

Epidemiological and clinical characteristics of HIV-infected persons entering care in Croatia in the period 2007-2015

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**UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE**

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**EPIDEMIOLOGICAL AND CLINICAL
CHARACTERISTICS OF HIV-INFECTED PERSONS
ENTERING CARE IN CROATIA IN THE PERIOD
2007-2015**

GRADUATION THESIS



Zagreb, 2016

This graduate thesis was made at the University of Zagreb School of Medicine at the Department of Infectious Diseases division HIV/AIDS, University Hospital Zagreb, mentored by professor Josip Begovac, M.D., PhD, and was submitted for evaluation in 2016.

Abbreviations

AIDS– Acquired Immunodeficiency Syndrome
ART– Antiretroviral Therapy
CNIPH– Croatian National Institute of Public Health
EU– European Union
GFTA M– Global Fund to Fight TB, AIDS and Malaria
HIV– Human Immunodeficiency Virus
IDU– Injecting drug user
LGBT-Lesbian, Gay, Bisexual and Transgender
MSM-Men who have sex with men
MTC-mother to child
PWID-People Who Inject Drugs
Hetero-Heterosexual
UHID- University Hospital of Infectious Diseases
NAHPP-National Aids Health Protection Program
STD- Sexually Transmitted diseases
VCT: voluntary Center Testing

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Title:**EPIDEMIOLOGICAL AND CLINICAL CHARACTERISTICS OF HIV-INFECTED PERSONS ENTERING CARE IN CROATIA IN THE PERIOD 2007-2015****Author:** Laval Alexandra

Summary:

Background: In Croatia, all people living with HIV receive care at one treatment center, at the University Hospital for Infectious Diseases (UHID) in Zagreb.

Objective: To describe the main characteristics of HIV infected persons who entered care at UHID in the period 2007-2015. We also assessed factors associated with late presentation to care.

Methods: We extracted data from the electronic HIV-database at UHID for all patients who entered care in the period 2007-2015. The following data were analysed: already diagnosed in another country, age, gender, place of living, risk group, CDC classification and CD4 cell count at entry into care. In the analysis of factors related to late presentation we included only adults who were not in care elsewhere before entering care at UHID and who acquired HIV by sexual transmission. Late presentation of care was defined as having < 350 CD4 cells/mm³ at presentation and logistic regression was done to assess factors related to late presentation.

Results: A total of 731 persons entered care at UHID in the period 2007-2015. Of those 731 persons 44 were coming from abroad and were already treated elsewhere. Of 687 who entered care for the first time 682 were adults (> 18 years). The number of HIV positive persons included in care for the first time more than doubled from 2007 (n=54) to 2015 (n=116). 39% of patients were in the age group 30 to 39 years, < 1% were younger than 18 years and 10% were older than 50 years. The proportion of persons living in Zagreb or Zagreb county ranged from 24% to 47% per calendar year. The main mode of transmission was sex between men (MSM; overall: 80%). The median CD4 cell count at entry into care was lowest in 2011 (209 per mm³), however, since then it has increased and reached 355 per mm³ in 2015. The proportion of persons presenting with clinical AIDS was highest in 2010 and 2011 (28.4%), and lowest in 2015 (15.5%). On multivariable analysis, the following factors were associated with late presentation to care (n=653): not living in Zagreb - heterosexual mode of transmission and older age.

Conclusion: The number of HIV infected persons entering care in the period 2007-2015 increased substantially. The dominant mode of transmission is sex between men. Late presentation to care is still common. Our data suggest that there is an increasing need for prevention efforts that focus on MSM. To improve earlier presentation to care there needs to be more focus on persons living outside Zagreb and older heterosexuals.

Keywords: HIV, AIDS, Croatia, Epidemiology

Introduction

The Human Immunodeficiency Virus (HIV), probably appeared between the 1910s and 1950s in East Africa, affects today 37 million people worldwide [1] .

The first cases of Acquired Immunodeficiency Syndrome (AIDS) were described in 1981 in the USA , it was called at that time called the " gay-related immunodeficiency " since it was first identified in Men Who Have Sex wit Men (MSM), it was then called the "lymphadenopathy associated virus" by the French investigators and Human T-lymphotropic virus Type III (HTLV-III) by the American researchers. In 1986 it was agreed that the name of the newly discovered virus should be HIV. HIV type1 was sequenced in 1985 and type 2 in 1987 .

Key dates of the discovery and support of HIV [2-3]

- End XIX - early XX century: Probable date of the passage of SIV (Simian Virus Immunodeficiency) from monkey to man, in which it turned into HIV if this theory is valid.
- 1981: First description of AIDS in the US.
- 1983: Discovery of the virus responsible for AIDS by a team from the Institut Pasteur in Paris (Pr F. Barre-Sinoussi, Montagnier L. Pr).
- 1984: Start of the controversy with Professor R. Gallo (USA) on "paternity" of the discovery of HIV.
- 1985: first HIV tests on the market.
- 1986:
 - Identification of a second type of HIV: HIV-2;
 - first ART treatment available: zidovudine.
- 1996: Discovery of protease inhibitors, which will revolutionize the prognosis and management of HIV infection as part of triple therapy (HAART).
- 2000:
 - availability of HAART in southern countries following the Durban International Convention;
 - lawsuit brought by 39 pharmaceutical companies against the South African government which had started manufacturing generic;
 - Launch of the global program "Access" signed by five pharmaceutical companies and five global organizations to make available to the southern countries ARVs at discounted prices from 80 to 95%, for considering the annual treatment costs between 100 and € 200 (against € 1000 monthly in industrialized countries).
- 2008: Award of Nobel Prize in Medicine to Professor F. Barre-Sinoussi and Montagnier L.

There is no cure for HIV infection; however, people receiving ART therapy, can reach a normal life-span and ART also limit transmission of HIV.

Unfortunately only 17 million people benefit from this treatment and nearly half of those infected are not aware of it.

ART therapy was introduced in 1996, before that the life expectancy was about 15 months after AIDS diagnosis, Thanks to this discovery, death rate started to decline, reaching a plateau around 1998 [4]. The use of ART in the mother also decreased mother-child transmission from more than 30% to less than 1% [2].

The distribution of ART treatment for infected person is quite unequal, with 44% for Americas region, 37% for Africa, 33% for South East Asia and Eastern Pacific region, 22% for European region and only 10% for eastern Mediterranean region [5].

Between 2000 and 2015, new HIV infections have fallen by 35%, AIDS-related deaths have fallen by 24% due to international efforts [4]. And maybe more life are going to be saved with the “treat all” new recommendation of WHO—*which specifies that* anyone infected with HIV should begin antiretroviral treatment as soon after diagnosis -- with these new guidelines from September 2015, WHO removes all limitations on eligibility for antiretroviral therapy (ART) [6].

Human immunodeficiency virus type 1 (HIV-1) infection is by far more responsible for the global AIDS pandemic, HIV type 2 (HIV-2) is mainly found in West Africa but has spread to other parts of the world ,in Europe, India, and the United States with migrations, it has different features of viremia, clinical findings, diagnosis and treatment [7].

