Loss to follow-up in HIV infected persons in Croatia in period 2006.-2017.

Hrnčić, Sandra

UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

Sandra Hrnčić

Loss to Follow-up in HIV Infected Persons in Croatia in Period 2006.-2017.

GRADUATE THESIS

Zagreb, 2018.

„This graduate thesis was made at Department of infectious diseases, University of Zagreb School of Medicine, mentored by prof. Dr. sc. Josip Begovac and was submitted for evaluation 2017./2018.“.

Mentor: prof. Dr. sc. Josip Begovac

Abbreviations

LTFU - loss to follow up
UHID - university hospital for infectious disease
AIDS - acquired immunodeficiency syndrome
HIV - human immunodeficiency virus
ART - antiretroviral therapy
VL - viral load
CD4 - CD4 positive T helper cells
MSM - men who have sex with men
IVDU - intravenous drug users
IRR - incidence rate ratio
GIP - gubitak iz praćenja

Summary:

Title: LOSS TO FOLLOW-UP IN HIV INFECTED PERSONS IN CROATIA IN PERIOD 2006-2017

Author: Sandra Hrnčić

In Croatia healthcare is public and antiretroviral therapy (ART) is covered by health insurance. The following study investigates the possible risk factors influencing rates of LTFU. Database of patients followed in the University hospital for infectious disease (UHIC) Zagreb, the centre holding data for all HIV infected persons followed in the period between 1.7.2006. and 1.7.2016. in Croatia was used. We extracted the data from the electronic database at UHID and included into study all Croatian residents ≥ 18 years old, with at least one year of follow-up and at least 2 visits. LTFU was defined as present if there was no visit for 12 months or the patient had no ART supplies for more than 3 months. The follow-up ended on december 31, 2017 or earlier if the patient died, moved or interrupted care. Associations between factors and LTFU rates were quantified using repeated measures Poisson regression. Of 1091 patients, 240 (22%) had a total of 336 episodes of LTFU. The rate of LTFU was 4.23 (95% CI, 3.80–4.70) per 100 person-years. Multivariable predictors of UHCI included viral load (VL) >200 copies/ml (Incidence Rate Ratio (IRR)) 1.77 (95% CI:1.42–2.20), age (per 10 years) IRR 0.84 (95% CI: 0.76–0.93), prior UHCI (per episode) IRR 3.49 (95% CI: 3.04–4.00), calendar year (2006–2009 vs 2010–2016) IRR 1.50 (95% CI 1.20–1.87) and time under follow-up (per year) IRR 1.14 (95% CI 1.11–1.18). Of 240 patients with at least one UHCI 16 (6.7%) died whereas of 851 without an LTFU 44 (5.2%) died (P=0.369). Measured < 200 cell/mm^3 had no definite correlation with LTFU rates when comparing bivariate and multivariate analysis. At the last visit at UHID, of 240 patients with an LTFU 127 (52.9%) had reentered care, 16 had died, 8 moved and 89 (37.1%) had an LTFU.

Keywords: HIV, loss to follow up, viral load

Sažetak

Naslov: GUBITAK OSOBA ZARAŽENIH HIV-OM IZ PRAĆENJA U REPUBLICI HRVATSKOJ U RAZDOBLJU OD 2006. DO 2017. GODINE

Autorica: Sandra Hrnčić

U Hrvatskoj zdravstvena zaštita je javna i antiretroviralna terapija (ART) je pokrivena zdravstvenim osiguranjem. Ovo istraživanje preispituje moguće faktore rizika koji utiču na stope gubitka iz praćenja (GIP). Korištena je baza podataka pacijenata praćenih Sveučilišnoj bolnici za infektivne bolesti klinike u Zagrebu, centra koji sadrži podatke svih osoba zaraženih HIV-om praćenih u Hrvatskoj u periodu između 1.7.2006. I 1.7.2016.Izvadili smo podatke iz elektronske baze podataka klinike za infektivne bolesti i uključili u istraživanje sve stanovnike Republike Hrvatske koji imaju ≥ 18 godina, sa barem godinu dana praćenja i barem 2 posjeta. Gubitak iz njege je definiran kao postojeći kada nema niti jednog posjeta klinici 12 mjeseci ili pacijent nije imao ART zalihe za više od 3 mjeseca. Praćenje je završilo 31. Prosinca, 2017. Ili ranije ako je pacijent umro, preselio se ili prekinuo sa njegom. Poveznice između faktora i stopa GIP su kvantificirane koristeći Poissonovu regresiju ponovljenih mjerenja.Od 1091 pacijenata, 240 (22%) je iskusilo ukupno 336 episode GIP. Stopa GIP je bila 4.23 (95% CI, 3.80–4.70) po 100 osoba-godina. Multivarijatni predkazivači GIP uključivali su koncentraciju virusa >200 kopija/ml (Incidence Rate Ratio (IRR)) 1.77 (95% CI:1.42–2.20), dob (per 10 years) IRR 0.84 (95% CI: 0.76–0.93), prijašnje GIC (po epizodi) IRR 3.49 (95% CI: 3.04–4.00), kalendarske godine (2006–2009 vs 2010–2016) IRR 1.50 (95% CI 1.20–1.87) i vrijeme praćenja (po godini) IRR 1.14 (95% CI 1.11–1.18). Od 240 pacijenata sa barem jednim GIP 16 (6.7%) je umrlo dok od 851 bez GIP 44 (5.2%) je umrlo (P=0.369). Izmjereni CD4 < 200 cell/mm^3 nisu imali korelaciju sa stopama GIP kada su bivarijatna i multivarijantna analiza uspoređene. Pri zadnjem posjetu bolnici, od 240 osoba sa GIP, 127 (52.9%) je ponovno ušlo u praćenje, 16 je umrlo, 8 se odselilo i 89 (37.1%) je imalo GIP.

