including Latvia[12]. In addition, the specialized care and therapy is related with noteworthy financial gains – by delaying the onset of AIDS, reducing mortality, the decrease in the financial losses resulting from productivity loss in workforce is obtained. Adequate HIV therapy and care also save on the cost of the treatment of opportunistic diseases[11]. It should be also underlined that HAART significantly decreases the risk of HIV transmission

(principle of „treatment as prevention" – „T as P")[13], thus saving the expenses that would be incurred treating a new cases of HIV.

In order to plan and implement targeted and appropriate activities of secondary and tertiary HIV prevention, it is necessary to clarify the factors associated with the increased AIDS incidence and with higher mortality rates among PLHIV. By studying the mentioned factors it is possible to determine PLHIV sub-populations and risk groups that require special attention. Similarly, it is possible to identify certain factors which, unlike social demographic indicators, are not permanent and can be changed in order to improve the situation. The scientific literature contains referential proof of various factors associated with the onset of AIDS and death that can be divided into three groups: sociodemographic factors, health behaviour, and factors related to health care and health status of the individual.

Although HIV is admitted as one of the most widely researched health conditions in the history of mankind[14], HIV research is nevertheless replete with unanswered questions and contradictory information regarding factors associated with HIV outcomes. For example, the literature contains controversial information about social and demographic characteristics of individuals. Some research shows a higher risk among women to show signs of early HIV outcomes[15,16,17,18]. However, other studies show the complete opposite[7,9,10,19,20,21,22,23] or they claim that there is no difference between men and women in regards to AIDS or *exitus letalis*[15,24,25,26,27,28,29,30]. Most research has found that the older the patient the worse the HIV prognosis[17,21,23,25,29,30,31,32,33]. However, other studies find no significant relationship between age and HIV outcomes or claim that old age can be a positive factor regarding HIV progress[20,31,34,35,36,37]. As far as ethnic origin is concerned, researchers agree that representatives of minority races and ethnicities have a more negative HIV prognosis than do members of majority races and ethnicities[8,38,39,40]. However, in several studies the mentioned

differences have not been identified[17,41]. Some research shows that the place of residence of an individual is a factor affecting HIV outcomes; the prognosis is relatively better for PLHIV residing in the urban (characterized as densely populated industrial territories, with higher social economic indicators, diverse life style etc.[42,43]) territories comparing to their rural counterparts[33,44,45,46]. Although most of the literature reports incarceration as a negative factor in relation to HIV outcomes[47,48,49], there is some research that presents that imprisonment can also promote the health of PLHIV[50].

There is also evidence in the literature that proves the association between health behaviour and HIV outcomes. Injecting drug use rarely is associated with positive HIV outcome[51,52]; it is most often associated with negative outcomes such as earlier onset of AIDS and *exitus letalis*[7,8,10,24,29,30,53,54,55,56]. As far as high risk sexual behavior is concerned, the literature most often reports no difference between homosexual and heterosexual behavior[17,25,29,30,57]. Very few studies report worse HIV outcome measures among men who have sex with men (MSM)[26].

Certainly health status of an individual as well as health care factors are related to the progress of HIV. Researchers unequivocally link the late diagnosis of HIV to worse HIV outcomes, i.e. late diagnosis is linked with early onset of AIDS and *exitus letalis*[23,25,58,59,60,61,62]. HIV viral load is also seen as an independent HIV progress marker in that a high number of viral RNA copies in the plasma is connected with earlier onset of AIDS and *exitus letalis*[7,16,57,63,64,65,66,67,68]. However, this effect persists only if the CD4 cell count is not less than 100/μl[69,70]. Undoubtedly, HIV progression is positively affected by care and therapy, especially when they are undergone with a good adherence[71,72,73]. According to the literature, co-infections, especially HCV, has a negative effect on HIV outcome indicators[9,74,75,76,77,78]. Although there are also instances reported in the literature that deny the negative effect of HCV[7,79,80,81].

In Latvia to date, no research on the statistical significance of the time trends of HIV outcome measures (AIDS incidence, mortality measures) nor on factors affecting these outcomes in the PLHIV population has been carried out and published. Latvia is still considered as a country with a high HIV incidence – it exceeded the EU average rate twice in 2010[5]. Similarly, in 2010 Latvia showed the highest AIDS incidence indicators in the EU (exceeding by six times the EU average[5]) and it takes third place according to HIV related deaths, exceeding the EU average three times[6]. Thus, HIV and its outcomes have to be seen as a significant public health issue in the country. A study of HIV outcomes and related factors could offer valuable input in addressing the issues of secondary and tertiary prevention of the infection.

Aim of the thesis

The aim of the study is to examine causal and statistical associations between HIV outcome measures and sociodemographic, health behaviour, health status and health care factors.

Objectives of the thesis

1) To characterize the population living with HIV in Latvia in terms of social demographic, health behaviour, health status and health care factors;
2) To determine the overall and gender specific AIDS incidence, changes therein over time and their statistical significance in the population living with HIV in Latvia;
3) To determine the overall, gender specific and standardized mortality and changes therein over time among the population living with HIV in Latvia;
4) To determine survival of various time periods using two endpoints (AIDS and *exitus letalis*) and the associated sociodemographic, health behaviour, health status and health care factors among the population living with HIV;

5) To calculate the years of potential life lost, changes therein over time and associated factors among the population living with HIV in Latvia;
6) To determine cause specific mortality, changes therein over time and associated factors among the population living with HIV in Latvia.

Hypotheses:

1) The incidence of AIDS, as well as overall and HIV cause specific mortality among the population living with HIV in Latvia, similar to the trends in Europe in general, has decreased over the last ten years;
2) HIV outcomes are associated to sociodemographic, as well as health behaviour, health status and health care factors.

Structure of the thesis:

The thesis is written in Latvian. It consists of ten sections: the introduction, literature review, materials and methods, results, discussion, conclusions, scientific novelty of the thesis, practical significance of the thesis, list of references and annexes. The thesis consists of 258 pages (188 pages without the list of references and annexes). The work contains 24 tables and 20 figures. Bibliography consists of 401 references.

2. MATHERIALS AND METHODS

2.1. Study format

It was conducted a retrospective cohort study among the population of persons living with HIV in Latvia. The research was approved by the RSU Ethics Commission (session dated 23.02.2012).

2.2. Data sources

Several sources of data were used during the study:

a) The database of the State register for HIV and AIDS (further in the text – Register). Notification of HIV is mandatory in Latvia. The data in the Registry is based on the medical documentation submitted by physicians within 72 hours of the confirmation of the diagnosis (using separate reporting forms for HIV, AIDS and death cases). Data on 4,888 individuals (100% of PLHIV registered in Latvia) was received in MS Excel format and did not include privately sensitive information.

b) The national Causes of Death database. Data on 690 individuals (93.5% of 738 PLHIV deaths registered in Latvia) was received in MS Excel format and did not include privately sensitive information. The information was made available by Register employees, since the Register quarterly receives information from the Causes of Death database.

c) Information from the medical records of ICL HIV/AIDS outpatient department. In order to process the data, an electronic data frame in SPSS was developed. Data selection and manual processing were done by the author of the thesis from August 2010 to December 2011. Information was collected on 3,273 individuals (98.9% of 3,311 PLHIV registered at ICL by December 31, 2010).

d) In order to compute the relative rates of the characteristics being studied, the author requested that a special data base be produced by the Central Statistical Bureau of the Republic of Latvia in MS Excel format. The data base

included statistics of population size of Latvia and cases of death from 1991 – 2010 based on gender and age.

2.3. Data processing

The three above mentioned databases were combined into one using MS Excel VLOOKUP and subsequently transferring the information to SPSS. In order to facilitate identification of concrete individuals in each of the three data bases, the following identifying information was used: ICL medical records number, anonymous patient ID number, the unique registration number of the HIV confirmatory test at ICL reference laboratory.

The following dependent variables were chosen for the study:

1) Individual's **AIDS status** in the Register – has AIDS been diagnosed. The variable is dichotomous with two categories – yes or no. Based on the information provided by ICL, AIDS diagnosis in Latvia is conducted using CDC criteria published in 1993[82].

2) Individual's **vital status** in the Register – has *exitus letalis* been confirmed. The variable is dichotomous with two categories – yes or no.

3) **Cause of death** – basically the variable is used as a categorical in relation to the three leading causes of death (B20-B24 / V+W+X+Y / I00-I99). In the study HIV as an underlying cause of death is coded based on ICD – 10 codes B20-B24. If the underlying cause of death code was not B20-B24, it was verified if the different underlying cause indicated was not an AIDS indicator disease (A02.1, A07.2, A07.3, A15-A19, A31.0, A31.8, A31.9, A43, A81.2, B00.3, B00.4, B00.7, B00.9, B25.0, B25.2, B25.8, B25.9, B37.1, B37.5, B37.6, B37.7, B38.3, B38.4, B38.7, B38.9, B39.3, B39.4, B39.5, B39.9, B45.1, B45.2, B45.3, B45.7, B45.8, B45.9, B58, B59, B78.1, B78.7, B78.9, C46, C53, C82, C83, C85, F02.4, J13-J18). If the underlying cause was not found among AIDS indicator diseases, it was examined if the indicator diseases had not been found in the list of antecedent causes. If the underlying cause of death or one of the antecedent causes was an indicator disease, the death case was accordingly

reclassified as HIV-related, similarly to the practice of other studies[9]. Underlying causes of death not related with HIV in the chapter 3.6.1. are grouped in more detail based on ICD-10 diseases groups: A00-B99, C00-C97, D50-D89, E00-E99, F00-F99, G00-G99+H00-H59, I00-I99, J00-J99, K00-K93, L00-L99, M00-M99, N00-N99, Q00-Q99, R00-R99, V+W+X+Y.

The above mentioned dependent variables were studied in relation to the following independent variables:

1) **Gender** – used as a dichotomous variable – male; female;

2) **Age** at time of HIV diagnosis – used both as a continuous and a categorical variable with 5 categories (0-13; 14-24; 25-34; 35-44; 45 years and older) or with 12 categories within 5-year age groups (0-14; 15-19; 20-24; 25-29; 30-34; 35-39; 40-44; 45-49; 50-54; 55-59; 60-64; 65 years and more). When the factors associated with HIV outcomes were discovered only individuals older than 13 years were included in the data analysis since the diagnostic, monitoring and therapy principles for individuals under the age of 14 are different from those for adults. However, individuals up to age 13 were included in several Results sections of the thesis (3.1.1., 3.2., 3.3., 3.4.1., 3.4.3., 3.5.1., 3.6.1.) with the purpose of fully evaluating HIV outcome measures within the total PLHIV population and comparing to mortality within the general population.

3) **Ethnic origin** – used as a categorical variable with three categories: Latvian; Russian; other.

4) **Place of residence** – a dichotomous variable: Riga; outside Riga. The categories were chosen taking into consideration the fact that HIV care have had a highly-centralized nature (till 2010 it was provided by one institution in the capital Riga (ICL), so people living outside Riga may have a limited access to the care.

5) **Incarceration** at the time of diagnosis – dichotomous variable: yes or no.

6) **Mode of transmission** – a categorical variable with three categories: injecting drug use; homosexual contact; heterosexual contact. PLHIV getting HIV infected through vertical transmission were under age of 13 and thus were excluded from the discovering of factors associated with HIV outcomes due to the considerations described above.

7) **Year of HIV diagnosis** – the variable was used in the study both on a continuous scale as well as a categorical variable defining three categories: 1987-1999; 2000-2007; 2008-2010. The formation of the categories takes into consideration the changes in the HIV pandemic process, both on a national and international level. The first category is referred to as the preHAART/early HAART period. The second and third categories evidence the observed changes in HIV epidemic in Latvia. I.e. prior to 2007 the main mode of HIV transmission was needle sharing among injecting drug users, while heterosexual transmission of HIV has been dominant since 2008.

8) **Timeliness of HIV diagnosis** – a dichotomous variable: late diagnosis; timely / unknown. The indicator is a combination of a CD4 cell count under 200/µl at the time of HIV diagnosis, and/or onset of AIDS at the time of diagnosis (i.e. within six months of HIV diagnosis[58]). Studying the survival with the endpoint AIDS the late diagnosis case definition was based only on the count of CD4 cells (under 200) as the outcome (AIDS) cannot be simultaneously included also in the independent variable studied (late diagnosis). As well studying AIDS free survival CD4 cell count over 200 has been grouped in more detailed manner: 200-349, 350-499, ≥500/µl. The basis for this distinction is the CDC classification system for HIV infection[82]. An additional cutoff point is a CD4 cell count up to 350/µl was chosen in line with the latest international guidelines for the initiation of HAART (cell count under 350/µl for asymptomatic patients[83]).

9) **Viral load** at the time of HIV diagnosis – a categorical variable. Viral load was observed within 6 months from HIV diagnosis[58]. Since the number of

viral RNA copies varies widely and its distribution within the population is notably asymmetric, a decimal logarithm of the number of RNA copies was used in the study. It classically is divided into these catagories[7,16,28,57]: <4; 4-5; ≥5 $\log_{10}$ copies/ml.

10) **HIV care and ART experience** – used as a categorical variable with four categories: has not received specialized health care (HIV diagnosis confirmed and included in Register, but is not registered at ICL); has received care, but is ART naïve; has received ART, but experienced interruption; has received ART with no interruption. To be considered as an ART receiver, an individual must have undergone ART for at least one month (irrespective of number and combination of medications)[73]. Interruption in therapy is defined as interrupting therapy for a period of at least two weeks during which time ART has not been taken in[9] (based on the outpatient medical records). The data analysis of care and therapy experience separates out pregnant women living with HIV (category "other"), who received ART medication only during pregnancy as a prophylaxis of the vertical transmission with specific criteria for starting and stopping the therapy.

11) Viral **hepatitis C coinfection** – used as a dichotomous variable: is or is not infected. The information was gained from ICL outpatient medical records. It was assumed that an individual has HCV if during the time period since HIV diagnosis he or she has had a positive HCV antibody test at least once[9].

2.4. Population studied

For the purposes of this thesis information on individuals who had been registered in the Register between January 1, 1987 and December 31, 2010 was used. In total, data on 4,888 HIV infected individuals, including 981 AIDS cases and 738 deaths, was analyzed. The total period of observation comprises 31,192.6 person years (median observation time – 6.8 py; average – 6.4 py (SD 3.7); range 0-23.9 py).

2.5. Statistical analysis

Within the thesis two HIV outcomes – AIDS and *exitus letalis* – has been studied. Overall and stratified indicators were calculated. Person-time at risk (py), which was determined directly (individually for each PLHIV), was used to calculate the rates of the indicators. The beginning of observation was defined as the date of confirmation of HIV diagnosis and the end of observation was defined as the date of onset of AIDS or death or December 31, 2010.

In order to determine whether mortality rates in the PLHIV population differ from those in the general population, the standardized mortality ratio (SMR) was calculated using an indirect standardization method with the standard being age-specific mortality rates in the general population of Latvia.

The years of potential life lost (YPLL) indicator was determined using the age of 65 as a cut-off point. The indicator was applied to 100,000 inhabitants of the general population up to the age of 65 as well as 1,000 PLHIV. Similarly, the YPLL indicator was used as an average number of years per death. A linear regression model was constructed to identify factors associated with premature mortality among PLHIV.

Before performing the regression analysis the collinearity between the independent variables was examined using tolerance statistics (collinearity was approved if the test result was significant at the level of 0.1). As well the multiplicative interaction (relationship between an independent variable and dependent variable, moderated by a third variable) was examined using the regression analysis (the statistical significance of the product of the two independent variables was examined).