HIV is transmitted by exchange of body fluids. In Sub-Saharan countries transmission occurs mostly via heterosexual intercourse, compared to highly developed countries where MSM transmission predominates. The infection due to blood and blood-derivates transfusion is today almost none due to careful monitoring of blood products .The mother-child transmission has been significantly reduced with the help of ART therapy for mothers. [4]Concerning Global epidemiology of HIV, Africa remains the most affected continent, with 25.8 million people affected (70 % of cases) [1-6].

Overview of Croatia



Figure 1: Map of Croatia [8]

The Republic of Croatia is an emerging and developing country which has a high income economy, according to International World Bank [9].

It is located in Southern Eastern Europe and is bordered by Bosnia, Serbia, Hungary and Slovenia, with a huge coastline of 1778km with the Adriatic Sea and about thousands islands (figure 1).

Concerning its recent history, it was part of Yugoslavia and declared its independency in 1991, which led to a war until August 1995. During the period 1991-1995 Croatia lost about 10% of its population because of migration and death due to the war. We can say that Croatia has experienced many socio-economical changes in the past 30 years passing from a communistic system to a Republic, entering the EU in July 2013 and experiencing the consequences of the world economical actual crisis since 2007; Today the unemployment rate is about 18%.

It is important to notice that services sector account for 64% of Croatian Gross Domestic Product with tourism services for 20% , exponentially developing (10millions visitors every year) , industrial sector for 29% and most of the rest is made by agriculture (6%) [10].

The population is 4,3 million inhabitants, mainly living in Zagreb, Split, Rijeka and Osijek and a low migrant prevalence (1,5 migrant per 1000 inhabitant, 90,4% of Croats)

According to the 2011 census 86.28% of Croatians are Catholics, while Orthodox Christians make up 4.44% of the population, Muslims 1.47 %, and Protestants 0.34% of the population. 3.81% of Croatians are not religious and atheists, 0.76% are agnostics and sceptics, and 2.17% are undeclared.

The education level is his high with a literacy rate of 99,65% for the 15-24 generation [9].

Weak cultural, social and political cooperation exists among the Country for Lesbian Gay and Bisexual Transgender acceptance, making prevention of HIV even more challenging, but Croatia denotes itself from other countries of ex-Yugoslavia being more liberal:

- About 90% of the population is Catholic and Catholic Church has a strong influence concerning the decision making in the country which can delay the population's behavior toward HIV infection and HIV infected persons (eg: Instauration of sex education in High School was not approved by Catholic Church and it still regulates what is taught at school).

- The history of the "Gay Pride" makes a good parallelism with the evolution of people state of mind in the country: The first one took place in 2002 (VS 1969 in NYC and 1971 in France) in a tense atmosphere .It was not a relaxing march: The pride master and 20 participants were injured. In 2006, a so-called "International Pride" took place in Zagreb, hosting in the Capital 13 countries of South- Eastern Europe where such event would have been impossible to organize. In 2011, the first pride occurred in Split and was chaotic: 300 participants VS 10000 opponents throwing rocks, cans and attacking them. After that event, in 2011 the first Pride Week happened in Zagreb, it was a way of empathizing what happened in Split. Currently "Gay Pride" marches are held without incidence in both Zagreb and Split.

Epidemiology of HIV in Croatia

Croatia has a very low prevalence of HIV/AIDS, with 1325 cases reported in the country from 1985 to 2015. Croatia had also one of the smallest rates of new HIV diagnoses in 2014 (figure 2) [11].

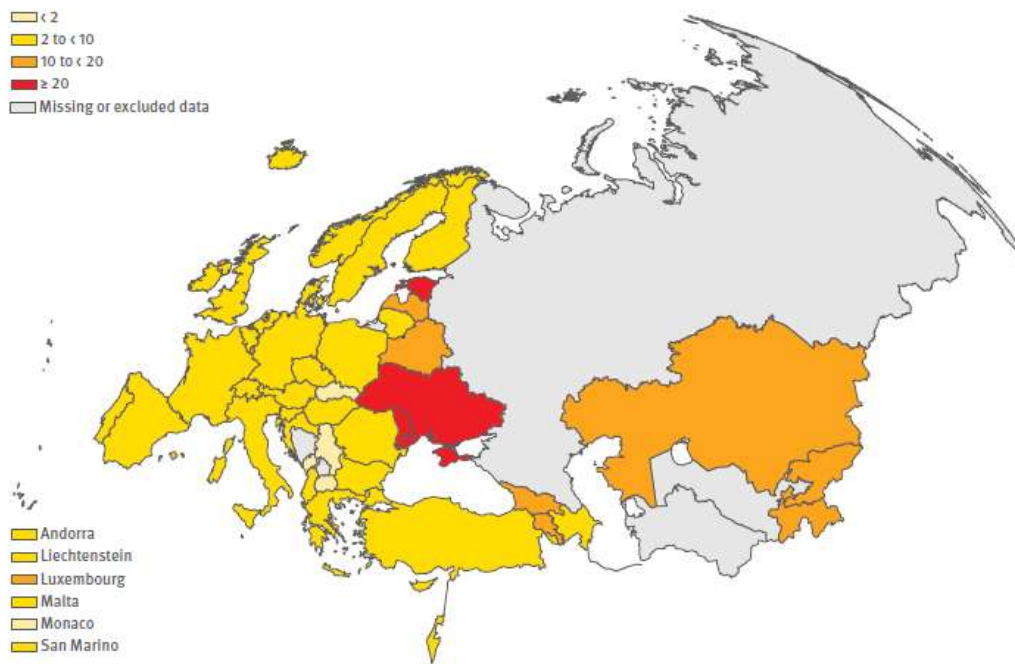


Figure 2: The rate of newly diagnosed individuals per 100 000 inhabitants in 2014 [11]

The first cases of HIV were documented in October 1985, from labor migrants who returned from Western Europe and seafarers. At that time Croatia was still part of Yugoslavia, and it was decided that HIV-infected patient should be treated in one of the three cities: Ljubljana, Belgrade or Zagreb, with only the 2 first Capitals performing HIV positive testing. In 1987 an extensive prevention campaign and prevention committee was started in Zagreb and the first measures for prevention were started in 1983 even before the first case in Croatia, it was based on education of Health workers and the general population. The first HIV testing and reference center in Croatia was established at the University Hospital of Infectious Diseases in 1992.[12-13] . At the beginning, the National AIDS Committee had very limited funds (up to 20 000 USD per year) for prevention activities. HAART therapy was introduced in April 1998 [15].

Croatia has a centralized system of treatment and care for HIV infection, all patients are treated in Zagreb UHID and only UHID can provide ART.

For a better regulation, Physicians, County Health Institutes and Reference Center for HIV (UHID Fran Mihaljevic) report every case or death related to AIDS to the Croatian Public Health Institute. Laboratory reports on any performed HIV testing and all the positives results are also reported.

All blood products are also tested since 1987 [14].

Regarding HIV treatment, Croatia can be considered a country with an individual approach to combination antiretroviral therapy (CART). Choice of drugs is limited (figure 3).

Antiretroviral drugs are only given from the hospital pharmacy at UHID. Health care is free of charge for patients; costs of antiretroviral and monitoring are fully covered since 1998. An individual can be tested in 23 voluntary counseling and testing sites (VCT), tests are anonymous and free.