Ključne riječi: HIV, gubitak iz njege, virusno opterećenje

Preface/introduction

Since its discovery in 1983.[1] human immunodeficiency virus (HIV) has become one of the major disease burdens globally. With its transmission through sexual and blood contact it has grown into a global pandemic. 36,7 million people were reportedly living with HIV in the year 2016.[2] of which 1,433 were of croatian resident citizens[3]. Of those reportedly infected 1,8 million cases were newly diagnosed that year of which 106 persons were Croatian resident citizens. This information makes it appear as a rising trend in this particular country as 5% of the individuals globally were infected this year, while this percentage in croatian relations was 7% placing it above the standard.

Antiretroviral therapy was introduced in 1996.[4] and improved the quality of life and prognosis for those suffering from the progression of the disease by reducing the viral load. Availability of these medication programmes reduced the probability of transmission and made HIV infection preventable. In a country with a public health system such as Croatia where antiretroviral therapy (ART) is completely covered by health insurance and available in several different regiments it is surprising to find that the rates of infection continued to rise in the present time.

HIV is one of the less common chronic infections found in the communicable disease group and therefore available for analysis in a long term cohort study. A method of loss to follow up is appropriate in observing the compliance of patients to therapy and investigating the factors responsible for the rise in the trend of infection and patient dropping out of care.

Loss to follow up is dropping patients out of care after being in care for a period of time. The following study is made to advance the knowledge about factors leading to loss to follow up in order to decrease its incidence as well as the disease spread.

Hypothesis

The hypothesis of this study is that LTFU is correlated to lower CD4 count, higher viral load and higher mortality rates. Also, it is hypothesized that it is related to time under treatment, age, gender, mode of transmission, location of residence, and coinfection with hepatitis B, and hepatitis C.

Objectives

The objective of this study is to examine aspects influencing LTFU. The following factors have been examined: age, gender, place of residence, CD4 count, VL, mode of exposure, time under follow-up, previous episode of LTFU and coinfection with either HCV or HBV.

Methods

Study setting

Persons included in the study are patients followed in the referent centre in Zagreb University hospital for infectious diseases (Fran Mihaljević), Croatia. This is the the sole centre holding data for all HIV infected persons in Croatia.

Patients

Data of HIV infected persons in Croatia collected in the period between 1.1.2006. and 1.7.2016. was included in the study, however the censor date for the data collection was 31.12.2017. Those individuals reported to have moved were excluded from the study as well as patients under 18 years of age due to ethical reasons. Visit was defined as patient seen in outpatient department or to have picked up prescription medication, hospitalizations were not included in this definition. Patients needed at least 2 visits or drug prescription within the same year to be considered being in care, therefore patients with only one visit were not considered to be in care to begin with. Patients needed to be followed at least one year to be considered in care. Those who moved would assumed to have moved 1 day after last visit. Patients with HIV type 2 infection were removed from the study.

Data collection

All the data was extracted from the hospital database. Information was recorded by the hospital staff at the time of the patient admission and visits. Due to the human error factor data had to be cleaned prior to processing. This included removing persons with

incorrect visit dates or times of death as well as those with variable values well out of range of normal limits.

LTFU definition

ART drug prescriptions at UHID in Zagreb can range in their duration from one month, two month, three month, six month and even twelve month prescription. Persons living outside of the capital where the centre is situated, those working seasonal jobs who are away for long periods of time and those with stable laboratory findings can benefit from this flexibility. For the patients who died LTFU was defined as being over 90 days prior to the last visit.

Considering the variation in drug prescription LTFU had to be defined differently for different groups of patients but it revolved around the patient having no visit or contact for over 3 months. For those whose ART prescriptions are issued for up to 9 months LTFU is defined as not being renewed for 12 months since the date of the issuing. Therefore the patient is potentially not in contact for 3 months since the last issuing. For the patients whose prescriptions are issued for 10, 11 or 12 months LTFU is defined as not being renewed for 3 months after the last issuing meaning the patient is out of contact from 1 up to 15 months.The last date of patient inclusion was made 1.7.2016. so that the newly received patients had an opportunity to be included into the study and experience LTFU. For patients who died LTFU was defined as last visit or prescription being over 3 months prior to date of death.