Linear regression was applied to define the statistical significance of time trends of the indicators calculated. To achieve linearity the logarithmic transformation of the outcome has been done.

For comparison of cause specific mortality rates between various strata (by calculating mortality rate ratio) as well as for evaluation of the independent effect of different factors on the HIV outcome the Poisson regression was used.

Survival analysis was performed using the Kaplan-Meier plots, defining survival of various time periods in total and in gender strata. Survival curves in strata of the independent variables were also compared. The statistical significance of survival curve differences was assessed using the Log-Rank test. Two endpoints has been chosen – AIDS and *exitus letalis*.

The Cox proportional hazards model was used to assess the independent effect of the factors studied on mortality. The proportional hazards assumption was examined using Log-Log Plots.

The following software was used for data processing and analysis: SPSS 19.0, MS Excel, and CIA. The statistical confidence of the results was rated by estimating significance level (p) and the 95% confidence interval. The results were considered statistically significant at $p<0.05$.

3. RESULTS

3.1. Description of the study population based on selected characteristics

In the general assessment of the HIV outcome measures and changes therein over time the entire PLHIV population was included regardless of age (n=4,888). Whereas identification of factors associated with outcomes from HIV did not include individuals who were 13 years old or younger at the time of HIV diagnosis (n=45; 0.9% of the total number of HIV infected individuals whose age was known) (see section 2.3. for arguments).

3.1.1. Description of the total PLHIV population in Latvia

Of the total study population (n=4,888), the majority – 69.5% - are males (95% CI 68.2-70.8; n=3,396) (here and after 95% CI continues to appear in brackets behind the indicators). Average age at the time of diagnosis is 28.9 (SD 9.6), median age is 27. Information about birthdate or year was unavailable in 18 cases. One half of the PLHIV are Russians – 49.6% (48.2-51.0; n=2,424), the second most prevailing ethnicity is Latvian – 26.0% (24.8-27.3; n=1,272). Other ethnicity was noted by 11.6% of the study population (10.8-12.5; n=568). The most often noted „other ethnicity" is Roma – 62.3% of all representatives of other ethnicities (n=354). Information on ethnic origin was not available for 624 individuals (12.8%). Most of the PLHIV (74.3%) lived in Riga at the time of diagnosis (73.0-75.5; n=3,630), 25.7% lived outside of Riga (25.7%; 24.5-27.0; n=1,258), most often in Pieriga region (n=525), least often in Latgale (n=46).

Most of the individuals in the study became HIV infected by sharing needles during injecting drug use – 58.9% (57.5-60.3; n=2,878). The second most common mode of transmission (25.0%) is heterosexual contacts (23.8-26.2; n=1,222). Homosexual contacts as the route of transmission was noted for 5.0% of individuals (4.4-5.6; n=243). 39 children (0.8%) became infected

through vertical transmission. Mode of transmission was not determined for 506 PLHIV or 10.3%; 9.5-11.2).

Of the entire PLHIV population, 10.1% (9.3-10.9; n=492) were infected in the pre-HAART or early HAART period, i.e. before 1999.

3.1.2. Description of HIV infected population over the age of 14

Describing the population of PLHIV aged 14 years and above (n=4,825 or 98.7% of the total population) in relation to the factors studied, it can be concluded that about one fourth (25.8%) of all individuals were imprisoned at the time of diagnosis (24.6-27.0; n=1,244). Information about the CD4 lymphocyte count at the time of diagnosis was available for one half of the study population (54.5%; n=2,628). The average cell count was 530.2 (SD 266.7) with the median cell count being 510.0. 9.9% of the individuals for whom the information was available showed a count less than 200 cells/µl (8.8-11.1; n=259). One half of the individuals showed a high cell count at the time of diagnosis, over 500 cells/µl (52.1%; n=1,369).

It must be noted that for 523 PLHIV (16.6%; 15.3-17.9 out of 3,151 individuals for whom the information on CD4 cell count was available) the period from the time of diagnosis to the first CD4 cell count determination (until they were seen by ICL infectologists) was longer than 6 months. For this reason, they were excluded from the number of persons with timely or late HIV diagnosis (i.e. were defined as with unknown timeliness of the diagnosis).

In Latvia in general the average time from HIV diagnosis to the first CD4 cell count determination is 5.1 months (SD 13.0) (median – 0.7 months or approx. 3 weeks). More than one half of the PLHIV – 59.8% - had their first CD4 cell count tested within a month of HIV diagnosis (58.0-61.5; n=1,883).

During the period of time studied 352 individuals over the age of 14 were diagnosed with AIDS within 6 months of HIV diagnosis (37.4% (34.4-

40.5) out of 941 AIDS cases in this group). 174 of these individuals showed a CD4 cell count greater than 200 cells/µl at the time of HIV diagnosis.

The average time from HIV diagnosis to AIDS diagnosis is 34.9 months (SD 36.4) or 2.9 years, median time is 24.3 months or approximately 2 years. The mentioned time period varies from 0-155.2 months or 12.9 years. For 26 individuals the time of HIV diagnosis coincided with the time of AIDS diagnosis. In addition, 10 individuals had died of AIDS related causes within 6 months since HIV diagnosis (i.e. AIDS was diagnosed at the time of death), thus it can be said that HIV diagnosis was late in these cases as well. Overall, HIV diagnosis can be considered as late in 9.2% of cases (8.4-10.0; n=443). Timely diagnosis can be claimed in 46.1% of cases (44.6-47.5; n=2,222), while in 44.8% of cases (43.4-46.2; n=2,160) there was lack of information to determine the timeliness of HIV diagnosis.

It must be emphasized that the proportion of late diagnoses among the newly identified HIV cases has increased over a 10 year period as shown in figure 3.1.2.1. If in 2001 only 3.1% of cases were diagnosed late (2.1-4.6), then by 2010 this percentage had grown to 21.3% (16.9-26.7).

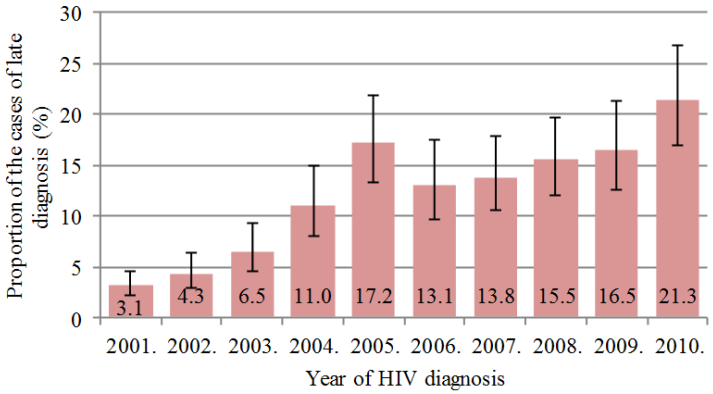

Fig. 3.1.2.1. Proportion of late HIV diagnoses of all diagnosed cases (2001-2010)

Information about viral load in the serum was available in 2,292 cases or 47.5% of all PLHIV who were over the age of 14 at the time of HIV diagnosis (in 629 cases the viral load (VL) was determined later than 6 months after HIV diagnosis and in the remaining 1,904 cases VL has not been determined).

For one sixth of the study population (15.3%; 14.3-16.3) the indicator was lower than 4 $\log_{10}$ RNA copies/ml (i.e. below 10,000 copies). In 13.9% of cases (12.9-14.9) the indicator was higher than 5 $\log_{10}$ RNA copies/ml, and in 18.3% (17.3-19.4) of cases the viral load was in the range of 4 – 5 $\log_{10}$ copies/ml. 3.4% (n=163) of individuals showed a VL under 400 copies/ml, which in the case of less sensitive laboratory methods is considered to be beyond detection levels. The average VL in the PLHIV population is 4.4 $\log_{10}$ copies/ml or approximately 25,000 copies/ml. The median viral load is 4.0 $\log_{10}$ copies/ml.

One third (32.5%) of PLHIV over the age of 14 have not registered at ICL since HIV diagnosis to receive care (31,2-33.9; n=1,570). 39,9% of individuals were registered at ICL and were ART naïve (38.5-41.2; n=1,923) (including 41 individuals who had started therapy, but had undergone it less than a month). 13.8% (12.9-14.8; n=668) had started ART, but during treatment had one or more interruptions of at least 2 weeks. 7.7% (7.0-8.5; n=372) of HIV infected individuals had received ART with no interruptions. Care and therapy designated as „other" pertains to 292 individuals, of whom 262 are pregnant females. For the remaining 30 individuals there is no information available regarding therapy experience (e.g. no medical records available at the moment of data collection).

In Latvia the average time from diagnosis to start of ART is 33.8 months (SD 36.7) or approximately 3 years (the time varies from 0 to 153 months). The median time period is 19.9 months or approximately 1.7 years.

The reason behind interruptions in ART in the case of 668 PLHIV is the lack of adherence – problems with adherence were identified in 79.9% of cases (76.6-82.7; n=533). The second most prevailing reason for interrupting ART (10.3%; 8.2-12.9; n=69) involves technical difficulties such as insufficient funds, lack of medications etc. In the case of 4.0% of individuals ART was stopped because of health related difficulties (side effects, resistance etc.) (2.8-5.8; n=27). 3.0% of individuals stopped ART upon reaching positive results in treatment of acute retroviral syndrome (ARVS) (1.9-4.6; n=20); 18 individuals emigrated from Latvia (2.7%; 1.7-4.2) and one individual noted other reason for stopping ART (not a Latvian citizen).

Information regarding the HCV status was available for 3,128 individuals. 47.8% out of all PLHIV (46.4-49.2; n=2,306) showed positive HCV antibody test results in the time period since HIV diagnosis. The highest number of positive HCV antibody test results was shown among PLHIV who became infected via drug injection – 95.7% (94.7-96.5).

3.2. AIDS incidence among PLHIV population

3.2.1. Overall AIDS incidence and the tendencies over time

The first case of AIDS in Latvia was reported in 1990 and by the end of 2010 there were 953 cases reported. In frame of the research additionally to the AIDS cases identified in the Register 28 individuals whose underlying cause of death was an AIDS indicator disease (i.e. it can be said that AIDS was diagnosed at death) were included in the incidence analysis thus bringing the total number of cases to 981.

Until 2000 the number of AIDS cases in Latvia was relatively low. In total within the studied time period AIDS incidence density among PLHIV was 35.4/1,000 py (33.4-37.5) (total follow-up time - 27,736.7 person years at risk). During the last 10 years the highest AIDS incidence was reached in 2005 (45.8/1,000 py (38.0-54.7)) with 122 cases reported.

Exploring the AIDS incidence tendencies over the last 10 years, it can be concluded that the indicator is static with no significant tendencies over time (see fig. 3.2.1.1.). The regression equation depicted in the figure shows a small annual decrease of AIDS incidence by 1.002 times ($e^{0.0022}$) or about 0.22%, but this observation is far from statistical significance (p=0.91).

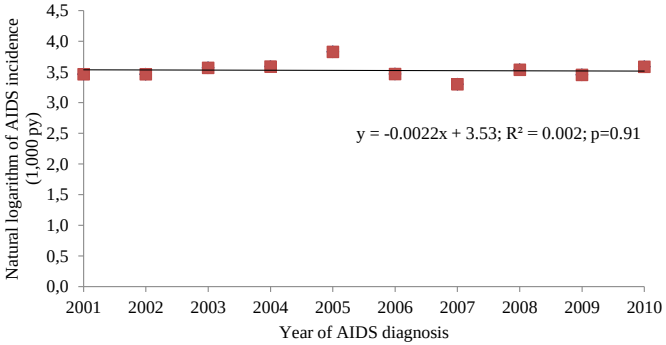

Fig. 3.2.1.1. Time trends of AIDS incidence density among people living with HIV in Latvia, 2001-2010

3.2.2. Gender specific AIDS incidence and its tendencies over time

The first case of AIDS among males was reported in 1990, i.e. three years after the first registered HIV case in the country. During the last 10 years the highest AIDS incidence among males, similar to the incidence within the total PLHIV population, was reported in 2005, with 77 cases being reported. This accounts for an incidence of 39.8 cases per 1,000 person years (95% CI 31.4-49.7). The lowest incidence, on the other hand, was reported in 2007 – 28.5/1,000 py (21.8-36.6), although the difference between the two years is not statistically significant.

The first HIV case among females was reported in 1994, and, just like in the male population, the first case of AIDS among females was reported three years later in 1997. The highest AIDS incidence among females was also reported in 2005 – 61.6/1,000 py (44.9-82.4; n=45) and the lowest - in 2007

with 23.7 cases per 1,000 person years (95% CI 14.7-36.6). The noted difference between the years of highest and lowest AIDS incidence is statistically significant.

Exploring the time-trends in AIDS incidence by gender, it can be concluded that the indicator is static from year to year with repeated minimal increases and decreases (p for time-trend among females is 0.46, among males p=0.75). So the conclusion is similar to the one made for the time-trends in overall AIDS incidence.

Calculating the AIDS incidence rate ratios between gender strata in relation to the year when AIDS was diagnosed, it can be concluded that gender differences in either year are not statistically significant. The only significant difference between gender strata is for the year 2005 which was the year reporting the highest incidence of AIDS in the last decade; AIDS incidence among females was considerably higher than it was among males (IRR=0.65; 0.45-0.93) and the statistical significance of this difference remains when adjusted for age. Overall incidence rate ratio for the entire period of 10 years (2001-2010) shows that the incidence is slightly lower among males than it is among females (IRR=0.94) although the difference cannot be considered as statistically significant (95% CI 0.82-1.08).

3.3. Description of the all-cause mortality measures

3.3.1. Overall mortality, its tendencies over time

During the period of observation 738 deaths were identified among the PLHIV population, which is 23.7 cases per 1,000 py (22.0-25.4). Prior to 1998 there were only 8 deaths reported, with none being reported in 1992, 1993, 1996, and 1997.

Considering mortality rate in the recent decade (by 2000 the number of deaths was relatively low, resulting in mortality rates with broad confidence intervals), it was concluded that the highest mortality rate had been observed in

2009 – 33.4 cases/1,000 py (27.9-39.6). In addition, mortality rate shows a statistically significant tendency to increase approximately 1.10 times ($e^{0.097}$) or by 10.1% annually (p=0.002) (see fig. 3.3.1.1.).

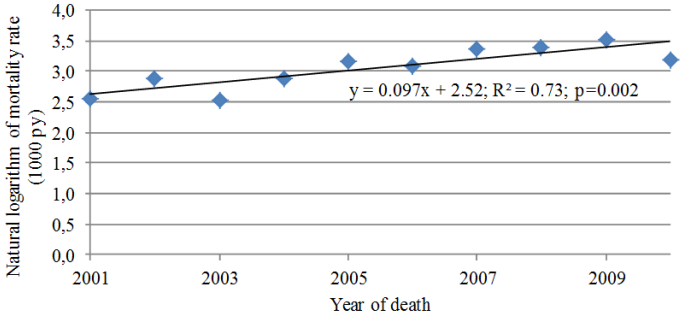

Fig. 3.3.1.1. Time trends of crude mortality rate among people living with HIV in Latvia, 2001-2010

3.3.2. Gender specific mortality, its tendencies over time

During the period of observation, the first death among HIV infected males in Latvia is registered in 1991. Overall by the end of 2010 556 cases were identified (75.3% of all deaths among the PLHIV population), thus the mortality rate among men was 24.8 cases/1,000 py (22.7-26.9). The first case of death among HIV infected females was in 1999 (182 cases by the end of 2010), showing a mortality rate of 20.8/1,000 py (17.9-24.1). The highest mortality rate among males, similar to the overall mortality, was identified in 2009 – 37.1/1,000 py (30.2-45.1) (disregarding mortality up to 1998, because, as mentioned above, there were only couple of cases t5hus the mortality rates were statistically unstable, with wide confidence intervals). The highest mortality rate among females was registered in 2008 – 28.5/1,000 py (19.5-40.3). It should be noted that there were no significant differences between gender strata in any of the years studied.