Surveillance activities for HIV/AIDS epidemic are performed since 1985. [12,14].

For the treatment, the preferred combination to start with is:

- 2NRTI + 1NNRTI or 2NRTI + 1PI or 2NRTI + II
- Preferred NRTI: ABC/3TC or TDF/FTC
- Third drug: EFV, DRV/r, RAL, DOL [12]

Antiretrovirals on the Drug List, Red=available in Croatia

Fusion	NRTI	NNRTI	PI	II
ENF	ZDV	NVP/NVP-XR	SQV	RAL
	ddI	EFV	r	DTG
antiCCR5	d4T	ETV	IDV	
Maraviroc	3TC/FTC	RPV	NFV	
	ABC		LPV/r	
ZDV/3TC/ABC	TDF		fAPV	
TDF/FTC/EFV			ATA	
TDF/FTC/RPV	ZDV/3TC		TPV	
TDF/FTC/ELV/c	3TC/ABC		DRV/DRV/c	
ABC/3TC/DTG	TDF/FTC			
TAF/FTC/ELV/c				

Source: UHID, 2016

Figure 3: Antiretrovirals on the Drug List, Croatia, 2016 (in red=available in Croatia) [13].

Since 1997, an electronic database is used by UHID, collecting data about HIV cases. The software respects secret of medical information. [12-14-15].

Concerning regulation of the disease, the “National Aids Health Protection Program” (NAHPP) and the “Act on Protection of Population from Infectious Diseases” put effort in controlling and preventing the disease, while the *Infectious Disease Epidemiology Service of the National Public Health Institute (CNIPH)* monitor the status of the infection, provides information about testing, transmission route, comorbidities and deaths and enter the data in the Croatian National HIV/AIDS Registry.

These Data are also used

- by the country to assess epidemiologic status and provide funds to the NAHPP and
- by the WHO to evaluate worldwide AIDS pandemic.

Additionally, Non-Governmental Organizations programs help in improving the surveillance, of AIDS in Croatia (some examples of NGOs: -NGO Iskorak, a LGBTIQQ group for promotion and protection of different sexual orientations,- The “Global Fund to Fight AIDS, Tb and Malaria”, -NGO Help, a youth help organization

-NGO Terra, -PRO-REPRO for education in, promotion and Protection of reproductive health, -The Croatian Red Cross, -International Organization for Migrations, -Croatian Association for HIV (CAHIV),...) [15]

Today recent data are showing that a MSM mode of transmission is predominant. From laboratory registries, an average of 180 000 persons are tested each year, and around 100 HIV positive tests are registered annually [13].

As previously mentioned, the HIV/ AIDS situation has been monitored in Croatia since 1985. To compare the evolution of the epidemics later on in our work, we can have a look at data from 1985 until December 2015 (figure 4).

HIV infections: 1325

AIDS cases: 459

Deaths: 228 (17%)

Women 171 (13%)

Children (perinatal) 15 (1.2%)

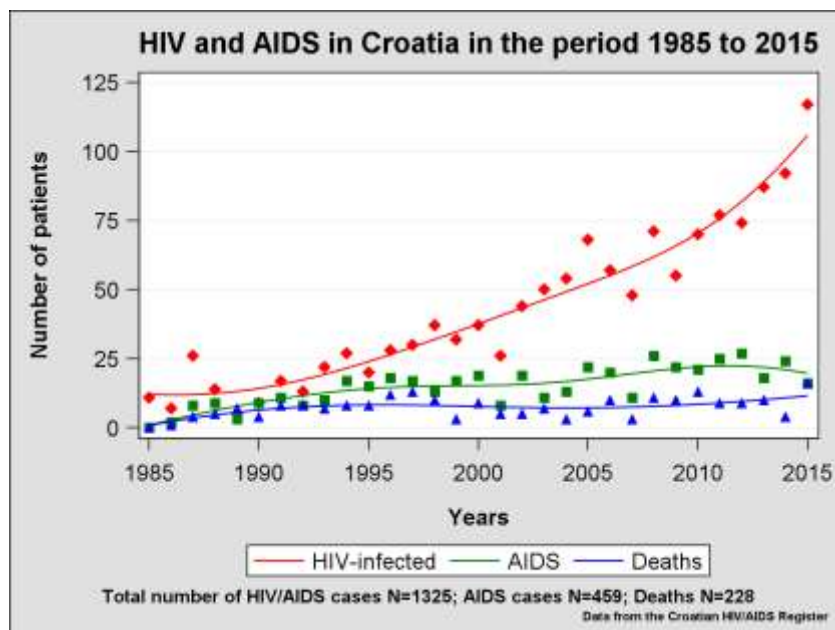


Figure 4: HIV, AIDS and related Death in Croatia from 1985 to 2015. Data from the HIV/AIDS Register from the Croatian Institute of Public Health.

Like in most other countries, men were more infected than females, the predominant mode of transmission were by MSM intercourse (61.7%);heterosexual route outside a stable relationship (18.4%);heterosexual with a steady partner (8.6%); IVDU (5.5%); haemophiliacs previously infected(1,1%);mother to child (1,1%); blood product contamination after 1985 (0,2%) and 3.4% unknown origin (figure 5)[13].

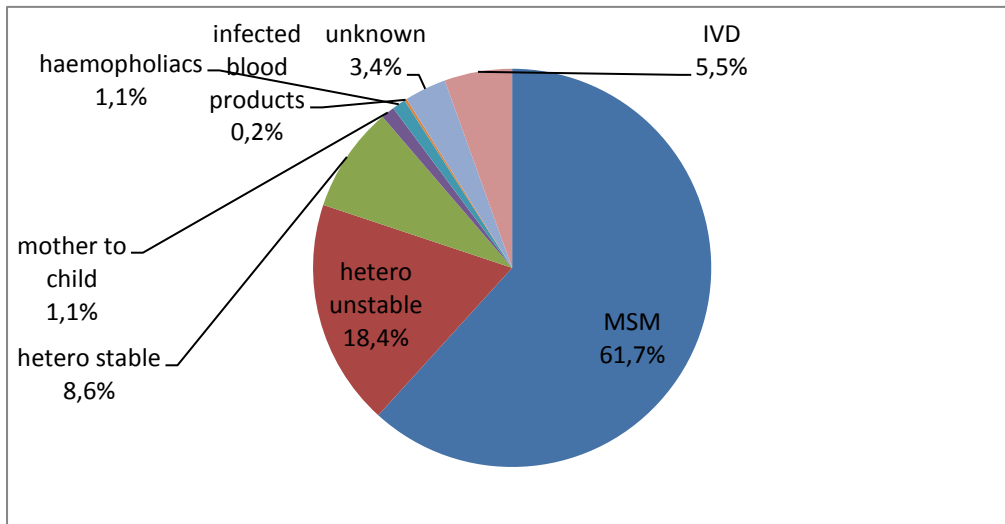


Figure 5: Probable mode of transmission of HIV in Croatia in the period 1985 to 2015. Data from the HIV/AIDS Register from the Croatian Institute of Public Health. [13].