Factors/variables measured

During the course of this study specific variables were analyzed in the context of measuring LTFU. Of the general variables age, gender, area of residence and mode of HIV transmissions were considered in measuring LTFU. Age was divided into several

groups, the first being ages 18-29, second 29-39, third 39-49 and fourth 50 and above years of age. Calendar year trends were noted and patients were divided into two groups to compare the trend of LTFU in the first half and second half of the study period. The main modalities focused on during measuring were viral load and CD4 count. Viral load was defined as when it was >200 copies/ml. CD4 count was divided into groups of greater or even than 500 cell/mm^3, equal to 200-499 cell/mm^3 or less than 200 cell/mm^3. These variables were compared in participants who had LTFU to those who did not have LTFU. We used first, last and lowest CD4 measurement. Infectious diseases other than HIV infections compared in this study were hepatitis C, hepatitis B and syphilis. Lastly, portion of patients who died and obtained AIDS were noted.

Study design and analysis

Loss the follow-up in HIV infected persons was analyzed in a form of a retrospective cohort study. Cohort censor date was 31.12.2017. Data was analyzed using statistical analysis software (SAS). Crude rates were calculated and Poisson regression analysis was made, with general estimating equations methods. Bivariate analysis was performed, the number of LTFU episodes was calculated for each variable, stating whether the LTFU occured (yes), was absent (no) and the corresponding p value was calculated. Incidence rate ratios were calculated for each variable to assess the probability that the variable is connected to LTFU. Bivariate and multivariate analysis was made.

Ethical statement

Patients in care are given a consent form for their data to be analysed in studies. This was part of the Croatian Science Foundation project (project number IP-2014-09-446, principal investigator dr. sc. prof. J. Begovac) for which ethical approval was given by UHID and University of Zagreb School of Medicine.

Patients that were under the age of 18 at the time of the first visit were excluded from the study due to ethical reasons.

Results

After the criteria was applied, according to crude calculation, the number of patients known to have had HIV in the period of 2006.-2016. included in the study was 1091 of which 1045 (95.8%) received ART. In this population median follow up was 7.5 years (Q1-Q3, 4.1–11.1).
Of 1091, 60 (5.5%) persons had died during the duration of the study, of which 42 had died within 90 days of the last visit and were therefore not considered out of care.
240 (22%) persons included in the study experienced LTFU with a total of 336 episodes. Frequency of LTFU episodes was calculated as well as frequency per number of episodes in a single patient. The results were shown in table 1.
Of those who experienced LTFU 127 (52.9%) reentered care, 16 (6.7%) had died and 8 had moved. Exactly 89 (37.1%) of those patients experienced LTFU after reentering care. The total follow up was added to be 7950.9 years and after incidence rate ratio (IRR) calculation it was found that the rate of follow up was 4.23 (95% CI 3.80 - 4.70) at 100 person years.

In the examined population 969 (88.8%) were males, whose IRR of LTFU were 4.23 (95% CI: 3.56 - 4.50). 433 (39.7) live inside of city of Zagreb county with a IRR of 3.76 (95% CI: 3.12 - 4.53), while outside of Zagreb were 658 (60.3%) with IRR 4.48 (95% CI: 3.93 - 5.10). Age was divided into different groups as explained earlier. The median age in sample population was 43.9 (Q137.0 - Q352.7), while the median age of patients with LTFU was, 41.5 (Q34.4 - Q49.8). Majority of the patients (n748 (68.6%)) had men who have sex with men (MSM) as the main route of HIV transmission.

According to bivariate analysis factors correlated to the increased rates of LTFU were age (0.7 (CI 95%: 0.62-0.78), year of first diagnosis (1.36 (95% CI: 1.13-1.63), CD4 count at inclusion ≥ 500 cells/mm3 (1.12 (95% CI: 1.07-1.17), time dependant viral load

≥ 200 copies/ml (4.39 (95% CI: 1.04-1.92), time under follow up (1.07(95% CI: 1.04-1.09) and previous LTFU (3.56 (95% CI: 3.19-3.98).

After the multivariate analysis was performed, when analyzing age, the highest IRR associated was associated with the youngest group with those 18-29 years of age and it was 2.07 (95% CI: 1.83 - 2.30). Intravenous drug users (IVDU) had the highest incidence of loss to follow up, but when it came to regression analysis MSM group had the incidence rate of 1.40 (95% CI: 1.26 - 1.54) while the non MSM patients together had an IRR of 1.50 (95% CI: 1.33 - 1.67).