Considering mortality trends over time, it can be concluded that they are increasing for both males and females. Since the number of deaths for

females is low up to the beginning of the 21st century, the time period from 2003 – 2010 was chosen for the analysis of time trends. The mortality rate among males increases 1.11 times annually ($e^{0.106}$) or roughly by 10.2% (p=0.03). The increase of mortality rate among females, however, is more rapid, increasing 1.12 times ($e^{0.113}$) or 12.0% annually.

Calculating the mortality rate ratios between gender strata in relation to the year of death, there gender differences in either year were not observed. Only one exception was identified which is the year 2007 when the mortality among males was twice as high as among females (MRR=1.7 (1.02-2.7). Also the MRR for the whole time period was statistically significant – 1.2 (1.02-1.4; males vs. females). However this distinction can be explained with the age differences as the statistical significance disappeared after adjustment by age (adjusted MRR=1,1 (0,9-1,3)).

3.3.3. Mortality among the population of PLHIV as compared with the general population

Estimating age standardized mortality in order to compare mortality between PLHIV and general population in Latvia, it was found that the rate among both populations is significantly distinct – mortality among PLHIV exceeded the rate among general population more than ten times in the recent years. Similarly to the crude mortality rate, the standardized mortality ratio (SMR) was also the highest in 2009 – 12.6 (10.5-14.9). In addition, standardized mortality ratio has a statistically significant trend of growing annually 1.07 times ($e^{0.067}$) or by 6.9% (p=0.008) (see fig. 3.3.3.1.).

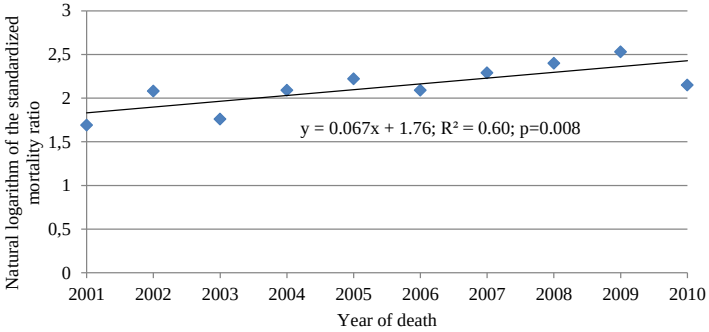

Figure 3.3.3.1. Time trends of standardized mortality ratio in Latvia, 2001-2010

Considering the mortality rates for gender strata among PLHIV and comparing those with the gender specific mortality among men and women in the general population, it can be concluded that the indicators are higher among the population of PLHIV for both genders. Among HIV infected females the difference is notably sharper than it is among males. During the period of observation the mortality rate among females was 16.0 times (13.9-18.6) higher than that of the females of general population in Latvia, while the SMR for males was 4.7 (4.3-5.1) for the time period 1991-2010. Looking at gender specific SMR time trends, it was observed that the ratio for males has a statistically significant tendency to increase 1.07 times ($e^{0.066}$) or by 6.8% annually (p=0.01). Among females, however, no consistent tendencies can be observed, the indicator is fluctuating from year to year (p=0.12).

Comparing mortality rates between age strata among the PLHIV population and those of the general population, it can be concluded that the mortality is higher among infected individuals in all age groups, with the differences becoming less significant as individuals get older – roughly by 19.2% per unit of change in age group* (regression equation: ln(y)=3.02-0.18x; R^2=0.77; p<0.001). The largest differences between PLHIV and the general

* Age groups compared are described in chapter 2.3.

population were observed in children and teens (0-14 and 15-19 years) with a respective SMR of 28.0 (9.1-65.3) and 10.7 (5.3-19.1), but statistical instability must be taken into account (broad confidence intervals). The indicator is also high for the 35-39 year age group, with a mortality almost 10 times greater among HIV infected individuals than it is among the general population (SMR=9.5; 8.0-11.2). However, in the age group 60-64, it is relatively low - only three times higher (SMR=3.1; 1.4-6.2) and among individuals over the age of 65 the mortality differs only by 1.4 times and this difference is not considered to be statistically significant (95% CI 0.4-3.5).

3.4. Survival of PLHIV and associated factors

3.4.1. AIDS-free survival in total population of PLHIV

Looking at the survival up to AIDS diagnosis among the entire PLHIV population, they logically are lower comparing to the survival when the death was chosen as the endpoint. One year after HIV diagnosis 91.6% (90.8-92.4) of the individuals were still with no diagnosis of AIDS. 83% (81.8-84.2) of all HIV infected individuals survived at least five years without AIDS; 73.3% (71.7-74.9) of infected individuals survived 10 years without AIDS. Similar to previous conclusion regarding gender stratified AIDS incidence, no significant differences by gender were observed if the AIDS-fee survival is considered.

3.4.2. Factors associated with AIDS-free survival

If we consider an individual's age at the time of HIV diagnosis, we can conclude that the proportion of survivors of a certain time period after HIV diagnosis decreases with age. For example, among individuals aged 14-24 at the time of HIV diagnosis 90.5% (89.1-91.9) survive without AIDS for 5 years; 82.3% (80.1-84.5) of the group survive 10 years without AIDS. Whereas among individuals over the age of 45 at the time of HIV diagnosis only 67.3% (61.4-73.2) survive 5 years without AIDS and only one half (50.8%; 39.2-62.4)

survive 10 years. In general, upon comparison of the survival curves, it can be concluded that there are significant differences between each two of age groups. There was no statistically significant difference only between the age categories 35-44 years and the over 45 (p=0.08).

Looking at the association between AIDS-free survival and ethnicity, individuals of Latvian ethnicity tend to show lower survival. For example, 5 years AIDS-free survival is 84.4% (81.3-87.5) for other ethnicities, 82.2% (80.6-83.8) for Russians and 79.1% (76.6-81.6) for Latvians. Statistically significant differences, however, were observed only between survival curves for Latvians and other ethnicities (p=0.02). This is shown also by the univariate proportional hazard model (see table 3.4.2.1.) – HR for other ethnicities compared to Latvians is 0.78 (0.63-0.97).

People living outside Riga tend to be diagnosed with AIDS earlier – 5 years AIDS-free survival is 80.9% (78.5-83.3) for those residing outside Riga and 83.6% (82.2-85.0) for PLHIV residing in Riga. The mentioned observation is approved also by comparison of Kaplan-Meier survival curves (p=0.047) as does also the univariate hazard analysis (HR (outside Riga vs. Riga) is 1.16; 1.001-1.33).

Higher proportion of survivors is observed also among individuals with experience of imprisonment. For example, among individuals being incarcerated at the time of HIV diagnosis, 87.3% (85.3-89.3) survive without AIDS for 5 years, while for individuals without this experience the proportion is 81.5% (80.1-82.9). Although over a longer period of time this difference diminishes (10 year survival for incarcerated individuals is 74.3% (71.0-77.6) and 73.0% (71.0-75.0) for those without prison experience). However, the survival curves shows that the difference is statistically significant (p=0.003).

The differences shown by survival curves are statistically significant between the mode of transmission categories (compared in pairs) (p<0.001). The lowest survival is among the PLHIV who became infected via homosexual

contacts (5 year survival – 64.9%; 58.0-71.8), followed by the ones who got infection through heterosexual contacts (80.0%; 77.5-82.5). A slightly better situation was observed in the IDU group, where 84.1% (82.7-85.5) survived at least five years without AIDS.

Individuals who were diagnosed with HIV more recently have higher risk regarding the early onset of AIDS. For example, 2 years without AIDS survived 90.8% of PLHIV diagnosed between 2000 and 2007 (89.9-91.8) and 89.7% of individuals diagnosed from 1987-1999 (87.0-92.4), while among individuals diagnosed from 2008-2010 the proportion was only 84.9% (82.4-87.4). As shown by the univariate hazard analysis, the difference between the period from 2000-2007 and that from 2008-2010 is statistically significant (HR=0.56; 0.45-0.69). However, the difference between the early period (1987-1999) and the time from 2008-2010 is not statistically significant (HR=0.84; 0.65-1.08) (see table 3.4.2.1.).

The hazard of early onset of AIDS is also associated with the timeliness of HIV diagnosis; i.e. the lower the CD4 cells count at the time of diagnosis, the greater the risk of early onset of AIDS. For example, at least 5 years without AIDS survive 86.0% (84.0-88.0) of individuals with a high CD4 cell count (over 500/μl). Individuals with a cell count of 200-349/μl show an proportion of 65.9% (60.4-71.4) and individuals with a cell count under 200/ μl - only 24.1% (14.1-34.1). In general, the differences between each pair of survival curves in groups of CD4 are statistically significant with a p-value below 0.001. The univariate hazard analysis shows that compared with individuals whose CD4 cell count exceeds 500/μl, individuals in the lowest cell count category (below 200/ μl) have over 13 times higher risk of early onset of AIDS ($p<0.001$) while the risk among individuals with a cell count of 350-499/ μl show 1.36 times the risk ($p=0.002$) (see table 3.4.2.1.).

A high HIV viral load at the time of diagnosis is also a risk factor in the premature onset of AIDS. Only 58.9% (54.8-63.0) of individuals with a VL

above 5 $\log_{10}$ copies survive 5 years without AIDS while in individuals whose VL does not exceed 10,000, this indicator is 85.1% (82.4-87.8). A comparison of survival curves also shows that the survival for individuals with a number of RNA copies below 10,000 is higher than that of individuals with a $\log_{10}$ copies from 4-5 ($p=0.02$) and higher than that of individuals with a $\log_{10}$ copies above 5 ($p<0.001$).

Similarly, lower survival was observed among individuals who have experienced ART with interruptions – 5 years AIDS free survival in the group was 43.8% (39.9-47.7), whereas among PLHIV who received ART with no interruptions the proportion was 53.6% (48.1-59.1). Survival curves between these two groups showed a considerable difference ($p=0.01$). High survival rates also were observed among individuals with no ART experience and among those not registered at ICL.

Among individuals with HCV coinfection survival rates are slightly higher than those of individuals without coinfection (5 year survival 77.1% (75.3-78.9) and 71.7% (68.2-75.2), respectively. The difference in survival curves can be considered as significant ($p<0.001$).

When the multivariate proportional hazard model was constructed, it was found that the age at the time of HIV diagnosis was the confounding factor in several associations. When adjusted by age, statistical significance of some associations disappeared, i.e. between the onset of AIDS and ethnicity, place of residence, imprisonment and HCV coinfection. Performing a stepwise adjustment also by other factors studied also the time period of HIV diagnosis lost its statistical significance.

Table 3.4.2.1. reflects the final multivariate model of proportional hazards (the adjustment performed by all the factors shown in the table). It can be concluded that, irrespective of other factors, age at the time of HIV diagnosis increases the risk of the early onset of AIDS, i.e. for each year increase the risk increases by 3% (or 1.03 times). The risk is also higher for

individuals who acquired the infection through homosexual transmission rather than heterosexual transmission (hazard ratio was significantly lower among heterosexually infected individuals – HR=0.73; 0.55-0.97). Late diagnosis also significantly increases the risk of AIDS – for individuals with a CD4 cell count under 200/μl the risk is almost 5 times higher ($p<0.001$) compared with PLHIV with a CD4 cell count that is considered as high (over 500 cells/μl). Among individuals with a cell count of 200-349/μl the risk of rapid onset of AIDS increased by 41% ($p=0.002$). A high HIV viral load (above 5 $\log_{10}$ or 100,000 RNA copies/ml) at the time of diagnosis also increases the risk of AIDS 1.62 times (1.30-2.02) compared with individuals whose VL does not exceed 10,000. After adjustment the statistical significance remain also for the association between early onset of AIDS and experience of interrupted ART. Individuals who have undergone ART with no interruptions have less risk than PLHIV experiencing interruptions (HR=0.70; 0.59-0.83). A statistically significant lower risk of AIDS is also exhibited by individuals with no ART experience and with no experience of specialized care.

Table 3.4.2.1.

Factors associated with early onset of AIDS, univariate and multivariate analysis

Factor	HR[a]	95% TI	p[b]	sHR[a,c]	95% TI	p[b]
Gender						
male vs. female	0.98	0.85-1.13	0.79	0.93	0.80-1.08	0.34
Age at diagnosis						
per year increase	**1.05**	**1.05-1.06**	**<0.001**	**1.03**	**1.03-1.04**	**<0.001**
Ethnicity						
other vs. Latvian	**0.78**	**0.63-0.97**	**0.02**	1.19	0.75-1.49	0.13
Russian vs. Latvian	0.87	0.75-1.00	0.06	1.07	0.92-1.24	0.39
unknown vs. Latvian	**0.35**	**0.26-0.45**	**<0.001**	0.75	0.56-1.01	0.06
Place of residence						
outside Riga vs. Riga	**1.16**	**1.00-1.33**	**0.048**	1.03	0.89-1.19	0.69
Imprisonment						
yes vs. no	**0.80**	**0.69-0.92**	**0.003**	0.90	0.76-1.06	0.22
Mode of transmission						
IDU vs. homosexual	**0.48**	**0.38-0.61**	**<0.001**	0.96	0.72-1.30	0.81
heterosexual vs. homosexual	**0.65**	**0.51-0.84**	**0.001**	**0.73**	**0.55-0.97**	**0.03**
unknown vs. homosexual	**0.21**	**0.14-0.30**	**<0.001**	0.95	0.64-1.44	0.84
Year of HIV diagnosis						
1987-1999 vs. 2008-2010	0.84	0.65-1.08	0.17	0.91	0.68-1.23	0.55
2000-2007 vs. 2008-2010	**0.56**	**0.45-0.69**	**<0.001**	0.86	0.68-1.09	0.22
CD4 count / µl						
0-199 vs. ≥500	**13.56**	**11.10-16.55**	**<0.001**	**4.82**	**3.80-6.11**	**<0.001**
200-349 vs. ≥500	**2.28**	**1.84-2.82**	**<0.001**	**1.41**	**1.13-1.76**	**0.002**
350-499 vs. ≥500	**1.36**	**1.12-1.65**	**0.002**	1.15	0.94-1.40	0.18
unknown vs. ≥500	**0.49**	**0.41-0.58**	**<0.001**	**1.32**	**1.00-1.74**	**0.047**
Viral load (log_{10} RNA copies/ml)						
≥5 vs. <4	**3.41**	**2.78-4.17**	**<0.001**	**1.62**	**1.30-2.02**	**<0.001**
4-5 vs. <4	**1.31**	**1.05-1.62**	**0.02**	1.21	0.97-1.52	0.09
unknown vs. <4	**0.69**	**0.56-0.84**	**<0.001**	**1.39**	**1.07-1.81**	**0.01**
Care and therapy						
ART with no interruption vs. with interruption	**0.82**	**0.69-0.96**	**0.01**	**0.70**	**0.59-0.83**	**<0.001**
ART naive vs. with interruption	**0.15**	**0.13-0.17**	**<0.001**	**0.18**	**0.16-0.22**	**<0.001**
no HIV specific care vs. with interruption	**0.01**	**0.01-0.02**	**<0.001**	**0.01**	**0.01-0.02**	**<0.001**
other vs. with interruption	**0.12**	**0.09-0.18**	**<0.001**	**0.18**	**0.12-0.26**	**<0.001**
HCV coinfection						
yes vs. no	**0.76**	**0.65-0.88**	**<0.001**	1.12	0.91-1.37	0.29
unknown vs. no	**0.07**	**0.05-0.10**	**<0.001**	1.38	0.92-2.05	0.12

[a] HR - hazard ratio, [b] p – p-value, [c] adjusted by all factors shown in the table

3.4.3. Survival up to exitus letalis among the total population of PLHIV

Considering the survival (by choosing the *exitus letalis* as the endpoint) in the total population of PLHIV, it was observed that 96.3% (95.7-96.9) of individuals survive one year after HIV diagnosis; 89.1% (88.1-90.1) survive at least 5 years and 78.6% (77.0-80.2) survive 10 years. It can also be concluded that survival proportions did not differ between genders in any of the chosen time periods (1, 5 or 10 years), although the proportions are slightly higher among females.