The prevalence and mode of transmission were not the same according to the region of the Country (figure 6):

- the prevalence is higher in coastal areas and in the Capital Zagreb
 - in the South of the coast, the main mode of transmission was found to be MSM intercourse while in Dalmatia (middle) part it was by heterosexual way (men who work abroad, mostly sealers, who infected their partners) and in Istria (North) part the main mode is IVDU.
- With the evolution of the country, the exponential development of tourism, the new immigration wave and the entrance inside UE in 2013, many factors are adding to each other and changing the epidemiology of HIV in the country.

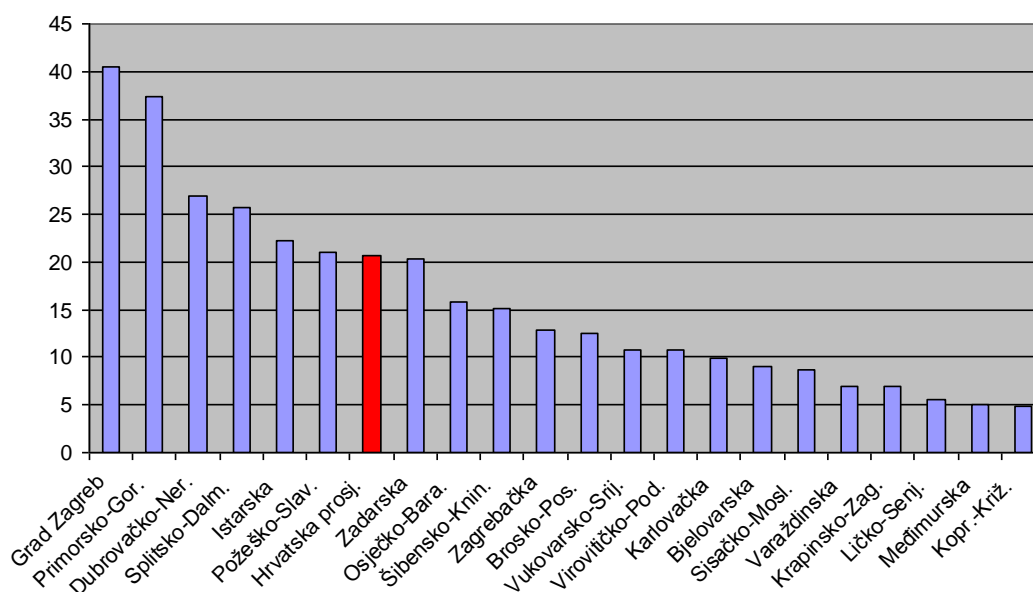


Figure 6: Prevalence of HIV in different part of Croatia (14). Data from the HIV/AIDS Register from the Croatian Institute of Public Health.

Objectives

The main objective of this paper is to describe the characteristics of HIV-infected persons entering care in Croatia, from 01/01/2007 until 31/12/2015. Specific objectives are:

- to make a review of main characteristics of people entering care in Croatia (country of birth, age, gender, way of transmission, area of residency) and-to analyse respective frequencies of clinical presentations at diagnosis.
- to analyse the frequency of concomitant AIDS conditions at entry into care
- to study the CD4 count at presentation and analyse late presentation (CD4 count < 350 cells/microl) and very late presentation (< 200 cells/microl)
- to analyse the trend in CD4 cell count at inclusion and the trend for late presenters
- we compared the frequency of new HIV cases in Zagreb compared to other part of the country
- we also analysed factors related to late presentation to care

Methods

Ethics statement:

The study is part of the project of the Ministry of Science and education for which Ethical Approval has been granted both by the University Hospital for Infectious Diseases (UHID), Zagreb, Croatia and University of Zagreb Medical School.

The data were studying from an anonymous database

Definitions

Presentation to care

Late HIV diagnosis was defined by a patient presenting with a CD4+ T-cells count < 350 cells/mm³. Very late presentation was defined with a CD4 cell count < 200 cells/mm³ or clinical AIDS.

The 1993 AIDS Surveillance Case Definition of the U.S. Centers for Disease Control and Prevention [16].

This staging is a combination of both clinical findings and CD4c count at presentation.

CD4 count categories		Clinical categories		
per mm ³	%	A	B	C
>499	29	A1	B1	C1
200-499	14-28	A2	B2	C2
<200	<14	A3	B3	C3

Table 1: description of Clinical categories of the classification

Category A	Category B	Category C
<ul style="list-style-type: none"> ▪ asymptomatic HIV infection ▪ persistent generalized lymphadenopathy (PGL) ▪ acute (primary) HIV infection with accompanying illness (sometimes known as seroconversion illness) or history of acute HIV infection 	<ul style="list-style-type: none"> ▪ Bacillary angiomatosis, ▪ candidiasis in the mouth and/or upper throat, ▪ candidiasis of the vagina and/or vulva ,persistent, frequent, or which responds poorly to treatment, ▪ cervical abnormalities of moderate or severe extent or cervical cancer, ▪ constitutional symptoms : fever (38.5°C) , diarrhea > 1 month ▪ herpes zoster (shingles) involving at least 2 distinct episodes or > 1 dermatome ▪ idiopathic thrombocytopenic purpura, ▪ listeriosis, ▪ oral hairy leukoplakia, ▪ pelvic inflammatory disease, ▪ peripheral neuropathy 	<ul style="list-style-type: none"> ▪ <i>Candida</i> in the esophagus, trachea, bronchi, or lungs ▪ invasive cervical cancer ▪ coccidioidomycosis ▪ <i>Cryptococcus</i> outside the lungs ▪ cryptosporidiosis with diarrhea lasting for >1 month ▪ CMV disease outside the liver, spleen, or lymph nodes ▪ CMV retinitis ▪ herpes simplex virus causing prolonged skin lesions or involving the lungs or esophagus ▪ <i>Pneumocystis jiroveci</i> (formerly <i>carinii</i>) pneumonia (PCP) ▪ recurrent bacterial pneumonia ▪ progressive multifocal leukoencephalopathy (PML) ▪ recurrent <i>Salmonella</i> septicemia ▪ toxoplasmosis of the brain ▪ HIV wasting syndrome

Inclusion and exclusion criteria

We included into the analysis all the patients entering UHID care from 01 January 2007 until 31 of December 2015 with documented HIV infection.

For the risk factors and trend of median, late presentation and very late presentation the inclusion criteria were adult age (>18y old) and those who haven't been in care in another

country. Because of the low number of persons who acquired HIV in a non-sexual way, in the analysis of factors related to late presentation to care we included only those with sexual transmission.

Methods

-The data was collected from the electrons database at UHID.

For transmission mode we divided individuals in 5 groups:

- heterosexual contact
- MSM (Men who have sex with men)
- PWID (People who inject Drugs)
- MTC (Mother To Child transmission)
- Unknown

Compared to the previously presented data, we didn't have a group of "infected with blood or blood products", because we didn't find a single person infected that way, for the period 2007 to 2015 There was only one person who reported both MSM and IDU risk and was classified as MSM. There were 3 persons who reported both heterosexual and IDU risks. All 3 were classified as IDU.

Results

A total of 731 persons entered care at UHID for HIV/AIDS in the period 2007-2015. Of those 731 persons 44 were coming from abroad and were already diagnosed , so in total there was 687 patient entering care in Croatia for the first time from 2007-2015.Of 731 entering care 725 were adults (> 18 years) and of 687 who entered care for the first time 682 were adults (> 18 years).