After the p value calculation the lowest was found in younger age, last VL measurement, first CD4 measurement and last CD4 measurement. Last VL measurement with a detectable count (>200 copies/ml), while both CD4 measurements were related to low counts (<200 cells/mm^3).

Infectious diseases other than HIV infections compared in this study were hepatitis C and hepatitis B none of which showed correlation to higher rates of LTFU.
Portion of patients who died and obtained AIDS were noted (n=293). However statistically the connection to increased LTFU was not established.

The aim of comparing the analyses of bivariate and multivariate analysis was to eliminate possible confounding factors. The variables highly correlated to rates of LTFU in both sets were younger age, detectable viral load at first measurement, time under follow up, and previous episodes of LTFU.

Table 1: LTFU frequencies using univariate analysis

Cumulative LTFU	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	853	78.04	853	78.04
1	170	15.55	1023	93.60
2	52	4.76	1075	98.35
3	12	1.10	1087	99.45
4	4	0.37	1091	99.82
5	2	0.18	1093	100.00

Table 2. Dichotomous table listing main variables and calculated p values

	LTFU yes/no			
Variables	**Total N=1091(%)**	**No N=851(%)**	**Yes N=240(%)**	**P Value**
Risk				*0.168* [†]
IVDU	7 (0.6)	7 (0.8)	0 (0.0)	
MSM	748 (68.6)	593 (69.7)	155 (64.6)	
Mother to child	2 (0.2)	1 (0.1)	1 (0.4)	
IVDU	41 (3.8)	27 (3.2)	14 (5.8)	
hetero	263 (24.1)	200 (23.5)	63 (26.3)	
unknown	30 (2.7)	23 (2.7)	7 (2.9)	
Risk1				*0.133*
MSM	748 (68.6)	593 (69.7)	155 (64.6)	
Non MSM	343 (31.4)	258 (30.3)	85 (35.4)	
Gender				*0.153*
female	122 (11.2)	89 (10.5)	33 (13.8)	
male	969 (88.8)	762 (89.5)	207 (86.3)	
Age				*<.001*
Median (q25 - q75)	43.9 (37.0 - 52.7)	44.6 (37.8 - 53.5)	41.5 (34.4 - 49.8)	
CD4 last				*<.001*
Median (q25 - q75)	609.0 (437.0 - 805.0)	626.0 (468.0 - 840.0)	522.5 (341.5 - 705.5)	
Minimal CD4				*0.136*

Median (q25 - q75)	199.0 (60.0 - 335.0)	195.0 (61.0 - 326.0)	218.0 (57.0 - 372.5)	
Min CD4				*0.915*
Median (q25 - q75)	266.0 (116.0 - 401.0)	264.0 (129.0 - 396.0)	273.0 (86.5 - 453.0)	
Live in Zagreb				*0.067*
No	658 (60.3)	501 (58.9)	157 (65.4)	
Yes	433 (39.7)	350 (41.1)	83 (34.6)	
Died				*0.369*
alive	1031 (94.5)	807 (94.8)	224 (93.3)	
died	60 (5.5)	44 (5.2)	16 (6.7)	
AIDS				*0.287*
Had AIDS	293 (26.9)	235 (27.6)	58 (24.2)	
No AIDS	798 (73.1)	616 (72.4)	182 (75.8)	
Last VL count				*<.001*
Greater or even to 200	82 (7.5)	20 (2.4)	62 (25.8)	
Less than 200	1009 (92.5)	831 (97.6)	178 (74.2)	
Last CD4 count				*<.001*
200 to 499	317 (29.1)	230 (27.0)	87 (36.3)	
ge 500	722 (66.2)	592 (69.6)	130 (54.2)	
lt 200	52 (4.8)	29 (3.4)	23 (9.6)	
First VL count				*0.897*

ge 200	833 (76.4)	649 (76.3)	184 (76.7)	
lt 200	258 (23.6)	202 (23.7)	56 (23.3)	
First CD4 count				*<.001*
200 to 499	497 (45.6)	389 (45.7)	108 (45.0)	
ge 500	303 (27.8)	209 (24.6)	94 (39.2)	
lt 200	291 (26.7)	253 (29.7)	38 (15.8)	
Hepatitis B				*0.560*
No	1028 (94.2)	800 (94.0)	228 (95.0)	
Yes	63 (5.8)	51 (6.0)	12 (5.0)	
Hepatitis C				*0.047*
No	1025 (94.0)	806 (94.7)	219 (91.3)	
Yes	66 (6.0)	45 (5.3)	21 (8.8)	