3.4.4. Factors associated with the survival up to exitus letalis

Survival curves in gender strata of the PLHIV population over the age of 14 show a statistically significant difference (p=0.03); the univariate proportional hazard analysis also shows a similar result (see table 3.4.4.1) - males have a 1.21 times higher risk of *exitus letalis* (p=0.03).

Statistically significant survival differences can be observed between the age groups. 94.9% (93.9-95.9) of individuals between the ages of 14 and 24 at the time of HIV diagnosis survived at least 5 years, in the 25-34 age group the survival was 89.0% (87.4-90.6), in the 35-44 age group - 80.4% (77.3-83.5) and in individuals over the age of 45 it was 70.1% (64.0-76.2). The 10 year survival shows a similar tendency. The older the individual at the time of HIV diagnosis, the lower the survival (p<0.001). The univariate hazard analysis shows that the risk of death increases by about 6% per one year increase in age (p<0.001).

As far as ethnicity is concerned, the survival curves do not show a statistically significant difference between Russians and other ethnic groups (Russian vs. Latvian – p=0.07; Russian vs. others – p=0.20). However, a difference can be observed between Latvian and „other ethnicity" (p=0.02).

Although there are no differences in 5 year survival proportions, there are differences in the 10 year survival (the proportion for Latvians is lower – 74.1%; 70.8-77.4, while it is higher for other ethnicities – 81.5%; 77.4-85.6). The same relationship is shown in the univariate hazard analysis (HR for other ethnicities vs. Latvians is 0.73; p=0.02).

No significant differences were observed in relation to place of residence – both 5 and 10 year survival proportions are nearly identical for both groups. For individuals living outside of Riga – 88.7% (86.7-90.7) and 77.5%; (74.4-80.6) respectively; for individuals living in Riga – 89.3% (88.1-90.5) and 79.1% (77.3-80.9). The difference between survival curves is not statistically significant (p=0.28).

The same can be concluded regarding the incarceration – although fewer individuals having been incarcerated survive at least 10 years after the HIV diagnosis (75.5%; 72.4-78.6) compared to individuals not having such experience (80.0%; 78.2-81.8), the differences between survival curves is not statistically significant (p=0.14).

Looking at the risky health behaviour as a variable, there are no significant differences between PLHIV who became infected via heterosexual contacts and those who got HIV via homosexual contacts (the survival curves do not differ – p=0.13, although homosexually infected individuals have a slightly higher 10 year survival – 84.2% (78.1-90.3) than do heterosexually infected individuals – 80.1% (75.8-84.4)). Similarly, there are no differences between the groups of heterosexually infected PLHIV and those infected via drug injection (p=0.47), although the survival proportions for IDU have a tendency to be lower (for IDU the 10 survival is 77.3% (75.3-79.3)). A difference can be observed, however, between homosexual individuals and IDU (p=0.02) with notably better survival for homosexually infected individuals, also confirmed by the univariate hazard analysis (see table 3.4.4.1.) - IDU shows a 64% higher risk of *exitus letalis* (HR=1.64; 1.09-2.46).

A disturbing situation can be observed in relation to the year of HIV diagnosis. No differences can be observed between individuals who were diagnosed prior to 1999 and those PLHIV diagnosed between 2000 and 2007 (p=0.96). However, individuals who were diagnosed in the last three year period (2008-2010) survival is notably lower (compared with 2000-2007 p=0.001; compared with 1987-1999 p=0.004). Reviewing the data for 2 year survival, the proportion for the time period up to 1999 is 95.7% (93.9-97.5); for the time period from 2000-2007 it is 95.4% (94.6-96.2) and for the time period from 2008-2010 it is 91.3% (89.1-93.5).

Especially distinct differences can be observed in relation to the timeliness of HIV diagnosis (p<0.001). Slightly more than one half of individuals diagnosed late survive more than 5 years (60.2%; 54.9-65.5), while the 5 year survival for the rest of the PLHIV (timely diagnosis or unknown timeliness of diagnosis) is 91.8%; 90.8-92.8. The difference is even more pronounced looking at the 10 year survival – 46.4% (38.0-54.8) and 81.2% (79.6-82.8), respectively. The difference between survival curves in this case can be considered as statistically significant (p<0.001). In general it can be said that for individuals with late diagnosis the risk of *exitus letalis* is more than 5 times higher than in the rest of PLHIV (HR=5.11; 4.28-6.10; see table 3.4.4.1.).

A high viral load at the time of diagnosis also has a positive association with lower survival. The difference is less pronounced between viral load groups <4 and 4-5 $\log_{10}$ RNA copies/ml (p=0.016). The 5 year survival is 91.8% (89.6-94.0) and 89.7% (87.5-91.9), respectively. The lower viral load group shows more pronounced differences with the stratum above 5 $\log_{10}$ RNA copies/ml (p=0.001), in which 5 year survival is relatively low – 77.2% (73.7-80.7). It must be noted that 10 year survival shows sharper differences – 82.2% (78.5-85.9) for the group under 4 $\log_{10}$ copies, 74.6% (70.5-78.7) for the group 4-5 $\log_{10}$ copies and only slightly more than one half (60.7%; 55.6-65.8) of individuals whose viral load at the time of diagnosis was

over 100.000 RNA copies/ml survive 10 years after HIV diagnosis. In general, it was observed that comparing PLHIV with a viral load under 10.000/ml and those with a viral load of over 100.000, the latter has three times higher risk of death (HR=2.63; 2.06-3.36).

Analyzing survival in the context of specialized care and ART, the lowest proportions for 10 year survival are shown by individuals who have undergone ART with interruptions (64.9%; 60.2-69.6). The proportion is higher for individuals having undergone ART with no interruptions – 77.1% (71.2-83.0). The proportion is slightly lower, but not statistically significant, for individuals registered with ICL, but not having started ART – 71.5% (69.0-74.0). Individuals not registered with ICL have the highest 10 year survival rate – 94.5% (93.3-95.7). It can be seen from the univariate hazard model (table 3.4.4.1.) that for the categories other than "ART with interruptions" the risk of *exitus letalis* is significantly lower (the statement is not statistically significant only for the individuals who are ART naïve – HR=0.93; 0.78-1.11).

Although individuals with HCV coinfection have slightly lower survival than do PLHIV without the coinfection (for example, 5 year survival is 86.6% (85.2-88.0) and 87.0% (84.3-89.7), respectively), the survival curves are not considered as significantly different (p=0.13).

Table 3.4.4.1.

Factors associated with *exitus letalis* hazard ratio, univariate and multivariate analysis

Factor	HR[a]	95% TI	p[b]	sHR[a.c]	95% TI	p[b]
Gender						
male vs. female	**1.21**	**1.02-1.43**	**0.03**	1.04	0.87-1.24	0.67
Age at diagnosis						
per year increase	**1.06**	**1.05-1.07**	**<0.001**	**1.06**	**1.05-1.06**	**<0.001**
Ethnicity						
other vs. Latvian	**0.73**	**0.57-0.95**	**0.02**	0.84	0.64-1.09	0.18
Russian vs. Latvian	0.86	0.72-1.01	0.07	0.94	0.79-1.12	0.50
unknown vs. Latvian	**0.48**	**0.36-0.63**	**<0.001**	0.93	0.69-1.26	0.65
Place of residence						
outside Riga vs. Riga	1.10	0.93-1.29	0.29	0.96	0.80-1.14	0.60
Imprisonment						
yes vs. no	1.13	0.96-1.32	0.14	0.96	0.81-1.15	0.67
Mode of transmission						
IDU vs. homosexual	**1.64**	**1.09-2.46**	**0.02**	**2.07**	**1.29-3.33**	**0.003**
heterosexual vs. homosexual	1.50	0.97-2.31	0.07	1.30	0.82-2.07	0.27
unknown vs. homosexual	1.28	0.80-2.06	0.30	**2.37**	**1.40-4.03**	**0.001**
Year of HIV diagnosis						
1987-1999 vs. 2008-2010	**0.50**	**0.36-0.70**	**<0.001**	**0.69**	**0.48-0.99**	**0.04**
2000-2007 vs. 2008-2010	**0.50**	**0.38-0.66**	**<0.001**	0.77	0.49-0.89	0.09
Timeliness of diagnosis						
late vs. no/unknown	**5.11**	**4.28-6.10**	**<0.001**	**3.81**	**3.14-4.88**	**<0.001**
Viral load (log_{10} RNA copies/ml)						
≥5 vs. <4	**2.63**	**2.06-3.36**	**<0.001**	**2.02**	**1.56-2.63**	**<0.001**
4-5 vs. <4	**1.34**	**1.04-1.72**	**0.03**	**1.30**	**1.00-1.68**	**0.049**
unknown vs. <4	0.93	0.74-1.17	0.55	**1.94**	**1.52-2.47**	**<0.001**
Care and therapy						
ART with no interruption vs. with interruption	**0.67**	**0.50-0.91**	**0.009**	-	-	-
ART naive vs. with interruption	0.93	0.78-1.11	0.43	-	-	-
no HIV specific care vs. with interruption	**0.21**	**0.16-0.27**	**<0.001**	-	-	-
other vs. with interruption	**0.26**	**0.16-0.43**	**<0.001**	-	-	-
HCV coinfection						
yes vs. no	1.21	0.99-1.49	0.07	1.29	0.99-1.68	0.06
unknown vs. no	**0.33**	**0.25-0.44**	**<0.001**	1.01	0.60-1.68	0.98

[a] HR - hazard ratio, [b] p – p-value, [c] adjusted by all factors showed in the table

Since the variable „HIV care and ART experience" did not correspond to the Cox proportional hazard model requirements regarding the hazard proportionality over time, it was not included in the multivariable analysis model, but model stratification was performed by the mentioned variable. After the adjustment it can be concluded that the majority of associations found in the univariate analysis did not lose their significance (see table 3.4.4.1.). It can be concluded that gender, ethnicity, place of residence, incarceration and HCV coinfection are not statistically significant risk factors affecting *exitus letalis* in the PLHIV population. However, it can be concluded that, independent of other factors, *exitus letalis* risk increases by 1.06 times for every year increase in the age at the time of HIV diagnosis (1.05-1.06). Injecting drug users, compared with individuals who became HIV infected through homosexual contacts, have twice as great a risk of death (HR=2.07; 1.29-3.33), but there is no difference in risk between the two sexual transmission strata (p=0.27). A greater risk of death was observed in individuals diagnosed HIV positive during the time period of 2008-2010 (PLHIV diagnosed between 1987 and 1999 have about half the hazard of *exitus letalis* - HR=0.69; 0.48-0.99); individuals diagnosed between 2000 and 2007 also show a lower risk of death (HR=0.77), but in the multivariate model the statistical significance of this association was lost (p=0.09). Late HIV diagnosis (p<0.001) pronouncedly increases the risk of death (by about 4 times). A high VL also contributes to an increased risk of death (risk increases 2 times for individuals with more than 100,000 HIV RNA copies/ml and by 30% for individuals with a viral load between 10,000 and 100,000 copies/ml compared with the PLHIV whose VL was under 10,000/ml).

3.5. Years of potential life lost (YPLL) in Latvia due to HIV

3.5.1. YPLL indicator and its tendencies over time

Of 738 cases of death, five were excluded from YPLL estimations for the following reasons: one individual's birth date was unknown, thus making it

impossible to determine age at the time of death, while 4 individuals were excluded according to the YPLL methodology guidelines - they were older than 65 at the time of death, thus loosing no years of potential life. HIV infected individuals tend to be relatively young people at the time of death – 99.5%; n=733/737 (98.6-99.8) had not reached the age of 65 at the time of death. The median age at the time of death was 35.4 years (average age 36.4, SD 10.2, age range 0.3 – 70.0).

Overall within the time of the observation 21,097.3 potential years of life were lost due to HIV/AIDS in Latvia. This means 50.4 lost years for every 100,000 inhabitants or 679.9 years per 1,000 person years in the PLHIV population. To paraphrase the last indicator, it can be said that in Latvia each infected individual is losing 0.7 potential years of life by living with HIV one year. Calculating the average YPLL it can be seen that one individual having died has lost on average 28.8 (SD 9.9) years of life because of dying prematurely. It should be noted that much like the previous chapters describing the time trends of mortality measures, the YPLL indicator per 100,000 inhabitants of the general population has a tendency to increase 1.2 times ($e^{0.19}$) or by 20,3% annually ($p<0.001$). The indicator was the highest in 2009 – 183.2/100,000 inhabitants. The indicator expressed per 1,000 py among PLHIV also shows a tendency to increase – 1.08 times ($e^{0.075}$) or by 7.8% annually ($p=0.02$). This indicator also reached the peak in 2009 – 881.2/1,000 py.

The average number of YPLL was the highest in 2002 – 33.9 (SD 10.0) and has the tendency to decrease over the last 10 years about 1.03 times ($e^{-0,025}$) or by 2.5% annually ($p=0.001$).

Considering the YPLL in gender strata of the general population, it can be concluded that males have lost considerably more potential years of life than have females – 15,967.9 years (80.7/100,000 inhabitants) and 5,129.5 (24.6/100,000 inhabitants) respectively. In addition, the burden of disease in terms of the general population continues to increase for men 1.2 times ($e^{0.17}$) or

by 18.5% annually (p=0.001) and for women 1.3 times ($e^{0.29}$) or by 33.6% annually (p=0.003). A similar trend can be observed looking at the gender strata of the PLHIV population – men have lost more potential years of life (715.0/1,000) than have women (589.7/1,000). The burden of the disease in terms of PLHIV population also increases annually – for men 1.1 times ($e^{0.07}$) or by 7.3% annually (p=0.03) and for women 1.2 times ($e^{0.14}$) or by 15.0% annually (p=0.04).

The average number of the years of potential life lost have a statistically significant tendency to decrease among males by about 2.5% annually (p=0.002), while among females since 2001 the indicator has remained persistent (p=0.12).

3.5.2. Factors associated with YPLL

Considering demographic and social factors associated with the average YPLL in the population of PLHIV aged 14 years and older (see chapter 2 for explanation of age restrictions in this work) it can be concluded that the age of men and women at the time of death does not differ (p=0.72). Although individuals residing in Riga and those with incarceration experience have a tendency to lose a greater number of potential years of life, these differences are not to be considered as statistically significant (p=0.2 and p=0.08, respectively).

However, there are significant differences in the number of aYPLL between ethnicity categories. Latvians have lost fewer potential years of life than have individuals of other ethnicities (p=0.006). Also a strong negative correlation between aYPLL and the age of the individual at the time of HIV diagnosis was observed, i.e. the older the individual, the fewer years of life he/she has lost (p<0.001).

Considering health behaviour, it can be seen that injecting drug use is related to a higher loss of potential years of life as compared to individuals who got HIV through unsafe sexual practices ($p<0.001$).