The number of newly diagnosed persons is still very low: 2,23 cases per /100000 in 2014.

Patients coming from abroad (figure 7)

44 persons who entered care in Croatia were already known to have HIV and previously treated in another country. 9 of them came from Germany, 7 from Spain, 5 from Africa (Cameroun, Somalia, Zimbabwe, Kenya), 4 from USA , the rest were coming from Italy, Switzerland, Slovenia, France, Japan , Nederland's and Montenegro.

In red shade we represent people coming from Europe (63,6%), in blue people from Africa (11,4%).

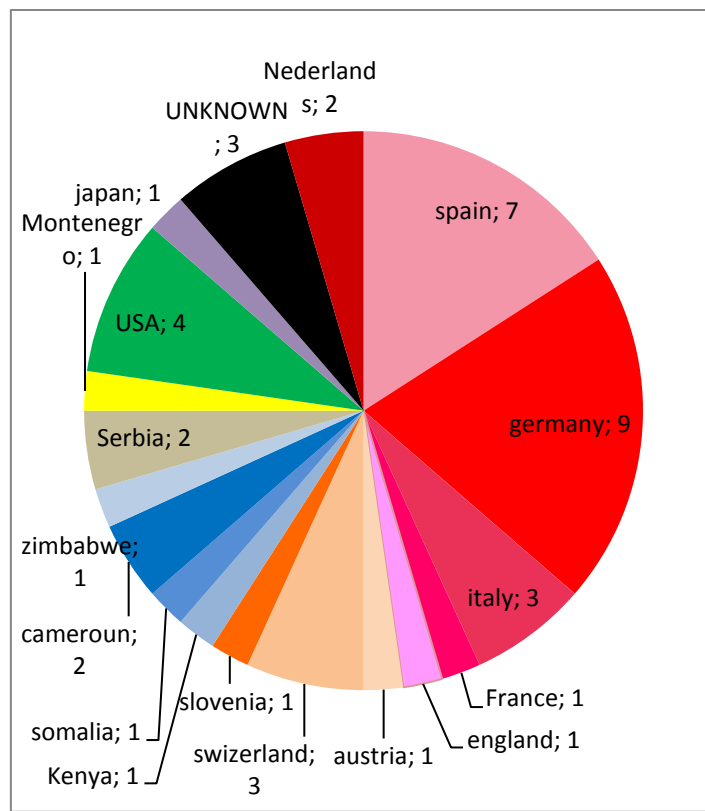


Figure 7: Number of patients coming from abroad in care in Croatia 2007-2015

HIV diagnosis from 2007 to 2015 (figure 8) at UHID

The number of HIV positive persons entering care doubled from 2007 (54 persons diagnosed) to 2015 (116 persons diagnosed HIV positive). According to the study, the rate of a new HIV positive test was 20,7 per million in 2013. The curve of Number of persons entering care at UHID for HIV for the first time (2007-2015) is quite stable from 2007 to 2011, and started to rise yearly from 2012, reaching its maximal value in 2015 (116 new persons entering care diagnosed).

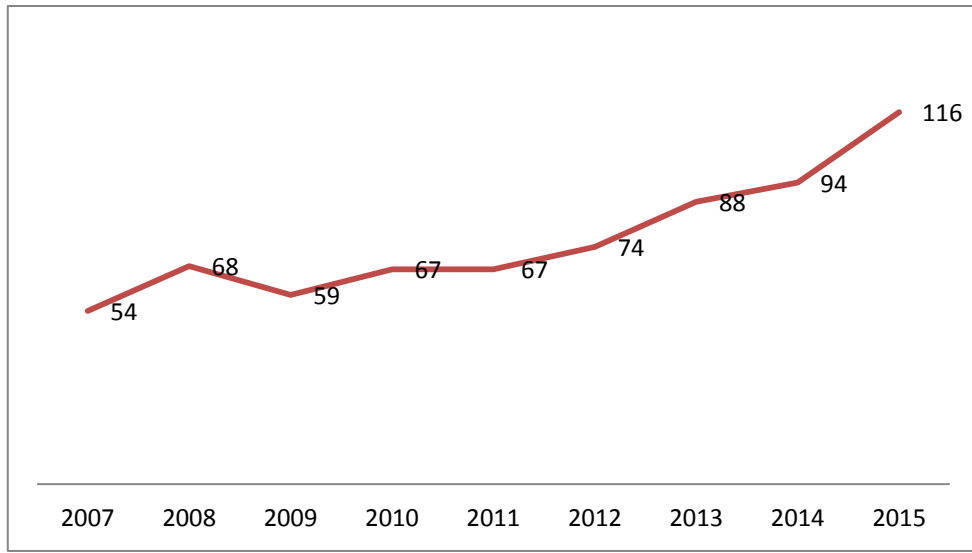


Figure 8: Number of persons entering care at UHID for HIV for the first time (2007-2015)

Study of age prevalence (figure 9)

The highest number of person diagnosed is in age distribution 30-39, followed by the ones 18-29. All curves are rising except people below 18, who are rarely diagnosed and stay at a low frequency (0 to 3 per year). People older than 50 are also rarely diagnosed but their number is increasing.

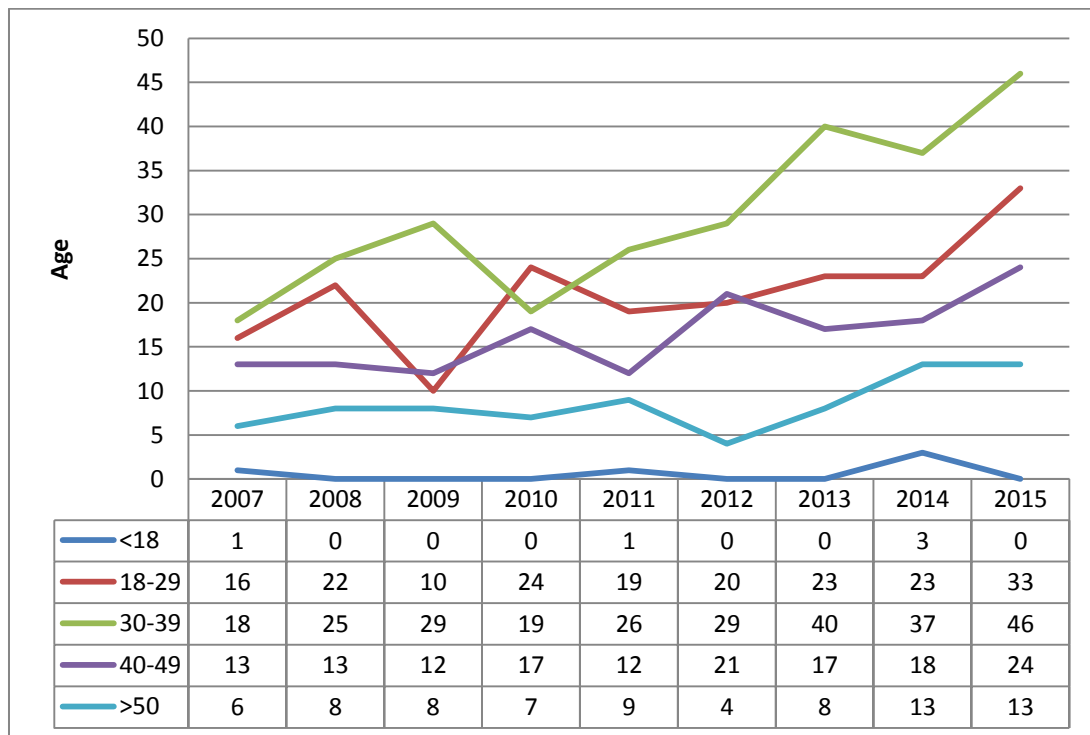


Figure 9: Age distribution of people infected by HIV at first presentation to care

Gender

From 2007 to 2015 the number of women entering HIV care was low (1 to 10 women per year); between 5 to 10% of newly diagnosed persons are women . In total there were 51 cases of women infected from this period of time which represents 7,4% of new HIV diagnosed persons from 2007 o 2015.