Table 3: Bivariate and multivariate analysis results

	Bivariate		Multivariate	
Variable	IRR (95% CI)	P-values	IRR (95% CI)	P-values
Gender				
Male	1	0.043		
Female	1.46 (1.01–2.11)			
Age		< 0.001		< 0.001
per 10 years older	0.7 (0.62–0.78)		0.84 (0.76–0.93)	
Exposure				
MSM	0.89 (0.69–1.15)	0.372		
non-MSM	1			
HCV (ever)		0.028		
No	0.63 (0.41–0.95)			
Yes	1			
HBsAg (ever)		0.302		
No	1.31 (0.78–2.2)			
Yes	1			
Year HIV positive		0.715		
< 2010	1.05 (0.81–1.35)			
ge 2010	1			
Year inclusion		< 0.001		
< 2010	1.36 (1.14–1.63)		1.50 (1.20–1.87)	
ge 2010	1			
CD4 cell count at inclusion		< 0.001		
per 100 cells	1.12 (1.07–1.17)			

CD4 cell count at inclusion				
≥ 500	2.56 (1.78–3.7)	< 0.001	0.79 (0.59-1.08)	0.118
200-499 cells/mm^3	1.66 (1.16–2.37)	0.005	0.82 (0.62-1.08)	0.152
< 200 cells/mm^3	1		1	
VL at inclusion, copies/ml		0.028		
≥ 200	1.41 (1.04–1.92)			
<200	1			
Viral load time dependent, copies/ml		< 0.001		< 0.001
≥ 200	4.39 (3.65–5.28)		1.77 (1.42–2.20)	
<200	1			
Time under follow-up		< 0.001		< 0.001
per 1 additional year	1.07 (1.04–1.09)		1.14 (1.11–1.18)	
Episode of previous LTFU		< 0.001		< 0.001
Yes	3.56 (3.19–3.98)		3.49 (3.04–4.00)	
No	1			
Living in Zagreb		0.383		
No	1.12 (0.87–1.46)			
Yes	1			

Discussion

From the result given the rate of LTFU in Croatia was 4.23 (95% CI, 3.80–4.70) per 100 person-years. In comparison, in an observational study performed in Europe the result was 3.72 (95% CI:3.58-3.86) per 100 person-years of follow-up[5] which brings us close to the European average .

In answer to the hypothesis the results have indeed shown that rates of LTFU were correlated to detectable VL in both bivariate (IRR 1.41 (95% CI: 1.04–1.92)) and multivariate (IRR 1.77 (95% CI: 1.42–2.20)) analysis. In an Australian observational study it was 1.19 (95% CI 1.14–1.23), which was also highly correlated to the LTFU rates making it also a strong predictor of LTFU.

Higher CD4 count was correlated to higher rates of LTFU in the bivariate analysis which would indicate direct correlation, whereas in the multivariate it was correlated to lower CD4 counts. This would indicate that the variable possibly has no correlation to the LTFU rate and is therefore a suppressor factor. When variable previous LTFU episode was removed from the multivariate analysis the CD4 count was correlating to the bivariate analysis which a point that deserves further analysis. Mortality rates were not correlated with the rates of LTFU in either of the analyses.

When observing figure 1 taken from Croatian department of public health it is obvious that the death rates continued to remain relatively constant throughout the years further emphasizing the lack of the correlation between LTFU and increased mortality together with the high p value (p = 0.369). While the EuroSIDA trial didn't record death rates, the Australian surveillance study[11] revealed similar results as Croatia. They compared the population against the death register and came to the finding that 10.5% of the patients who died were linked to LTFU whereas in Croatia this percentage was 6.7%.

Time under follow-up was directly correlated to increased rates of LTFU in both bivariate (IRR 1.07 (95% CI: 1.04–1.09)) and multivariate (IRR 1.14 (95% CI:

1.11–1.18)) analyses. This may be explained by the fact that it is more likely to experience a longer period of absence from care in the longer time under care. Previous episode of LTFU was also highly correlated to increased rates of repeated LTFU episode with high IRR results, for bivariate analysis being 3.56 (95% CI: 3.19–3.98) and multivariate analysis being 3.49 (95% CI: 3.04–4.00). Considering the high degree of correlation between the two analyses it may be interpreted as resulting from the variable itself as much as from the sum of other variables.

When observing the trend in LTFU in those infected by HIV it is easily noted by both the frequency and incidence rate that the amount of people experiencing LTFU decreased in the second half of the interval chosen (figure 2). However, the total amount of patients increased in those years as well as can be seen from the Croatian department of public health epidemiological analysis (figure 1). This decrease may be due to the free HIV screening standardized on the European Union level and introduced in 2013.[9] together with treatment promotion as can be observed from the graph.