As far as health status and health care factors are concerned, there is no significant association between aYPLL and the viral load at the time of diagnosis observed ($p=0.09$). However, a weak but statistically significant negative correlation between aYPLL and the year of HIV diagnosis can be seen ($p=0.006$). It has also been observed that individuals with HCV coinfection are prone to premature death ($p<0.001$).

There were no statistically significant differences observed regarding aYPLL for individuals having undergone disrupted ART and those having undergone ART with no interruptions ($p=0.7$) or those not registered with ICL (not receiving specialized care) ($p=0.08$). But it was observed, that individuals not having undergone ART (naïve) died at an earlier age ($p<0.001$) comparing to PLHIV having experienced ART interruptions. Fewer aYPLL are lost by individuals having been diagnosed late ($p<0.001$) which may point to the presence of a confounder in the association between timeliness of diagnosis and aYPLL.

As mentioned before, age at the time of HIV diagnosis has a strong correlation with aYPLL. By performing univariate linear regression analysis it arrived at the determination coefficient 0.896; that is to say that age at the time of diagnosis explains about 90% of aYPLL variations. Collinearity between independent variables was not found, thus making it possible to freely incorporate them in the multivariate model.

Since age is a pronouncedly determining factor, due to its inclusion in the regression model the statistical significance of several associations disappeared or the association was changed (from causing an increase in years to eliciting a decrease). An important association was discovered between the year of HIV diagnosis and aYPLL – choosing the more recent years as the

reference (2008-2010), individuals diagnosed from 1987 – 1999 lose about 3 years less and individuals diagnosed from 2000 – 2007 lose about 1.5 years less. Thus, in general it can be said that individuals having been diagnosed within the last three years tend to die more prematurely ($p<0.001$). It should be noted that prior to adjustment (see table 3.5.2.1.), this relationship was quite the opposite and has changed its direction precisely upon the adjustment by age. Since there was no interaction between year of HIV diagnosis and age at the time of diagnosis, it can be concluded that age, in this case, is a confounding factor.

A similar conclusion can be drawn regarding the timeliness of HIV diagnosis. After adjustment for age, the association changed direction and it can be said that late diagnosis causes the PLHIV to lose two more years of potential life ($p<0.001$) (see table 3.5.2.1.).

Upon adjustment statistical significance remained for the association between the aYPLL and the ethnicity of PLHIV. Individuals of other ethnicities lose 0.74 more potential years of life than do Latvians ($p=0.03$).

Similarly, statistical significance remained for the tendency that individuals having not undergone ART lose more years of life than do individuals having experienced ART with interruptions. Upon adjustment by age it can be also concluded that individuals not registered with ICL and those having undergone uninterrupted ART lose more years of life ($p=0.01$) (see table 3.5.2.1.).

Table 3.5.2.1.

Factors associated with average number of the years of potential life lost, univariate and multivariate analysis

Factors	Regression coefficient	p-value	Regression coefficient [a]	p-value
Gender				
male vs. female	0.57	0.49	0.13	0.57
Age at diagnosis				
per year increase	**-0.91**	**<0.001**	**-0.98**	**<0.001**
Ethnicity				
other vs. Latvian	**3.62**	**0.004**	**0.74**	**0.03**
Russian vs. Latvian	**1.73**	**0.03**	0.28	0.20
unknown vs. Latvian	0.58	0.66	**1.14**	**0.003**
Place of residence				
Riga vs. outside Riga	0.88	0.28	0.11	0.63
Imprisonment				
yes vs. no	**1.57**	**0.04**	**-0.57**	**0.01**
Mode of transmission				
IDU vs. heterosexual	**6.21**	**<0.001**	-0.07	0.80
homosexual vs. heterosexual	1.92	0.33	0.34	0.56
unknown vs. heterosexual	-1.29	0.30	0.27	0.53
Year of HIV diagnosis				
1987-1999 vs. 2008-2010	**4.04**	**0.004**	**-3.12**	**<0.001**
2000-2007 vs. 2008-2010	**5.66**	**<0.001**	**-1.50**	**<0.001**
Timeliness of diagnosis				
no/unknown vs. late	**3.70**	**<0.001**	**-2.27**	**<0.001**
Viral load (log_{10} RNA copies/ml)				
≥5 vs. <4	-1.35	0.25	0.23	0.48
4-5 vs. <4	0.90	0.46	-0.44	0.20
unknown vs. <4	-1.23	0.27	-0.29	0.35
Care and therapy				
ART with no interruption vs. with interruption	-0.71	0.87	**0.98**	**0.01**
ART naive vs. with interruption	**3.89**	**<0.001**	**1.87**	**<0.001**
no HIV specific care vs. with interruption	-0.71	0.58	**1.72**	**0.01**
other vs. with interruption	5.66	0.02	-0.67	0.33
HCV coinfection				
yes vs. no	**5.17**	**<0.001**	-0.43	0.19
unknown vs. no	1.60	0.22	**1.77**	**0.01**

[a] adjusted by all factors showed in the table

The association discovered upon adjustment regarding incarceration is interesting – individuals having been incarcerated lose 0.57 fewer years of life than do individuals with no such experience (p=0.01). Upon review of this factor in relation to other variables studied, an interaction with the gender was determined (see table 3.5.2.2.).

Table 3.5.2.2.

Statistical interaction between gender and imprisonment related to average number of years of potential life lost

Factor	Regression coefficient	p-value	Regression coefficient[a]	p-value
Constant (β_0)	28.5	<0.001	58.6	<0.001
Gender (β_1)	-0.73	0.42	0.14	0.64
Imprisonment (β_2)	-3.77	0.08	**-1.79**	**0.009**
Gender * imprisonment (β_3)	**6.10**	**0.008**	0.60	0.42

[a] adjusted by age at HIV diagnosis

The graphic explanation of the interaction is shown in figure 3.5.2.1. Taking into consideration the dichotomous coding principles that were used (female – 0, male – 1, not having been incarcerated – 0, having been incarcerated – 1), the regression equation seen in Table 3.5.2.2. (aYPLL = β_o + β_1 gender + β_2 incarceration + β_3 gender*incarceration) are to be interpreted as follows:

a) The constant reflects the aYPLL for women without incarceration experience (28.5 years);
b) β_1 (that is, -0.73) reflects the gender difference in the base category of incarceration (0) – see fig. 3.5.2.1. line segment „a"; men who have not been incarcerated lose 0.73 years of life less than women who have not been incarcerated;
c) β_2 (that is, -3.77) reflects the effect of incarceration on the base category of gender (female); women who have been incarcerated lose about 4 years of life less than do women who have not been incarcerated;

d) β_3 (that is, 6.10) shows gender differences between categories of incarceration or the sum of line segments „a" and „b" in fig. 3.5.2.1. Upon review of line segment „b" it can be concluded that women who have been incarcerated lose 5.37 years less than do men who have been incarcerated.

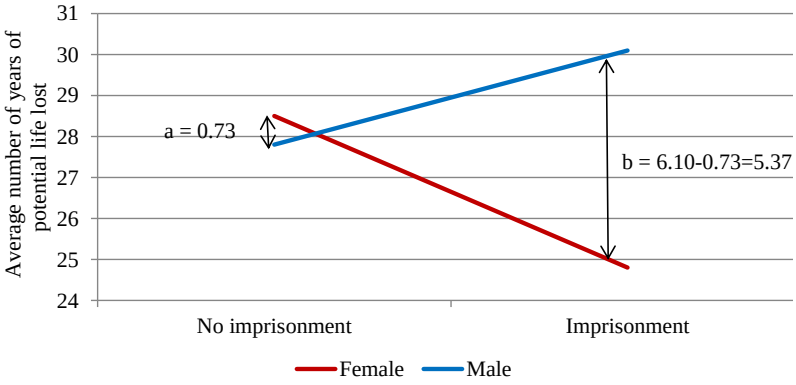

Fig. 3.5.2.1. Statistical interaction between gender and imprisonment related to average number of years of potential life lost

As it can be seen in table 3.5.2.2., after adjustment by age at the time of HIV diagnosis, the overall effect of the interaction lost its statistical significance (women incarcerated at the time of HIV diagnosis were older (median age 34.2) than men (median age 28.5). However, the difference between women with and without incarceration experience remains statistically significant and cannot be explained by age differences.

3.6. HIV cause specific mortality, its tendencies over time and associated factors

3.6.1. Proportional mortality, cause specific mortality and their tendencies over time

Within the period studied, HIV infection was indicated to be the underlying cause of death of approximately one half of cases – 51.4% (47.7-

55.2), which is 11.4 cases per 1,000 py (10.2-12.6). HIV resulting in mycobacterial infection was the most frequently indicated cause of death in the group (B20.0). Frequently, unspecified HIV infection was mentioned as the underlying cause of death (B24) (see Table 3.6.1.1.).

Table 3.6.1.1.

Number of deaths and proportional mortality among people living with HIV according to underlying causes of death, 1991-2010

Code, International Statistical Classification of Diseases and Related Health Problems 10th Revision	Number of deaths	Proportional mortality (%)	95% confidence interval
B20-B24 (Human immunodeficiency virus [HIV] disease), including:	355	51.4	47.7-55.2
*B20.0 (*HIV disease resulting in mycobacterial infection*)*	*110**		
*B23.2 (*HIV disease resulting in hematological and immunological abnormalities, not elsewhere classified*)*	*64*		
*B24 (*Unspecified human immunodeficiency virus [HIV] disease*)*	*34*		
V,W,X,Y (External causes of morbidity and mortality), including:	150	21.7	18.8-25.0
*X40-X49 (*Accidental poisoning by and exposure to noxious substances*)*	*50*		
*X60-X84 (*Intentional self-harm*)*	*29*		
*X85-Y09 (*Assault*)*	*19*		
I00-I99 (Cardiovascular diseases), including:	65	9.4	7.5-11.8
*I30-I52 (*Other forms of heart disease*)*	*42*		
*I20-I25 (*Ischemic heart diseases*)*	*16*		
*I60-I69 (*Cerebrovascular diseases*)*	*6*		
K00-K93 (Diseases of the digestive system)	50	7.2	5.5-9.4
C00-D48 (Neoplasms)	18	2.6	1.7-4.1
A00-B99 (Certain infectious and parasitic diseases)	17	2.5	1.5-3.9
F00-F99 (Mental and behavioral disorders)	9	1.3	0.7-2.5
G00-G99 (Diseases of the nervous system)	7	1.0	0.5-2.1
J00-J99 (Diseases of the respiratory system)	6	0.9	0.4-1.9
R00-R99 (Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified)	4	0.6	0.2-1.5
L00-L99 (Diseases of the skin and subcutaneous tissue)	3	0.4	0.1-1.3
Q00-Q99 (Congenital malformations, deformations and chromosomal abnormalities)	2	0.3	0.1-1.1
D50-D89 (Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism)	1	0.1	-
M00-M99 (Diseases of the musculoskeletal system and connective tissue)	1	0.1	-
N00-N99 (Diseases of the genitourinary system)	1	0.1	-
E00-E90 (Endocrine, nutritional and metabolic diseases)	1	0.1	-
Total	**690**	**100**	
Cause of death unknown	48		

* Including 20 cases of tuberculosis recoded from underlying causes A15-A19

It has to be marked that proportional mortality of the above cause of death continues to increase annually. If HIV was established as the underlying cause of 27.3% cases of crude mortality in 2001 (9.7-56.6), then in 2005, the proportion reached 44.9% (33.8-56.6), and 63.2% (53.1-72.2) in 2010. Similarly, cause-specific mortality associated with HIV as the underlying cause of death continues to increase 1.25 times ($e^{0.22}$) or by 24.6% annually. The time trend can be viewed as statistically significant ($p<0.001$).

The second most frequent group of underlying cause is the so-called external causes of death causing one fifth of all deaths among PLHIV (21.7%; 18.8-25.0). Proportional mortality was the highest in 2002, when external causes had been associated with half of death cases (50.0%, 33.2-66.8). In 2010, the proportion was statistically significantly lower – 8.4% (4.3-15.7). Among the external causes, poisoning dominates (X40-X49) (see table 3.6.1.1.), precisely, the group X42 - accidental poisoning by and exposure to narcotic and psychodysleptic (hallucinogen) substances (which could mean drug overdose, as large part of the deceased PLHIV are injection drug users), and intentional self-harm (X60-X84), most frequently X70 – intentional self-harm by hanging, strangulation or suffocation.

During the period of observation, mentioned cause specific mortality among the HIV infected population was 4.8/1,000 py (4.1-5.6). The cause-specific mortality associated with external causes of death has no significant time trend ($p=0.26$).

The third most frequent group of death causes considering PLHIV in Latvia is cardiovascular diseases (I00-I99) (9.4%; 7.5-11.8) corresponding to 2.1 cases per 1,000 py (1.6-2.7). It is usually indicated that the person has died of “other form of heart disease” (I30-I52), specifically, I42.9 – unspecified cardiomyopathy. The second most frequent cause of death in the group is ischemic heart diseases (I20-I25), specifically, I25.1 – atherosclerotic

cardiopathy. The highest proportional mortality within the decade was estimated in 2006 – 15.2% (8.4-25.7). In 2010, the indicator was 8.4% (4.3-15.7).

A slight but statistically significant (p=0.04) trend of annual increase can be observed considering the cause-specific mortality from cardiovascular diseases – 0.19 cases per 1,000 py annually (p=0.04).

3.6.2. Factors associated with cause specific mortality

This chapter covers the search for factors associated with three leading causes of death among the PLHIV (HIV as the underlying cause of death, external causes, and cardiovascular disorders).

3.6.2.1. Factors associated with HIV cause specific mortality

Table 3.6.2.1.1. shows factors associated with HIV cause specific mortality before and after adjustment. Gender, ethnicity, place of residence and incarceration experience were not identified as statistically significant associated factors. One of the most significant factors is the age of the individual at the time of HIV diagnosis. Upon adjustment by other independent variables, it can be concluded that for each year of increase of the age HIV cause specific mortality increase by 4% (MRR=1.04; 1.03-1.05).

Mode of transmission was found to have a positive association with the increased mortality due to HIV related causes. Table 3.6.2.1.1. shows that mortality is increased for IDU as well as for individuals who became HIV infected via heterosexual contacts (comparing to persons getting HIV via homosexual contacts). However, after adjustment, only the injecting drug use can be considered as statistically significant factor associated with increased risk of dying from HIV related causes (MRR=2.28; 1.16-4.49). The leading confounding factor in the association between mode of transmission and HIV cause specific death was age (age diminished the impact of heterosexual transmission on the outcome, but MRR for injecting drug users increased).

As it was mentioned in chapter 3.6.1., the significance of HIV as a specific cause of death has a tendency to increase over time. This is confirmed by multivariable analysis as well. For PLHIV diagnosed over the last three years the chance of dying from HIV related causes is greater than for individuals who were diagnosed HIV positive prior to 1999 or during the period from 2000-2007. Upon adjustment by other factors, the two time periods showed mortality rate ration of 0.37 (0.23-0.59) and 0.47 (0.33-0.66), respectively.

Late HIV diagnosis was also confirmed as a factor affecting a higher mortality due to HIV related causes. Upon adjustment by other factors studied, late HIV diagnosis increases HIV cause specific mortality 5 times (MRR=4.78; 3.54-6.45).

A high viral load has a similar association with the cause specific mortality. I.e. individuals with a VL above 100,000/ml and those with VL between 10,000-100,000 /ml report higher HIV cause specific mortality rates of 3,24 (2.12-4.93) and 1.57 (1.01-2.45), respectively (comparing with PLHIV with a viral load under 10,000 RNA copies/ml).

Although the results show that individuals having undergone disrupted ART have a higher risk of dying from HIV related causes than individuals with experience of ART with no interruptions, this difference is not considered to be statistically significant. A significantly lower risk is reported among individuals not receiving specialized HIV care ($p<0.001$).