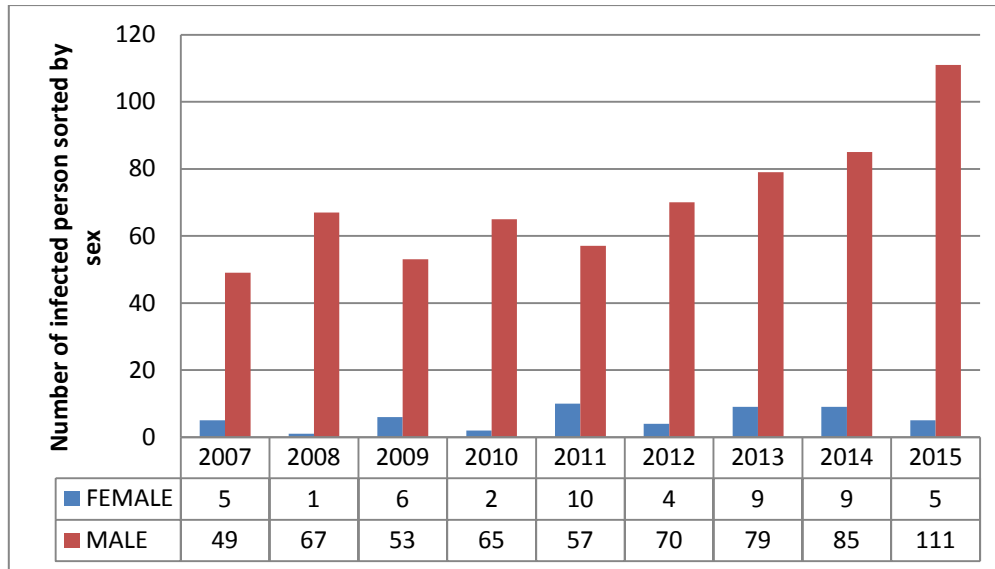


Figure 10: female-male distribution of HIV in 687 persons entering care at UHID for the first time

Mode of transmission (figure 11 and 12)

For the question of transmission route, we got the following results (figure 12): 80% was consequence of MSM contact, 15% heterosexual contact, about 2% IDU , almost none for MTC (only 3 cases from 2007 to 2015) and not a single case of accident with blood product: it decreased from 2% to not a single case this last 9 years.

By looking at figure 11 and table 2, we can see that the number of heterosexual transmission cases stayed quiet stable from this period (8 to 16 new infection), like PWID (0 to 3 cases each year), MTC and unknown modes. An evolution is only seen from 2011, for MSM mode of transmission, which increased dramatically year after year, in correlation with figure 8, “increasing of HIV diagnosed patients in general population”.

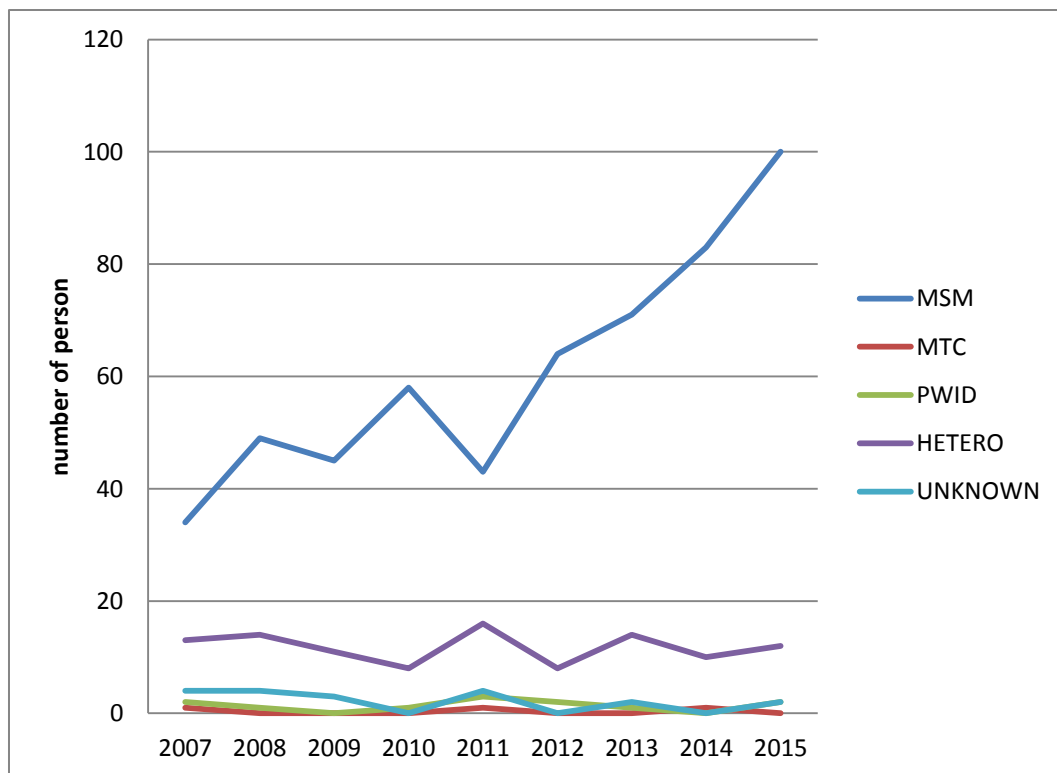


Figure 11: Mode of transmission of HIV from in persons entering care in the period 2007 to 2015 (N=687).