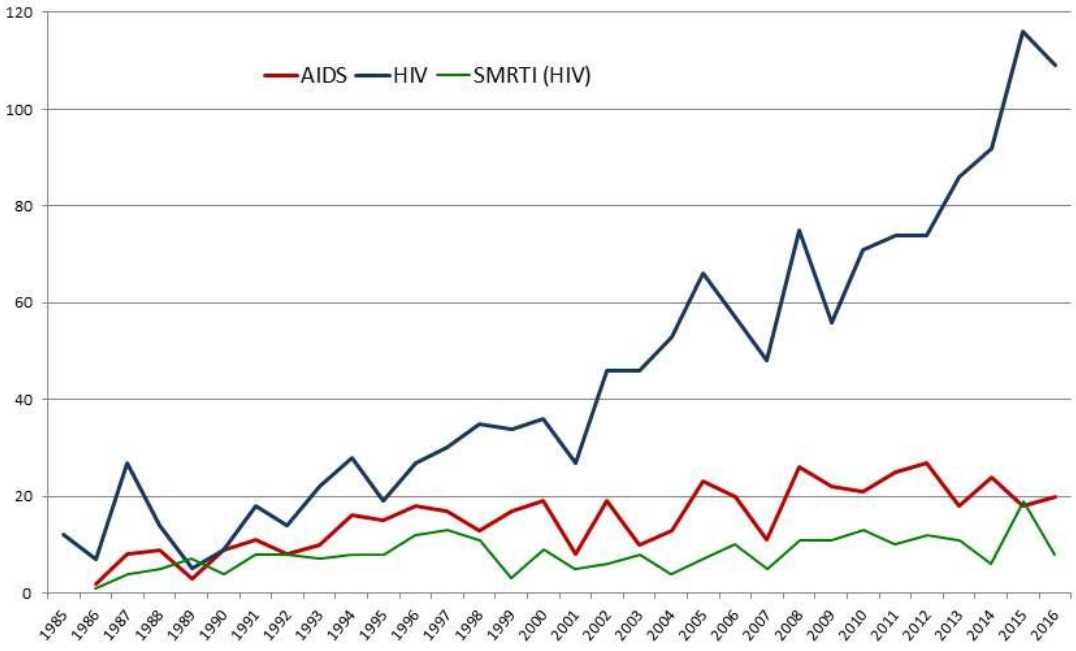

Figure 1: HIV infection, death and AIDS trends in Croatia between years 1985. And 2016. Taken from Croatian Department of Public Health[10]

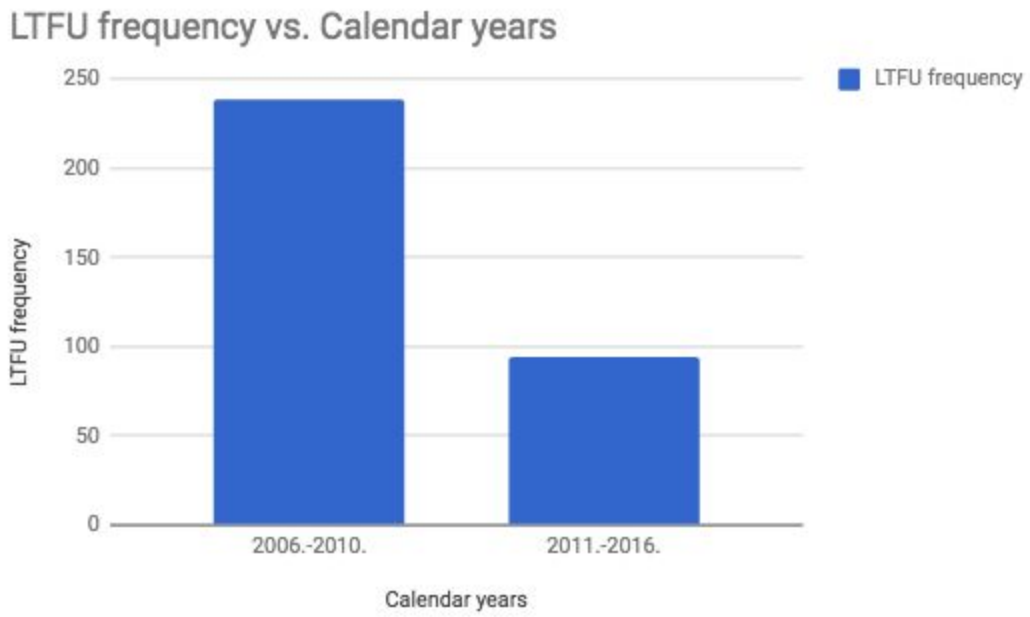

Figure 2: LTFU number of episodes in two different year intervals

When it comes to age in the EuroSIDA [12]trial the older patients were more likely to have lower rates of ltfu as it shows that those 10 years older on average had an IRR of 0.85 (95% CI: 0.80–0.89) which was also the case in the Croatian trial where the age group of 18-29 years old had the highest rates 2.07 (95% CI: 1.83 - 2.30). Mode of transmission in the same study had increased IRR in IVDU (IRR 2.16 CI: 1.84 - 2.53 p<0.001), whereas in a Croatia MSM patients had the lowest LTFU rates.