Table 3.6.2.1.1.

Factors associated with HIV cause specific mortality, univariate and multivariate analysis

Factor	MRR[a]	95% TI	p[b]	sMRR[a,c]	95% TI	p[b]
Gender						
male vs. female	1.06	0.84-1.35	0.61	0.99	0.76-1.28	0.93
Age at diagnosis						
per year increase	**1.06**	**1.05-1.07**	**<0.001**	**1.04**	**1.03-1.05**	**<0.001**
Ethnicity						
other vs. Latvian	0.84	0.59-1.18	0.31	1.01	0.71-1.44	0.96
Russian vs. Latvian	0.81	0.64-1.04	0.10	0.86	0.67-1.09	0.21
unknown vs. Latvian	**0.24**	**0.14-0.40**	**<0.001**	0.60	0.34-1.04	0.07
Place of residence						
outside Riga vs. Riga	1.09	0.85-1.39	0.51	0.85	0.66-1.09	0.20
Imprisonment						
yes vs. no	1.08	0.85-1.36	0.53	1.14	0.87-1.48	0.35
Mode of transmission						
IDU vs. homosexual	1.63	0.91-2.92	0.10	**2.28**	**1.16-4.49**	**0.02**
heterosexual vs. homosexual	**1.91**	**1.04-3.51**	**0.04**	1.63	0.84-3.15	0.15
unknown vs. homosexual	0.95	0.46-1.95	0.89	**2.95**	**1.37-6.38**	**0.006**
Year of HIV diagnosis						
1987-1999 vs. 2008-2010	**0.25**	**0.17-0.38**	**<0.001**	**0.37**	**0.23-0.59**	**<0.001**
2000-2007 vs. 2008-2010	**0.32**	**0.23-0.44**	**<0.001**	**0.47**	**0.33-0.66**	**<0.001**
Timeliness of diagnosis						
late vs. no/unknown	**7.99**	**6.34-10.07**	**<0.001**	**4.78**	**3.54-6.45**	**<0.001**
Viral load (log_{10} RNA copies/ml)						
≥5 vs. <4	**5.27**	**3.52-7.88**	**<0.001**	**3.24**	**2.12-4.93**	**<0.001**
4-5 vs. <4	**1.71**	**1.10-2.64**	**0.02**	**1.57**	**1.01-2.45**	**0.046**
unknown vs. <4	1.43	0.96-2.12	0.08	**3.82**	**2.54-5.73**	**<0.001**
Care and therapy						
ART with no interruption vs. with interruption	0.84	0.58-1.20	0.33	0.89	0.61-1.30	0.55
ART naive vs. with interruption	**0.70**	**0.55-0.90**	**0.005**	1.28	0.97-1.70	0.09
no HIV specific care vs. with interruption	**0.08**	**0.05-0.13**	**<0.001**	**0.15**	**0.06-0.35**	**<0.001**
other vs. with interruption	**0.29**	**0.16-0.55**	**<0.001**	0.74	0.38-1.42	0.36
HCV coinfection						
yes vs. no	1.13	0.85-1.50	0.41	1.34	0.94-1.93	0.10
unknown vs. no	**0.17**	**0.11-0.27**	**<0.001**	0.77	0.37-1.60	0.48

[a] MRR - mortality rate ratio
[b] p – p-value
[c] adjusted by all factors showed in the table

3.6.2.2. Factors associated with cause-specific mortality related to external causes of death

As far as death of external causes is concerned, it can be concluded that there is no significant association with an individual's ethnicity, place of residence, timeliness of HIV diagnosis or viral load at the time of HIV diagnosis.

Gender up to now has had little or no effect on mortality, but it becomes significant in relation to external causes of death (see table 3.6.2.2.1.). I.e. men die from external causes almost twice as often as women (MRR=1.58; 1.001-2.51) (the mentioned association was observed after the adjustment by other factors studied). An individual's age also is related to increased cause specific mortality related to external causes of death – per one year increase, mortality increases by 4% (MRR=1.04; 1.02-1.06).

Although before adjustment incarceration was related to a higher mortality rate of external causes, after adjustment this relationship disappeared (mode of HIV transmission is a notable confounder for the association). A similar conclusion can be drawn regarding the year of HIV diagnosis – prior to adjustment the factor had notable significance (see table 3.6.2.2.1.), however, after adjustment the association disappeared. Here again the mode of transmission played a significant confounding role. Also HCV coinfection was a death promoting factor prior to adjustment, but the observation is not true looking at the adjusted mortality rate ratio.

A significant independent factor in promoting deaths from external causes is the mode of HIV transmission. The mortality rate is 6 times higher for injecting drug users compared to individuals infected through homosexual contacts (MRR=5.96; 1.31-27.14). Individuals infected through heterosexual contacts also have a higher mortality rate comparing to homosexually infected

PLHIV, but the relationship cannot be considered as statistically significant (p=0.32).

A higher mortality rate has also been reported for individuals receiving specialized HIV care, but not having started ART compared to the PLHIV experiencing ART with interruptions – MRR=2.38 (1.43-3.96).

3.6.2.3. Factors associated with cardiovascular diseases specific mortality

A higher mortality rate due to cardiovascular disorders was associated with only three independent variables prior to adjustment: a greater age at the time of HIV diagnosis, late HIV diagnosis and individuals not receiving specialized HIV care. After adjustment, however, only the age retained a statistically significant association. I.e. for one year increase of age the chances of dying from cardiovascular disease increases by 10% or 1.10 times (1.07-1.12).

The mortality rate due to circulatory system disorders tends to be higher among individuals of Russian ethnicity, those living outside Riga and individuals experienced disrupted ART. However, these associations cannot be considered as statistically significant.

Table 3.6.2.2.1.

Factors associated with mortality due to external causes of death, univariate and multivariate analysis

Factor	MRR[a]	95% TI	p[b]	sMRR[a,c]	95% TI	p[b]
Gender						
male vs. female	**1.91**	**1.24-2.93**	**0.003**	**1.58**	**1.001-2.51**	**0.049**
Age at diagnosis						
per year increase	**1.02**	**1.01-1.04**	**0.01**	**1.04**	**1.02-1.06**	**<0.001**
Ethnicity						
other vs. Latvian	0.90	0.50-1.59	0.70	0.89	0.50-1.59	0.70
Russian vs. Latvian	0.98	0.66-1.46	0.93	0.98	0.66-1.46	0.93
unknown vs. Latvian	0.80	0.47-1.38	0.43	1.36	0.73-2.53	0.33
Place of residence						
outside Riga vs. Riga	0.89	0.60-1.31	0.55	0.86	0.57-1.28	0.45
Imprisonment						
yes vs. no	**1.56**	**1.12-2.18**	**0.009**	0.88	0.62-1.26	0.48
Mode of transmission						
IDU vs. homosexual	**5.23**	**1.29-21.15**	**0.02**	**5.96**	**1.31-27.14**	**0.02**
heterosexual vs. homosexual	2.01	0.45-8.90	0.36	2.21	0.47-10.33	0.32
unknown vs. homosexual	2.10	0.44-10.09	0.36	3.91	0.74-20.61	0.11
Year of HIV diagnosis						
1987-1999 vs. 2008-2010	**8.44**	**1.16-61.62**	**0.04**	6.83	0.91-51.19	0.06
2000-2007 vs. 2008-2010	6.25	0.87-44.73	0.07	5.33	0.73-38.68	0.10
Timeliness of diagnosis						
late vs. no/unknown	1.20	0.61-2.35	0.60	1.46	0.69-3.09	0.32
Viral load (log_{10} RNA copies/ml)						
≥5 vs. <4	0.97	0.56-1.67	0.91	1.18	0.67-2.09	0.57
4-5 vs. <4	0.99	0.61-1.58	0.95	1.10	0.67-1.78	0.73
unknown vs. <4	**0.55**	**0.36-0.85**	**0.007**	1.22	0.76-1.95	0.41
Care and therapy						
ART with no interruption vs. with interruption	0.39	0.13-1.13	0.08	0.47	0.16-1.39	0.17
ART naive vs. with interruption	**2.00**	**1.25-3.20**	**0.004**	**2.38**	**1.43-3.96**	**0.001**
no HIV specific care vs. with interruption	**0.36**	**0.19-0.69**	**0.002**	0.55	0.14-2.18	0.40
other vs. with interruption	0.38	0.11-1.27	0.12	1.06	0.33-3.36	0.93
HCV coinfection						
yes vs. no	**2.11**	**1.21-3.67**	**0.008**	0.95	0.49-1.83	0.87
unknown vs. no	**0.49**	**0.24-0.98**	**0.04**	0.61	0.16-2.32	0.47

[a] MRR - mortality rate ratio
[b] p – p-value
[c] adjusted by all factors showed in the table

3.6.2.4. Factors associated with cause specific mortality related to other causes of death

Looking at the causes of death not discussed in chapters 3.6.2.1., 3.6.2.2. or 3.6.2.3., it can be concluded that mortality tend to be higher for men, for individuals living outside Riga, injecting drug users, individuals diagnosed with HIV from 2008-2010 and individuals experienced ART with interruptions. These associations, however, are not seen as statistically significant.

Prior to adjustment, individuals of Latvian ethnicity tended to die more frequently than other ethnicities due to other causes, but after adjustment the significance of the association disappeared (p=0.08) with age playing the confounding role. Age turned out to be a negative confounder in the case of HCV coinfection. Prior to adjustment individuals with HCV coinfection showed a higher risk of dying from causes other than HIV, external causes or cardiovascular diseases, but this was not statistically significant. After adjustment by age, however, statistical significance increased and was retained even after adjustment by the other variables (MRR=2.0; 1.02-3.93).

Age was a statistically significant factor associated with death of other causes both prior to and after adjustment – per one year increase of age the mortality rate increases by 7% or 1.07 times (1.05-1.09). Late HIV diagnosis increases the mortality rate twice (MRR=1.94; 1.05-3.60). Also a high viral load at the time of diagnosis increases the mortality rate twice (MRR=2.08; 1.10-3.92). Individuals having received specialized HIV care but not having started ART are also at a greater risk of dying from causes other than HIV, external causes or cardiovascular disorders (MRR=1.94; 1.15-3.35).

4. CONCLUSIONS

1. Among the population of persons living with HIV in Latvia 70% are males, 61% are of ethnicities other than Latvian, 74% live in Riga, 59% have become infected through injecting drug use and at the time of diagnosis are of a median age of 27 years. Of individuals older than 14 at the time of diagnosis, 26% were incarcerated, 9% underwent late HIV diagnosis, 15% had a viral load below 10,000 RNA copies/ml at the time of HIV diagnosis, 14% had experienced interruptions in ART, 8% had received uninterrupted ART, 48% were co-infected with viral hepatitis C.
2. During the time of observation the incidence of AIDS among the PLHIV in Latvia was 35.4/1,000 py. The incidence of AIDS during the past 10 years has remained static both for males and females.
3. During the time of observation the mortality rate among PLHIV in Latvia was 23.7/1,000 py. Over the last 8 years the mortality rate in the male population has had a tendency to increase by 10% annually; for females the annual increase is 12%.
4. In Latvia the mortality rate among PLHIV exceeds that of the general population 7 times. During the last 10 years this discrepancy continues to grow at a rate of 7% annually. The mentioned discrepancy is more pronounced among females.
5. 83% of HIV infected individuals in Latvia live at least 5 years before the onset of AIDS, 73% live at least 10 years. 89% of HIV infected individuals live at least 5 years prior to *exitus letalis*, 79% live at least 10 years.
6. The risk of earlier onset of AIDS is by 37% higher for individuals who became HIV infected through homosexual contacts (as compared with heterosexual transmission), by 43% higher for individuals experiencing ART interruptions, 5 times higher for individuals having received a late HIV diagnosis and by 62% greater for individuals with a viral load over

100,000 RNA copies/ml (vs. 10,000) at the time of HIV diagnosis. Per one year increase of age at time of diagnosis the risk increases by 3%.

7. In Latvia the risk of earlier *exitus letalis* is twice as high for HIV infected individuals having been infected by drug injection (as compared with homosexual transmission), by 45% higher for those diagnosed during the period from 2008-2010 (as compared with 1987-1999), 4 times higher in case of late HIV diagnosis and twice as high if the viral load at the time of HIV diagnosis was over 100,000 RNA copies/ml. The risk increases by 6% per one year increase of age at the time of HIV diagnosis.
8. During the time of observation a total of 21,097 years of potential life were lost due to HIV in Latvia. Among PLHIV in Latvia individuals of other ethnicities (vs. Latvians) lose 0.7 potential years of life more, individuals who were diagnosed HIV positive from 2008-2010 (vs. 1987-1999) lose 3 potential years more and individuals not receiving specialized HIV care lose 2 potential years of life more. In the case of late HIV diagnosis an additional 2 years are lost. With each additional year of age at the time of diagnosis the number of years of potential life lost decreases by 0.98 years. Females having been incarcerated lose 2 potential years less than do females with no incarceration experience.
9. HIV related causes of death are still dominant among the PLHIV in Latvia (51% of deaths), external causes are responsible for the second highest number of deaths (22%) and the third cause is cardiovascular diseases (9%).
10. HIV specific mortality among the PLHIV in Latvia has continued to grow by about 25% annually. HIV specific mortality is twice higher for individuals having become infected by injecting drug use (as compared with homosexual transmission), 3 times higher for individuals having been diagnosed from 2008-2010 (as compared with 1987-1999), 5 times higher in case of late HIV diagnosis and 3 times higher if at the time of

diagnosis the viral load exceeded 100,000 RNA copies/ml. The mortality rate increases by 4% for every additional year of age at the time of HIV diagnosis.

11. During the last 10 years the mortality due to external causes of death has remained unchanged. It is by 60% higher in men and 6 times higher among injecting drug users (as compared with persons infected via homosexual contacts). The mortality rate increases by 4% for every additional year of age at the time of HIV diagnosis.
12. During the last 10 years mortality due to cardiovascular diseases in the PLHIV population in Latvia have increased by 2 cases per 100 py. Mortality from cardiovascular diseases increases by 10% for every additional year of age at the time of HIV diagnosis.

5. SCIENTIFIC NOVELTY OF THE THESIS

As a result of this thesis information from three data sources was merged for the first time in HIV/AIDS field in Latvia: from two national data bases and medical records of HIV infected individuals. The results of the study confirm the benefits and usefulness of the electronization of medical documentation and merging of the several data sources.

One of the advantages of the study is the extensive time period covered – from the first reported case of HIV infection in Latvia on 1987 to the end of 2010. In total, the study gathered data over a 23 year period, including all diagnosed and registered cases of HIV infection in Latvia during this time period. Considering that the data used in the study include the whole country, conclusions can be drawn on a national level. With certain limitations the results also can pertain to other Eastern European countries experiencing a similar history of HIV epidemics (that is, a large proportion of cases transmitted by injecting drug users, limited access to HAART etc.) such as Estonia, the Ukraine and other former Soviet countries.

Another advantage of the study is the extensive number of independent variables analyzed. In the study there different sociodemographic factors, as well as health behaviour, health status and health care factors were included. Actually data analysis included the most significant factors reflecting research trends elsewhere in the world.

It should also be emphasized that there representative data processing techniques were used proving the statistical significance of the time trends of HIV outcome measures as well as identifying the impact of a single specific factor on the outcome independently from other factors studied. Thus, it was possible to draw credible and evidence-based conclusions regarding each factor included in the data analysis.