Tableau 2: mode of transmission of HIV from 2007 to 2015

MODE	MSM	MTC	PWID	HETERO	UNKNOWN
YEAR					
2007	34	1	2	13	4
2008	49	0	1	14	4
2009	45	0	0	11	3
2010	58	0	1	8	0
2011	43	1	3	16	4
2012	64	0	2	8	0
2013	71	0	1	14	2
2014	83	1	0	10	0
2015	100	0	2	12	2

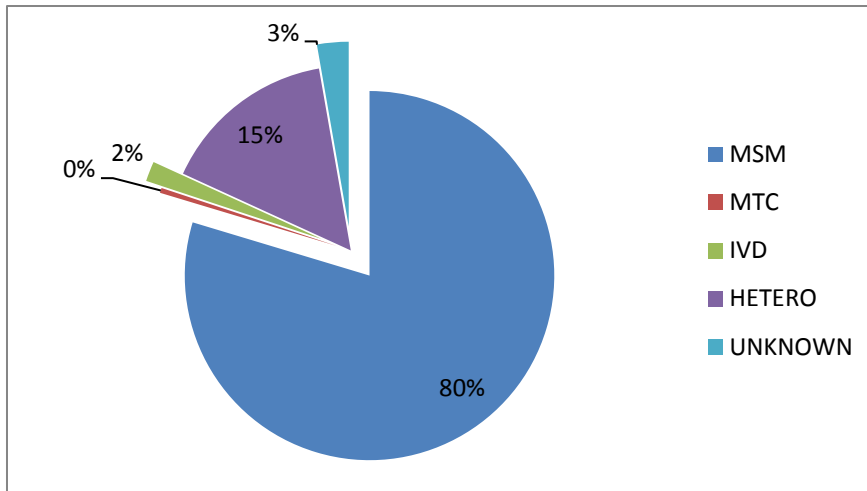


Figure 12: The proportion of persons entering care according to mode of transmission from 2007 to 2015

The problem of late presentation to care

Diagnosis at first presentation

Figure 13 presents the stage of HIV infection at entry into care using “The 1993 AIDS Surveillance Case Definition of the USA Centers for Disease Control and Prevention” staging system.

The green area is representing presentation to care with >500 cells/umol.

Between 2007 and 2015 the presentation A2 (26,9%)>A1 (22,1%)>C3 (21,2%) were accounting for 70% of first presentation to care.

37,4% patient came at first presentation with CDC <200 cells /umol (A3+B3+C3, red area), 38,6% with CDC 200-500 cells/umol (A2+B2+C2=blue area), 24,2% with CDC >500 cells/umol (A1+B1+C1=green area).

We can see that the year 2010 and 2011 had the highest proportion of persons with very late (A3, B3, C3) presentation to care ;2011 was the year with the least of those presenting with CD4 cells > 500 per microliter (12%) and one of the most very late presentation (40,4%).

Today recent data are suggesting an improvement and the results are now at the lowest point: 2015 was the year with the least cases of first presentation at very late stage (22,4%) compared to a mean of 35% for the last 9 years and 39% for 2007).

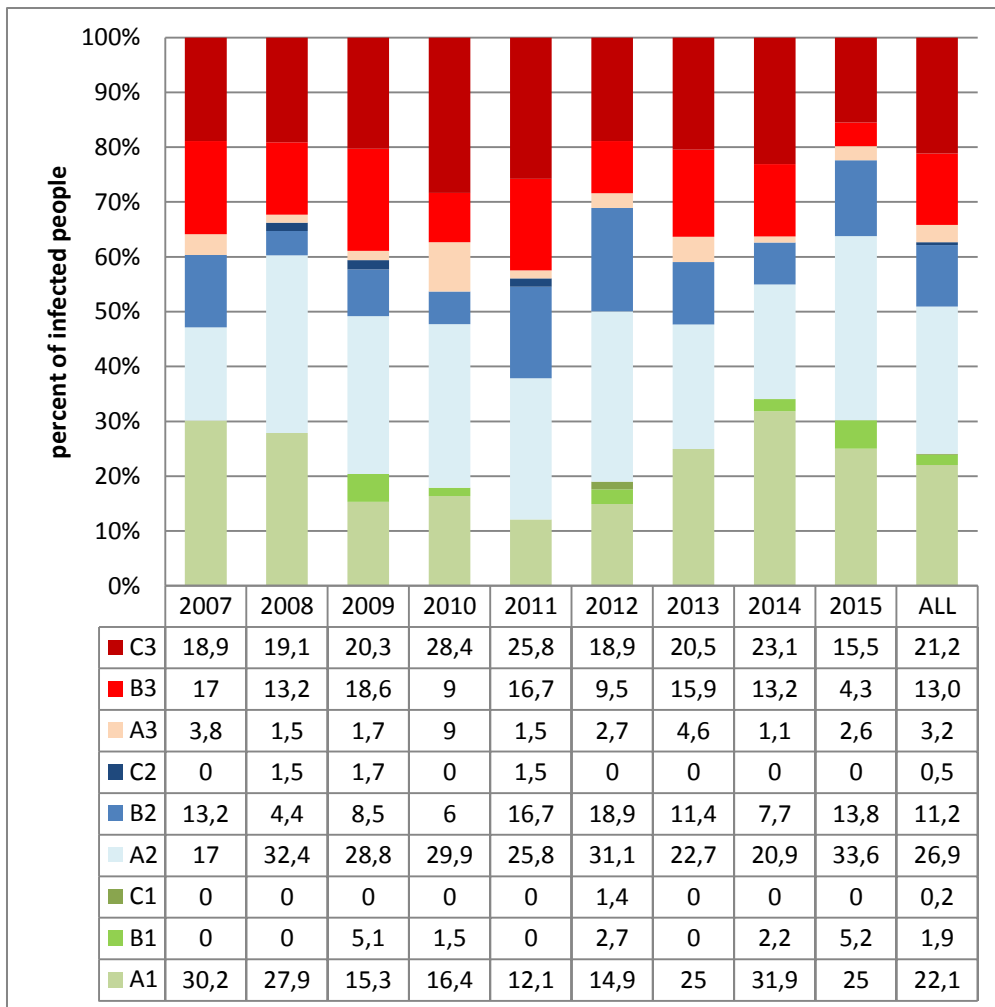


Figure 13; Evolution of Staging at first presentation to care in adults (N=682) from 2007 to 2015 (results in percent)

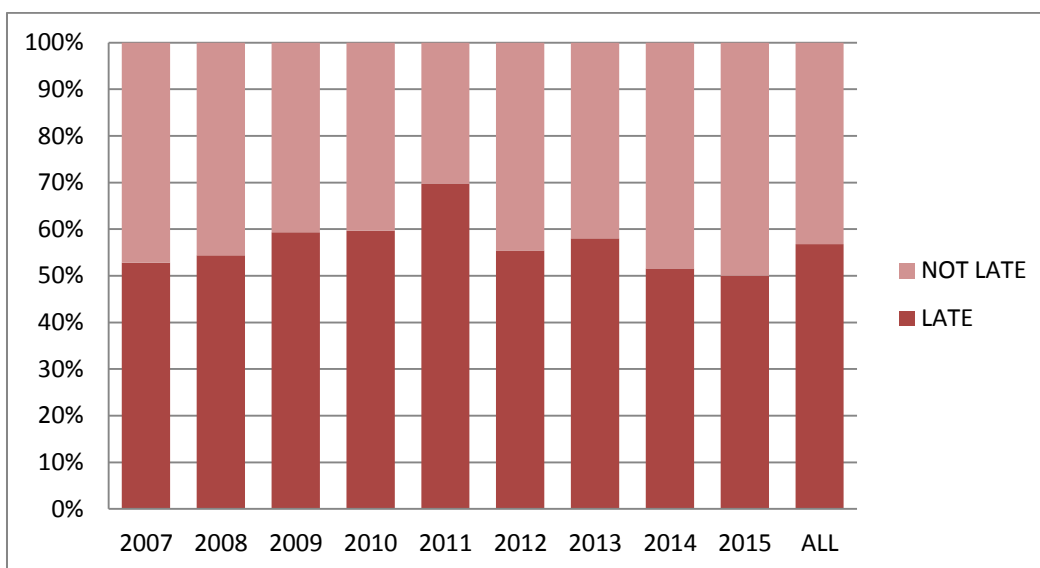


Figure 14: Late (CD4+ cell counts < 350 per microliter) and not late presentation to care in the period 2007 to 2015 (N=682).