Considering the major findings of this cohort, all of the above mentioned studies showed similar results. In the Australian study[13] LTFU in patients with low CD4 had a median of 480 (Q1-Q3, 320–665), in Guinea-Bissau[14] it was 210 (Q1-Q3, 97–391), in EuroSIDA[15] study 261 (Q1-Q3, 120-420) while in this study the CD4 count at the last measurement had a median of 522.5 (Q1-Q3, 341.5–705.5) per mm^3. This would strongly connect the finding of LTFU correlating to a lower CD4 count, however as it was aforementioned, this was not the case when the variables were analysed as set in this study.

Some of the things that might have influenced the results were the definition variety of LTFU, especially when comparing it to appropriate studies from other areas. More so, there is a potential for bias from provider of health care considering prescriptions that might have influenced patients and therefore results. In a study performed in Zambia[16] it was shown that longer drug prescription de-burdened the clinics and corresponded to lower rates of LTFU.

Furthermore, the only centre for treatment is in the capital, around 520 km from furthest city of the country which, accessibility might have had to do with compliance of a certain population but it was not correlated to definite lower rates of LTFU. It is encouraging to see how the organisation of the care is still providing adequate coverage for the surface area of the country.

Lastly, when it comes to definition itself, as it was stated before LTFU was defined in a very specific parameters. In a study done in South Africa, Asia and South America by comparing specificity and sensitivity of definitions it was established that LTFU defined as absence of 180 days had the lowest rate of misclassification. However, in the study performed in Zagreb that was difficult to execute considering the difference in patient visits since the centre is situated so far from the furthest point of the country.

Considering the rates calculated and the amount of people to have experienced LTFU according to the established definition (22%) according to certain studies that is above the limit of validity. However, when compared to similar studies in the HIV population in different countries Croatian population was not on the upper side especially if comparing rates. A study in Guinea-Bissau [6]showed the highest rate of LTFU of 51.1 per person years , a study in Nigeria showed a rate of 12.3 while the European standard from a EuroSIDA[7] study involving 12 304 patients from across Europe showed a LTFU incidence of 3.72 (95% CI: 3.58-3.86) but the results did vary from 0.67 to 13.35 according to the region. Australian[8] population was at the very bottom with 1.63 (95% CI: 1.45 - 1.84). Croatia therefore cuts closest to the European standard with 4.23 (95% CI 3.80 - 4.70).

Some variables covered by other studies that would be useful to investigate in the future are prior episodes, time between visits and BMI. Lower BMI of patients in particular was investigated in the Guinea-Bissau research[17] and found to be correlated to the LTFU perhaps due to the fact that those with other chronic comorbidities might frequent to the physician more or due to possible high AIDS rates as anorexia is part of the symptoms and the study hasn't monitored mortality.

In further investigation I would introduce a control as well as examine whether the prescription influences the follow up of the patient for the intervals longer than 6 months. Considering the variety in side effects the patients might have lower compliance for some regiments considering that they do not feel ill when they are not medicated but this is a matter that would require a questionnaire. Likewise, it would be useful to examine whether the patients with longer prescription of the medications are more compliant to take them since they are given more independence by the physician which was the case in a study done in Zambia[18] or, on the other hand, the patients with shorter prescription would make sure to take them regularly as they will be controlled at the clinic. In addition, considering distance was connected to the compliance of the patient it would be interesting to see which region in particular had higher LTFU rates and whether it was indeed proportional to how far away the patient lives from the centre. Another interesting parameter to examine would be patient education, investigating whether the patients are perhaps not understanding the gravity of their illness and the simplicity of the treatment. It would be informative to compare LTFU in different levels of education as well as depending on how well their physician educated them on the disease.

Conclusions

LTFU has been statistically correlated to detectable VL, time under care and previous episode of LTFU but it hasn’t influenced the patient mortality nor has it been definitely connected to higher CD4 counts at inclusion. Younger age, male gender, distance from the health center, as well as IVDU was connected to greater rates of LTFU but they didn’t seem to provide definite answers.

Acknowledgements

I would like to thank my thesis mentor Dr. Josip Begovac for inspiring me to pursue this path and supporting me in finishing the graduation paper. I would also like to thank my friends and family for their infinite patience and support, and Freddie Mercury for lifting me up when I was at my lowest.