The study nationally is the first to offer proof of the large proportion of HIV cases diagnosed late among the annually registered ones and its

increasing tendency over a long period of time. This study is also the first time that a statistically evaluated effect of late HIV diagnosis, interrupted ART and high viral load on the early onset of AIDS and *exitus letalis* has been presented. For the first time, a statistical interaction has been identified between gender and incarceration experience in relation to HIV outcomes, pointing to possible discrepancies in health related conditions in men's and women's prisons in Latvia.

6. PRACTICAL SIGNIFICANCE OF THE THESIS

For the purposes of the study, information from two national data bases as well as PLHIV patient records was merged. Patient medical records were made available in handwritten format and for the purposes of the study were transferred to electronic format. The methodology and results of the study prove the benefits and usefulness of the electronization of medical documentation and merging of the several data sources. It is highly recommended to continue the practice of systematic merging of both national data bases (HIV and causes of death). Also implementation of electronic PLHIV patient records is recommended in the future in order to facilitate follow-up of different health status indicators of PLHIV at an individual level as well as at levels of population and its sub-populations thus helping also to identify factors affecting various changes therein.

The study provides evidence that the situation regarding the HIV/AIDS epidemics is critical in Latvia. The results presented in the study on factors associated with HIV outcomes can be used by the public health sector in the development and implementation of evidence based measures of primary, secondary and tertiary prevention (for example, in formulating a national program for the elimination of the spread of HIV for the next planning period – the present plan is in effect until 2013). I.e. the results of the study point to late HIV diagnosis as one of the main detrimental factors in HIV outcomes, the PLHIV subgroup notwithstanding. Interruptions in ART are also shown to be a detrimental factor, which clearly points to the need to make ART more widely available along with measures promoting the understanding on the importance and benefits of adherence. It would be useful to conduct further studies among the PLHIV in order to identify special needs regarding ART availability and adherence obstacles in order to assure that planned and implemented measures reflect the true needs of PLHIV subpopulations.

During the course of the study, it also became possible to identify certain groups that require special attention as political planning documents and primary, secondary and tertiary preventive measures are developed. For example, it would be very important to conduct scientifically and culturally based activities in the Roma community. The study also points to the need for broadening present and adding additional measures and activities among injecting drug users, e.g. special attention should be turned to the prevention of overdose deaths. It is vital that Latvia implement special measures required by the community of men having sex with men; such measures to date are non-existent. The study also discovered that prisons can be a positive factor for the health promotion of PLHIV in case if favorable conditions are ensured for the individual while incarcerated. This is taking place in women's prisons, but special attention should be paid to efforts to attain these results in men's prisons as well.

7. APPROBATION OF THE THESIS

Approbation of the thesis „Factors associated with outcomes from human immunodeficiency virus infection" took place at the joint meeting of the RSU Department of Public Health and Epidemiology and the Public Health Association of Latvia on August 27, 2012. The topic of this thesis has been presented in five scientific publications (1 international, 4 national) and 19 conference abstracts (12 international and 7 national conferences).

Publications:

1. **Karnite A.,** Brigis G., Uuskula A. Years of potential life lost due to HIV infection and associated factors based on national HIV surveillance data in Latvia (1991-2010). Scandinavian Journal of Infectious Diseases, 2012 (approved, in press. DOI:10.3109/00365548.2012.717710)
2. **Karnīte A.,** Briģis Ģ., Upmace I. Vai informētība par savu HIV statusu maina injicējamo narkotiku lietotāju veselības uzvedību? Rīgas Stradiņa universitātes Zinātniskie raksti 2011, 1.sējums. 225.-233.lpp. *[In Latvian; Does knowledge of HIV status change the health behaviour of injecting drug users?]*
3. **Karnīte A.,** Briģis Ģ., Skrule J., Lazdiņa A., Upmace I. Potenciāli zaudētie dzīves gadi cilvēka imūndeficīta infekcijas dēļ Latvijā laikaposmā no 1991. līdz 2008.gadam. Rīgas Stradiņa universitātes Zinātniskie raksti 2010. 2.sējums. 87.-99.lpp. *[In Latvian; Years of potential life lost due to HIV infection in Latvia, 1991-2008]*
4. Konova Š., **Karnīte A.,** Briģis Ģ., Upmace I. Paaugstināta HIV inficēšanās riska seksuālās uzvedības izplatība injicējamo narkotiku lietotāju vidū Latvijā. Rīgas Stradiņa universitātes Zinātniskie raksti 2010. 2.sējums. 231.-243.lpp. *[In Latvian; Prevalence of high risk sexual behaviour among injecting drug users in Latvia]*

5. **Karnīte A.,** Briģis Ģ., Ferdats A., Brokere I., Bulmistre I., Upmace I. HIV prevalenci ietekmējošie faktori injicējamo narkotiku lietotāju vidū Latvijā. Rīgas Stradiņa universitātes Zinātniskie raksti 2009. 331.-339.lpp. *[In Latvian; HIV prevalence and associated factors among injecting drug users in Latvia]*

Conference abstracts:

1. **Karnite A.**, Brigis G. Trends in mortality rates and factors associated with cause specific mortality among HIV infected individuals in Latvia from 1987 to 2010. International Journal of Infectious Diseases, 2012. Volume 16. Supplement 1. 43.101.
2. **Karnite A.** Trends in Mortality and Underlying Causes of Death Among Young Adults Living with HIV in Latvia (1991-2010). International scientific conference „Youth in Latvia. Europe. Globe: Opportunities and Risks" Abstracts Book, 2012. pp. 38-39.
3. **Karnīte A.**, Briģis Ģ. Mirstības un nāves pamatcēloņu tendences Latvijas HIV inficēto personu populācijā. 2012.gada Zinātniskās konferences tēzes. Rīga: Rīgas Stradiņa universitāte, 2012, 167.lpp. *[In Latvian; Trends in mortality and underlying causes of death in the population of people living with HIV in Latvia]*
4. Upmace I., Lazdina A., Mavcutko V., **Karnite A.** Epidemiological trends of HIV. syphilis and co-infection in Latvia. Abstracts book. 26th IUSTI – Europe Congress "Staying alert for sexual health", 2011, p. 57
5. Mozalevskis A., **Karnite A.,** Upmace I., Schmidt A. J. Quality of STI testing among men who have sex with men (MSM) in Latvia. Abstracts book. 26th IUSTI – Europe Congress "Staying alert for sexual health", 2011, p. 72

6. **Karnite A.,** Upmace I., Freimane A. HIV testing and associated factors among men who have sex with men in Latvia. Abstract book. European Conference "HIV in European Region - Unity and Diversity", 2011, p. 33
7. **Karnite A.,** Dompalma E., Stoniene L., Rotberga S. HIV related risk and preventive behaviours among primary opioid and amphetamine injectors in Latvia and Lithuania. Abstract book. European Conference "HIV in European Region - Unity and Diversity", 2011, p. 73
8. **Karnīte A.,** Briģis Ģ., Upmace I. Vai informētība par savu HIV statusu maina injicējamo narkotiku lietotāju riska uzvedību? 2011.gada Zinātniskās konferences tēzes. Rīga: Rīgas Stradiņa universitāte, 2011., 91.lpp. *[In Latvian; Does knowledge of HIV status change the health behaviour of injecting drug users?]*
9. **Karnite A.,** Brigis G., Skrule J., Lazdina A., Upmace I. Potential years of life lost due to human immunodeficiency virus (HIV) infection in Latvia from 1991 to 2008. European Journal of Public Health, 2010. Volume 20. Supplement 1. p. 204
10. Upmace I., Mavcutko V., Lazdina A., Skripste I., **Karnite A.** Epidemiological situation of HIV and sexually transmitted infections and HIV Prevention Network for injecting drug users in Latvia. Baltic Public Health Conference, 2010 – Accomplishments and Challenges Abstract Book. p. 30
11. **Karnīte A.,** Trapencieris M., Briģis Ģ. Asins transmisijas infekcijas, asociētā riska un preventīvā uzvedība amfetamīnu un opioīdu injicētāju vidū Latvijā. 2010.gada Zinātniskās konferences tēzes. Rīga: Rīgas Stradiņa universitāte, 2010., 182.lpp. *[In Latvian; Blood borne infections and associated risk and preventive behaviour among primary opioid and amphetamine injectors in Latvia]*
12. Konova Š., **Karnīte A.,** Briģis Ģ. Paaugstināta HIV inficēšanās riska seksuālās uzvedības izplatība injicējamo narkotiku lietotāju vidū Latvijā.

2010.gada Zinātniskās konferences tēzes. Rīga: Rīgas Stradiņa universitāte, 2010., 175.lpp. *[In Latvian; Prevalence of high risk sexual behaviour among injecting drug users in Latvia]*

13. **Karnite A.,** Dudareva S. Men who Have Sex with Man (MSM): A „Bridge" Group for HIV Transmission in Latvia. Dublin City University, 2010. http://www.dcu.ie/salis/conferencesexualitystudies2010/conference_abstracts.shtml (skat. 05.07.2010.)
14. **Karnite A.,** Brigis G. Social and behavioural factors associated with the HIV prevalence among injecting drug users in Latvia. European Journal of Public Health, 2009. Volume 19. Supplement 1. pp. 184-185
15. **Karnite A.** HIV, B vīrushepatīta un C vīrushepatīta izplatība injicējamo narkotiku lietotāju un viņu seksa partneru vidū Latvijā. 6.Latvijas Ārstu kongresa tēzes. Rīga, 2009.gada 19.-21.jūnijs. 39.lpp. *[In Latvian; HIV, hepatitis B and C prevalence among injecting drug users and their sex partners in Latvia]*
16. **Karnīte A.,** Briģis Ģ. HIV prevalenci ietekmējošie faktori injicējošo narkotiku lietotāju vidū Latvijā. 2009.gada Zinātniskās konferences tēzes. Rīga: Rīgas Stradiņa universitāte, 2009., 131.lpp. *[In Latvian; HIV prevalence and associated factors among injecting drug users in Latvia]*
17. Upmace I., **Karnite A.,** Lazdina A. Trends of HIV spread related to the presence of other STDs in Latvia. Baltic Association of Dermatovenerologists. Abstract Book of the 6th Congress "Precise diagnostics – foundation for a successful skin and STD therapy". Rīga, 2006. 47.lpp.
18. **Karnīte A.,** Briģis Ģ. HIV transmisiju ietekmējošie faktori Latvijā. Rīgas Stradiņa universitātes 5. zinātniskās konferences tēzes. Rīga, 2006. *[In Latvian; Factors related to HIV transmission in Latvia]*

19. **Karnite Anda,** Brigis Girts. Sexual behaviour and demographic factors related to the HIV sexual transmission in Latvia. Конференция по вопросам ВИЧ/СПИДа в Восточной Европе и Центральной Азии. Сборник материалов, 2006. 54.lpp.

ACKNOWLEDGEMENTS

I wish to thank the supervisor of my thesis **Prof. Ģirts Briģis** for his patience, valuable advice and his insistence on academic excellence both during my doctoral studies and during elaboration of my thesis. I sincerely thank all of my colleagues at the RSU Department of Public Health and Epidemiology. Their understanding and moral support served to inspire and waylay fatigue. Special thanks to **Doc. Ieva Strēle**, who I admire tremendously, for her invaluable support and consultations in biostatistics. I thank **Doc. Inese Gobiņa** for her suggestions regarding the structural organization of my thesis. I thank **Lect. Inese Stars** for her responsiveness and help with terminology issues and consultations regarding theories of social medicine. I thank **Lect. Lilita Bražinska**, who shared an office with me both on good days and bad, for her friendship and encouragement.

I wish to thank **Prof. Baiba Rozentāle**, head of the Riga Eastern Clinical University Hospital's Stationary "Infectology Center of Latvia" for her trust and the exclusive opportunity to access patient files. I thank the entire 2nd HIV/AIDS outpatient department and especially the head of the department **Dr. Inga Januškeviča**, for their patience and moral support during the extensive data collection process. I thank **Doc. Gunta Stūre** for consultations regarding clinical issues and **Dr. Tatjana Kolupajeva** for her advice on laboratory questions.

My sincerest thanks to **Dr. Aija Vilde** for her friendly assistance in helping resolve clinical issues and prepare publications.

I wish to especially thank **Prof. Anneli Uusküla** for her inspiration. for the opportunity to learn from her extensive research experience, for her genuine interest in the issues brought forth, for her invaluable advice and practical help.

Sincerest thanks to my trainers, excellent personalities **Dr. Andris Ferdats**. **Dr. Inga Upmace**. and **Iveta Skripste** who instilled in me a

permanent and lasting interest in the field of HIV and a human compassion for those suffering from it; I thank them for their encouragement and help during the hard times. I thank my colleague **Anda Lazdiņa** for her practical support and consultations in issues of data selection and processing.

I wish to thank all my friends and colleagues in the field of public health for their moral support and belief in me. I wish to thank the congregation of Old St. Gertrude's Lutheran Church in Riga for its spiritual support. My most heartfelt thanks to my parents, who raised me to appreciate education as a value and who have always been there for me with their love and support. I thank my sister and her family for being there for me during this process, for the many talks and properly timed jokes and laughter. A special thanks to my husband and daughter for their unending love, patience and understanding. Without that this work would never have been done. And above all, I thank God, because "The fear of the Lord is the beginning of wisdom…" (Psalms 111:10).

REFERENCES

[1] United Nations. Resolution: United Nations Millennium Declaration. General Assembly Fifty-fifth session, 18.09.2000.

[2] Pasaules Veselības organizācija. Veselība-21: veselību visiem politikas pamatnostādnes PVO Eiropas reģionam. Kopenhāgena: Pasaules Veselības organizācija, Eiropas Reģionālais birojs, 1999. - 48.-59.lpp.

[3]Gallo R. C., Montagnier L. The Discovery of HIV as the Cause of AIDS // The New England Journal of Medicine, 2003; 349 (24): 2283-2285.

[4]Joint United Nations Programme on HIV/AIDS (UNAIDS). Global report: UNAIDS report on the global AIDS epidemic 2010. Switzerland, Geneva: UNAIDS, 2010.

[5]European Centre for Disease Prevention and Control, WHO Regional Office for Europe. HIV/AIDS surveillance in Europe 2010. Stockholm: European Centre for Disease Prevention and Control, 2011. – Pp. 21-69.

[6]European Commission, Eurostat. Search Database, Population and social conditions //http://epp.eurostat.ec.europa.eu/portal/page/portal/statistics/search_database (sk. 12.05.2012.)

[7]The Data Collection on Adverse Events of Anti-HIV drugs (D:A:D) Study Group. Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D study // AIDS, 2010; 24: 1537-1548.

[8]McDavid Harrison K., Song R., Zhang X. Life Expectancy After HIV Diagnosis Based on National HIV Surveillance Data From 25 States, United States // Journal of Acquired Immune Deficiency Syndromes, 2010; 53 (1): 124-130.

[9]Lohse N., Hansen A. B. E., Pedersen G., et al. Survival of Persons with and without HIV Infection in Denmark, 1995-2005 // Annals of Internal Medicine, 2007; 146 (2): 87-96.

[10]Lewden C., Bouteloup V., De Wit S., et al. All-cause mortality in treated HIV-infected adults with CD4 $\geq$500/mm^3 compared with the general population: evidence from large European observational cohort collaboration // International Journal of Epidemiology, 2012; 41: 433-445.

[11] Haacker M. The Impact of HIV/AIDS on Government Finance and Public Services // The Macroeconomics of HIV/AIDS / Ed. By Haacker M. – Washington, D.C.: International Monetary Fund, 2004. – Pp. 198-258.

[12] Rugāja Z., Tuča I. Pārskats par HIV/AIDS ārstēšanai paredzēto zāļu iekļaušanu kompensējamo zāļu sarakstā 2010.gadā. Rīga: Veselības ekonomikas centrs, 2011. - 4.-13.lpp.