References

1. UpToDate. [cited 2018Jun18]. Available from: https://www.uptodate.com/contents/the-natural-history-and-clinical-features-of-hiv-infection-in-adults-and-adolescents
2. HIV/AIDS [Internet]. World Health Organization. World Health Organization; [cited 2018Jun18]. Available from: http://www.who.int/mediacentre/factsheets/fs360/en/
3. Epidemiologija HIV infekcije i AIDS-a u Hrvatskoj [Internet]. Hrvatski. [cited 2018Jun18]. Available from: https://www.hzjz.hr/sluzba-epidemiologija-zarazne-bolesti/epidemiologija-hiv-infekcije-i-aids-a-u-hrvatskoj/
4. Early loss of HIV-infected patients on potent antiretroviral therapy programmes in lower-income countries [Internet]. World Health Organization. World Health Organization; 2011 [cited 2018Jun18]. Available from: http://www.who.int/bulletin/volumes/86/7/07-044248/en/
5. Sullivan AK, Sperle I, Raben D, Amato-Gauci AJ, Lundgren JD, Yazdanpanah Y, et al. HIV testing in Europe: Evaluating the impact, added value, relevance and usability of the European Centre for Disease Prevention and Control (ECDC)'s 2010 HIV testing guidance. Eurosurveillance. 2017;22(48).
6. Hønge BL, Jespersen S, Nordentoft PB, Medina C, da D, da ZJ, et al. Loss to follow-up occurs at all stages in the diagnostic and follow-up period among HIV-infected patients in Guinea-Bissau: a 7-year retrospective cohort study. [Internet]. Advances in pediatrics. U.S. National Library of Medicine; 2013 [cited 2018Jun18]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24163204
7. Mocroft A, Kirk O, Aldins P, Chies A, Blaxhult A, Chentsova N, et al. Loss to follow-up in an international, multicentre observational study. [Internet]. Advances

in pediatrics. U.S. National Library of Medicine; 2008 [cited 2018Jun18]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/18400074

8. McManus H, Petoumenos K, Brown K, Baker D, Russell D, Read T, et al. [Internet]. Advances in pediatrics. U.S. National Library of Medicine; 2015 [cited 2018Jun18]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4424189/
9. Sullivan AK, Sperle I, Raben D, Amato-Gauci AJ, Lundgren JD, Yazdanpanah Y, et al. HIV testing in Europe: Evaluating the impact, added value, relevance and usability of the European Centre for Disease Prevention and Control (ECDC)'s 2010 HIV testing guidance. Eurosurveillance. 2017;22(48).
10. Epidemiologija HIV infekcije i AIDS-a u Hrvatskoj [Internet]. Hrvatski. [cited 2018Jun18]. Available from: https://www.hzjz.hr/sluzba-epidemiologija-zarazne-bolesti/epidemiologija-hiv-infekcije-i-aids-a-u-hrvatskoj/
11. Mcmanus H, Petoumenos K, Brown K, Baker D, Russell D, Read T, et al. Loss to follow-up in the Australian HIV Observational Database. Antiviral Therapy. 2014;20(7):731–41.
12. Mocroft A, Kirk O, Aldins P, Chies A, Blaxhult A, Chentsova N, et al. Loss to follow-up in an international, multicentre observational study. HIV Medicine. 2008;9(5):261–9.
13. Mcmanus H, Petoumenos K, Brown K, Baker D, Russell D, Read T, et al. Loss to follow-up in the Australian HIV Observational Database. Antiviral Therapy. 2014;20(7):731–41.
14. Hønge BL, Jespersen S, Nordentoft PB, Medina C, Silva DD, Silva ZJD, et al. Loss to follow-up occurs at all stages in the diagnostic and follow-up period among HIV-infected patients in Guinea-Bissau: a 7-year retrospective cohort study. BMJ Open. 2013;3(10).

15. Mocroft A, Kirk O, Aldins P, Chies A, Blaxhult A, Chentsova N, et al. Loss to follow-up in an international, multicentre observational study. HIV Medicine. 2008;9(5):261–9.
16. Mody, Aaloke, Roy, Monika, Thea, Holmes, et al. Improved Retention With 6-Month Clinic Return Intervals for Stable Human Immunodeficiency Virus-Infected Patients in Zambia | Clinical Infectious Diseases | Oxford Academic [Internet]. PLOS Biology. Public Library of Science; 2017 [cited 2018Jun27]. Available from: https://doi.org/10.1093/cid/cix756
17. Hønge BL, Jespersen S, Nordentoft PB, Medina C, Silva DD, Silva ZJD, et al. Loss to follow-up occurs at all stages in the diagnostic and follow-up period among HIV-infected patients in Guinea-Bissau: a 7-year retrospective cohort study. BMJ Open. 2013;3(10).
18. Mody, Aaloke, Roy, Monika, Thea, Holmes, et al. Improved Retention With 6-Month Clinic Return Intervals for Stable Human Immunodeficiency Virus-Infected Patients in Zambia | Clinical Infectious Diseases | Oxford Academic [Internet]. PLOS Biology. Public Library of Science; 2017 [cited 2018Jun27]. Available from: https://doi.org/10.1093/cid/cix756

Biography

Sandra Hrnčić is a 6th year medical student finishing the Medical Studies in English program of the University of Zagreb, Croatia. She has shown interest in the area of medicine since early age, a love that has deepened after enrolling into the medical faculty. Her true passion has shown to become infectious disease and tropical medicine after completing the course, leading her to enrol into a MSF preparatory course at the University of Copenhagen the following summer. After finishing the studies she plans to pursue a specialisation in the field and hopefully do an internship in southeast Asia.