[13]Granich R., Crowley S., Vitoria M., et al. Highly active antiretroviral treatment as prevention of HIV transmission: review of scientific evidence and update // Current Opinion in HIV and AIDS, 2010; 5: 298-304.

[14]McIntosh W. A., Thomas J. K. Economic and other societal determinants of the prevalence of HIV: A Test of Competing Hypotheses // The Sociological Quarterly, 2004; 45 (2): 303-324.

[15]Walmsley S. L., Loutfy M. R. Meeting the Unique Needs of HIV-Positive Women // HIV/AIDS in the post-HAART era: manifestations, treatment and epidemiology / Ed. By Hall J. C., Hall B. J., Cockerell C. J. – USA: People's Medical Publishing House, 2011. – Pp. 613-647.

[16]Braga P., Cardoso M. R. A., Seguardo A. C. Gender Differences in Survival in an HIV/AIDS Cohort from São Paulo, Brazil // AIDS Patient Care and STDs, 2007; 21 (5): 321-328.

[17]Poundstone K. E., Chaisson R. E., Moore R. D. Differences in HIV disease progression by injection drug use and by sex in the era of highly active antiretroviral therapy // AIDS, 2001; 15: 1115-1123.

[18]McDonald K., Bartos M., Rosenthal D. Australian women living with HIV/AIDS are more skeptical than men about antiretroviral treatment // AIDS Care, 2001; 13 (1): 15-26.

[19]Jarrin I., Geskus R., Bhaskaran K., et al. Gender Differences in HIV Progression to AIDS and Death in Industrialized Countries: Slower Disease Progression Following HIV Seroconversion in Women // American Journal of Epidemiology, 2008; 168 (5): 532-540.

[20]Mills E. J., Bakanda C., Birungi J., et al. Male gender predicts mortality in a large cohort of patients receiving antiretroviral therapy in Uganda // Journal of the International AIDS Society, 2011; 14: 52.

[21]Fang C. T., Chang Y. Y., Hsu H. M., et al. Life expectancy of patients with newly-diagnosed HIV infection in the era of highly active antiretroviral therapy // QJM, 2007; 100: 97-105.

[22]Losina E., Schackman B. R., Sadownik S. N., et al. Racial and Sex Disparities in Life Expectancy Losses among HIV-Infected Persons in United States: Impact of Risk Behavior, Late Initiation, and Early Discontinuation of Antiretroviral Therapy // Clinical Infectious Diseases, 2009; 49: 1570-1578.

[23]Mulissa Z., Jerene D., Lindtjørn B. Patients Present Earlier and Survival Has Improved, but Pre-ART Attrition Is High in a Six-Year HIV Cohort Data from Ethiopia // PLoS ONE, 2010; 5 (10): e13268.

[24]Hogg R., Lima V., Sterne J. A. C., et al. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies // The Lancet, 2008; 372: 293-299.

[25]Mocroft A., Gill M. J., Davidson W., et al. Are There Gender Differences in Starting Protease Inhibitors, HAART, and Disease Progression Despite Equal Access to Care? // Journal of Acquired Immune Deficiency Syndromes, 2000; 24: 475-482.

[26]Babiker A., Darby S., De Angelis D., et al. Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active antiretroviral therapy: a collaborative re-analysis // The Lancet, 2000; 335: 1131-1137.

[27]Prins M., Meyer L., Hessol N. A. Sex and the course of HIV infection in the pre- and highly active antiretroviral therapy eras // AIDS, 2005; 19: 357-370.

[28]Nicastri E., Angeletti C., Palmisano L., et al. Gender differences in clinical progression of HIV-1-infected individuals during long-term highly active antiretroviral therapy // AIDS, 2005; 19: 577-583.

[29]Egger M., May M., Chêne G., et al. Prognosis of HIV-1 infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies // The Lancet, 2002; 360: 119-129.

[30]Porter K., Babiker A. G., Darbyshire J. H., et al. Determinants of survival following HIV-1 seroconversion after the introduction of HAART // The Lancet, 2003; 362: 1267-1274.

[31]Micheloud D., Berenguer J., Bellón J. M., et al. Negative influence of age on CD4+ cell recovery after highly active antiretroviral therapy in naïve HIV-1-infected patients with severe immunodeficiency // Journal of Infection, 2008; 56: 130-136.

[32]Shah R., Bradbeer C. Women and HIV – revisited ten years on // International Journal of STD & AIDS, 2000; 11: 277-283.

[33]Espinoza L., Hall I., Hu X. Diagnoses of HIV infection Among Hispanics/Latinos in 40 States and Puerto Rico, 2006-2009 // Journal of Acquired Immune Deficiency Syndromes, 2012; 60 (2): 205-213.

[34]Cook J. A., Grey D., Burke J., et al. Depressive Symptoms and AIDS-Related Mortality Among a Multisite Cohort of HIV-Positive Women // American Journal of Public Health, 2004; 94 (7): 1133-1140.

[35]Starace F., Ammassari A., Trotta M. P., at al. Depression Is a Risk Factor for Suboptimal Adherence to Highly Active Antiretroviral Therapy // Journal of Acquired Immune Deficiency Syndromes, 2002; 31: S136-S139.

[36]Tumbarello M., Rabagliati R., de Gaetano Donati K., et al. Older age does not influence CD4 cell recovery in HIV-I infected patients receiving Highly Active Anti Retroviral Therapy // BMC Infectious Diseases, 2004; 4: 46.

[37]Goodkin K., Shapshak P., Asthana D., et al. Older age and plasma viral load in HIV-1 infection // AIDS, 2004; 18 (1): S87-S98.

[38]Cargill V. A., Stone V. E. HIV/AIDS: A Minority Health Issue // The Medical Clinics of North America, 2005; 89: 895-912.

[39]Brown D. C., Hubbard McCree D., Eke A. N. African Americans and HIV: Epidemiology, Context, Behavioral Interventions, and Future Directions for Prevention // HIV/AIDS in the post-HAART era: manifestations, treatment and epidemiology / Ed. By Hall J. C., Hall B. J., Cockerell C. J. – USA: People's Medical Publishing House, 2011. – Pp. 656-678.

[40]Rubin M. S., Colen C. G., Link B. G. Examination of Inequalities in HIV/AIDS Mortality in the United States From a Fundamental Cause Perspective // American Journal of Public Health, 2009; 100 (6): 1053-1059.

[41]Pantazis N., Morrison C., Amornkul P. N., et al. Differences in HIV Natural History among African and Non-African Seroconverters in Europe and Seroconverters in Sub-Saharan Africa // PLoS ONE, 2012; 7 (3): e32369.

[42]United Nations Statistics Division. Population density and urbanization: concepts and definitions // http://unstats.un.org/unsd/demographic/sconcerns/densurb/densurbmethods.htm (sk. 26.06.2012.)

[43]European Commission, Eurostat. Eurostat regional yearbook 2010. Luxembourg: Publications Office of the European Union, 2010. - Pp. 240-249.

[44]Ohl M., Tate J., Duggal M., et al. Rural Residence Is Associated With Delayed Care Entry and Increased Mortality Among Veterans With Human Immunodeficiency Virus Infection // Medical Care, 2010; 48 (12): 1064-1070.

[45]Lahey T., Lin M., Marsh B., et al. Increased Mortality in Rural Patients with HIV in New England // AIDS Research and Human Retroviruses, 2007; 23 (5): 693-698.

[46]Heckman T. G., Solami A. M., Peters J. Et al. Barriers to care among persons living with HIV/AIDS in urban and rural areas // AIDS Care, 1998; 10 (3): 365-375.

[47]Youmans E., Burch J., Moran R., et al. Disease progression and Characteristics of HIV-infected Women With and Without a History of Criminal Justice Involvement // AIDS Behavior, 2011; DOI 10.1007/s10461-011-0057-1.

[48]Iralu J., Duran B., Pearson C. R., et al. Risk Factors for HIV Disease Progression in Rural Southwest American Indian Population // Public Health Reports, 2010; 125 (supplement 4): 43-50.

[49]Palepu A., Tyndall M. W., Li K., et al. Alcohol Use and Incarceration Adversely Affect HIV-1 RNA Suppression Among Injecting Drug Users Starting Antiretroviral Therapy // Journal of Urban Health, 2003; 80 (4): 667-675.

[50]Caylà J. A., Marco A., Bedoya A., et al. Differential Characteristics of AIDS Patients with a History of Imprisonment // International Journal of Epidemiology, 1995; 24 (6): 1188-1196.

[51]Pehrson P. O., Lindbäck S., Lidman C., et al. Longer survival after HIV infection for injecting drug users than for homosexual men: implications for immunology // AIDS, 1997; 11: 1007-1012.

[52]Ouvernay E. P., Teixeira S. L. M., Silva-de-Jesus C., et al. HIV-1 binding and neutralizing antibodies of injecting drug users // Brazilian Journal of Medical and Biological Research, 2005; 38: 1313-1320.

[53]Lloyd-Smith E., Brodkin E., Wood E., et al. Impact of HAART and injection drug use on life expectancy of two HIV-positive cohorts in British Columbia // AIDS, 2006; 20 (3): 445-450.

[54]Pérez-Hoyos S., del Amo J., Muga R., et al. Effectiveness of highly active antiretroviral therapy in Spanish cohorts of HIV seroconverters: differences by transmission category // AIDS, 2003; 17: 353-359.

[55]Bermudez-Tamayo C., Martin J. J. M., Ruiz-Pérez I., et al. Factors associated with improvement in disability-adjusted life years in patients with HIV/AIDS // BMC Public Health, 2008; 8:362.

[56]Grigoryan A., Hall H. I., Durant T., Wei X. Late HIV Diagnosis and Determinants of Progression to AIDS or Death after Diagnosis among Injecting Drug Users, 33 States, 1996-2004 // PLoS ONE, 2009; 4 (2): e4445.

[57]Rodríguez-Arenas Á., Jarrín I., Del Amo J., et al. Delay in the Initiation of HAART, Poorer Virological Response, and Higher Mortality among HIV-Infected Injecting Drug Users in Spain // AIDS Research and Human Retroviruses, 2006; 22 (8): 715-723.

[58]Sobrino-Vegas P., García-San Miguel L., Caro-Murillo A. M., et al. Delayed Diagnosis of HIV infection in a Multicenter Cohort: Prevalence, Risk Factors, Response to HAART and Impact on Mortality // Current HIV Research, 2009; 7: 224-230.

[59]Keruly J. C., Moore R. D. Immune Status at Presentation to Care Did Not Improve among Antiretroviral-Naive Persons from 1990 to 2006 // Clinical Infectious Diseases, 2007; 45: 1369-1374.

[60]Chow K. Y., Anf L. W., Verghesse I., et al. Measurable Predictive Factors for Progression to AIDS among HIV-infected Patients in Singapore // Annals of the Academy of Medicine, Singapore, 2005; 34: 84-89.

[61]Kee M. K., Lee J. H., Kim E. J., et al. Improvement in survival among HIV-infected individuals in the Republic of Korea: Need for and early HIV diagnosis // BMC Infectious Diseases, 2009; 9: 128.

[62]Nakagawa F., Lodwick R. K., Smith C. J., et al. Projected life expectancy of people living with HIV according to timing of diagnosis // AIDS, 2012; 26 (3): 335-343.

[63]Goujard C., Bonarek M., Meyer L., et al. CD4 Cell Count and HIV DNA Level Are Independent Predictors of Disease Progression after Primary HIV Type 1 Infection in Untreated Patients // Clinical Infectious Diseases, 2006; 42: 709-715.

[64]Touloumi G., Hatzakis A., Rosenberg P. S., et al. Effects of age at seroconversion and baseline HIV RNA level on the loss of CD4+ cells among persons with hemophilia // AIDS, 1998; 12: 1691-1697.

[65]Mellors J. W., Kingsley L. A., Rinaldo C. R., et al. Quantification of HIV-1 RNA in Plasma Predicts Outcome after Seroconversion // Annals of Internal Medicine, 1995; 122: 573-579.

[66]Hubert J. B., Burgard M., Dussaix E., et al. Natural history of serum HIV-1 RNA levels in 330 patients with known date of infection // AIDS, 2000; 14: 123-131.

[67]Phillips A. N., Pezzotti P. Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral-naive individuals and those treated in the monotherapy era // AIDS, 2004; 18: 51-58.

[68]Olsen C. H., Gatell J., Ledergerber B., et al. Risk of AIDS and death at given HIV-RNA and CD4 cell counts, in relation to specific antiretroviral drugs in the regimen // AIDS, 2005; 19: 319-330.

[69]Langford S. E., Ananworanich J., Cooper D. A. Predictors of disease progression in HIV-infection: a review // AIDS Research and Therapy, 2007; 4: 11.

[70]Arduino J. M., Fischl M. A., Stanley K., et al. Do HIV type 1 RNA levels provide additional prognostic value to CD4(+) T lymphocyte counts in patients with advanced HIV type 1 infection? // Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 2001; 17 (12): 1099-1105.

[71]Barrón Y., Cole S. R., Greenblatt R. M., et al. Effect of discontinuing antiretroviral therapy on survival of women initiated on highly active antiretroviral therapy // AIDS, 2004; 18: 1579-1584.

[72]Giordano T. P., Gifford A. L., White A. C., et al. Retention in Care: A Challenge to Survival with HIV infection // Clinical Infectious Diseases, 2007; 44: 1493-1499.

[73]Ortego C., Huedo-Medina T. B., Llorca J., et al. Adherence to Highly Active Antiretroviral Therapy (HAART): A Meta-Analysis // AIDS and Behavior, 2011; 15: 1381-1396.

[74]Braitstein P., Yip B., Montessori V., et al. Effect of serostatus for hepatitis C virus on mortality among antiretrovirally naive HIV-positive patients // Canadian Medical Association Journal, 2005; 173 (2): 160-164.

[75]Greub G., Ledergerber B., Battegay M., et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus Coinfection: the Swiss HIV Cohort Study // The Lancet, 2000; 356: 1800-1805.

[76]Operskalski E. A., Kovacs A. HIV/HCV Co-infection: Pathogenesis, Clinical Complications, Treatment, and New Therapeutic Technologies // Current HIV/AIDS Reports, 2011; 8: 12-22.

[77]d'Arminio Monforte A., Cozzi-Lepri A., Castagna A., et al. Risk of Developing Specific AIDS-Defining Illnesses in Patients Coinfected with HIV and Hepatitis C Virus With or Without Liver Cirrhosis // Clinical Infectious Diseases, 2009; 49: 612-622.

[78]Dorrucci M., Valdarchi C., Suligoi B., et al. The effect of hepatitis C on progression to AIDS before and after highly active antiretroviral therapy // AIDS, 2004; 18: 2313-2318.

[79]Kim A. Y., Chung R. T. Coinfection With HIV-1 and HCV - A One-Two Punch // Gastroenterology, 2009; 137 (3): 795-814.

[80]Sulkowski M. S., Moore R. D., Mehta S. H., et al. Hepatitis C and Progression of HIV Disease // Journal of the American Medical Association, 2002; 288 (2): 199-206.

[81]Rockstroh J. K., Mocroft A., Soriano V., et al. Influence of Hepatitis C Virus Infection on HIV-1 Disease Progression and Response to Highly Active Antiretroviral Therapy // The Journal of Infectious Diseases, 2005; 192: 992-1002.

[82] Castro K. G., Ward J. W., Slutsker L., et al. 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults // Morbidity and Mortality Weekly Report, 1992; 41 (No RR-17).

[83] World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach, 2010 revision. Geneva: WHO Press, 2010. – Pp. 24-30.