The chart on figure 14 is showing the variation between late and not late first presentation in care for adult patients. During the overall 9 years intervall, the results were quite stable with a mean of 56% late presentation. Like on the other data 2011 was the year with the most late presentation (69%) and 2015 with the least (50%).

The chart 15 is giving details for late presentation: giving results for late and very late first presentation in care among patients coming from this 9 year period.

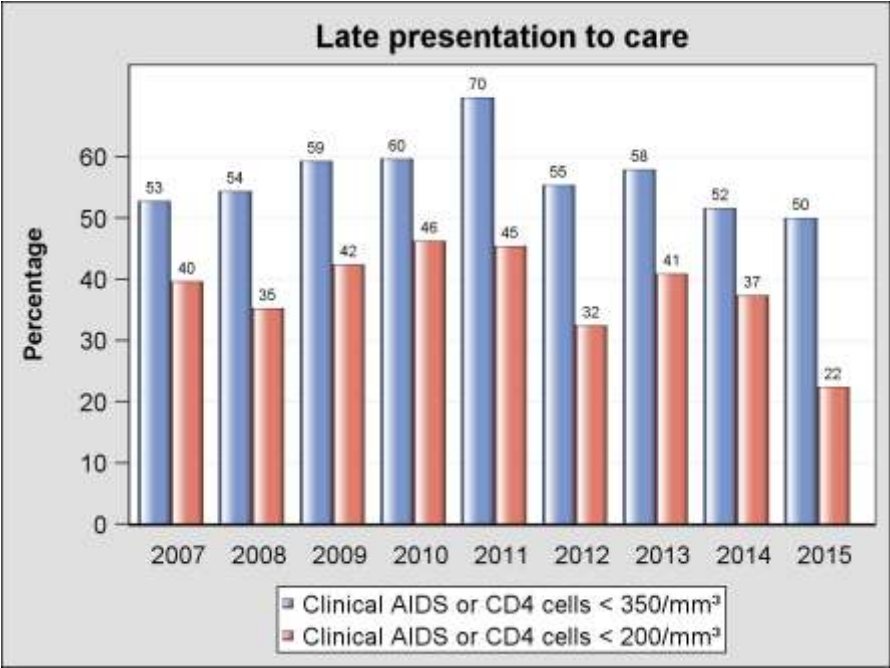


Figure 15: analysis of late presentation to care (late VS very late)

By looking at the median CD4 cell count on figure 16, we can say that the curve is evolving toward an increase of CD4 cell count at first presentation since 2011, which confirm results of figure 13, 14 and 15.

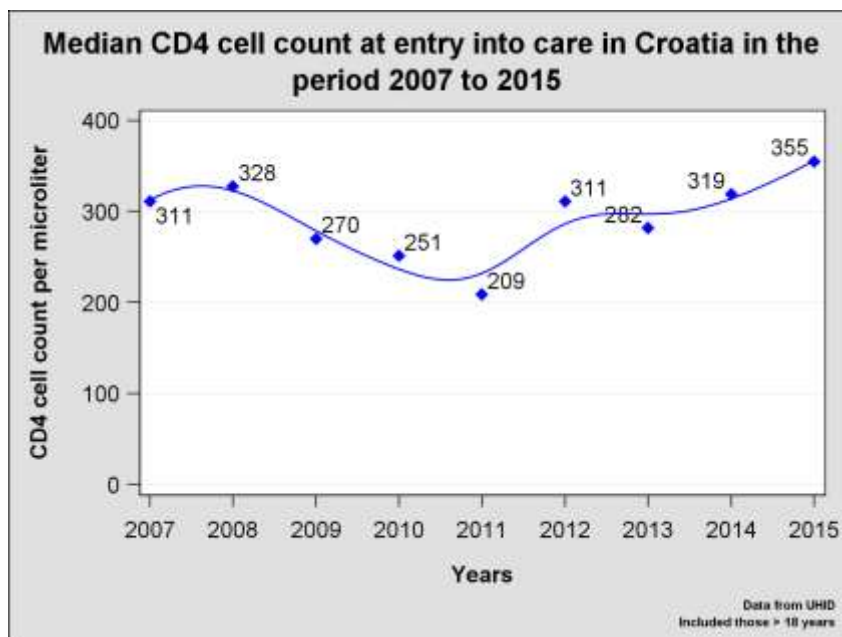


Figure 16: median CD4 cell count at entry into care from 2007 to 2015 in Croatia

Factors related to late presentation to care from 2007 to 2015

We also examined factors related to late presentation to care (CD4 cells less than $<350/\text{mm}^3$ or clinical AIDS). This analysis was done in persons who acquired HIV by sexual intercourse (N=653). Factors associated with seeking care with CD4 $<200/\text{mm}^3$ were analysed by ordinal logistic regression. For all tests, we considered a P value <0.05 as statistically significant. On bivariable analysis -female gender, -not living in Zagreb, -having acquired HIV by heterosexual intercourse and -older age were associated with late presentation to care (Table 3). On multivariable analysis -gender was not significantly associated with late presentation to care. So only -not living in Zagreb (OR = 1.70 (1.22-2.38)); -heterosexual Intercourse (OR= 2.20 (1.14-4.24) and -older age (OR= 1.84 (1.53-2.21)) were considered as risk factors for late presentation to care.

The findings were similar when the analysis was done in males only (Table 4) , risk factor for late presentation were -not living in Zagreb (OR = 1.70 (1.22-2.38)); -heterosexual Intercourse (OR= 2.18 (1.13-4.44) and -older age (OR= 1.85 (1.53-2.23)).

Table 3. Factors associated with late presentation to care^a in 653 patients entering care at the University Hospital for Infectious Diseases, Zagreb, 2007 to 2015.

Variable	No.	Bivariable analysis		Multivariable analysis ^b	
		OR (95% CI)	P-value	OR (95% CI)	P-value
Gender					
Male	609	ref.	0.048	ref.	0.702
Female	44	1.96 (1.01-3.83)		0.83 (0.33-2.11)	
Living in Zagreb					
Yes	265	ref.	< 0.001	ref.	0.002
No	388	1.96 (1.43-2.70)		1.70 (1.22-2.380)	
Transmission					
MSM	547	ref.	< 0.001	ref.	0.02
Heterosexual	196	2.67 (1.67-4.26)		2.20 (1.14-4.24)	
Age (per 10 years)	653	1.90 (1.59-2.27)	< 0.001	1.84 (1.53-2.21)	< 0.001

^aIncluded were persons who acquired HIV through male to male sex and those with heterosexual mode of transmission.

^bThe analysis was also adjusted for the calendar year (nonsignificant). MSM, men who have sex with men.

Table 4. Factors associated with late presentation to care^a in 609 male patients entering care at the University Hospital for Infectious Diseases, Zagreb, 2007 to 2015.

Variable	No.	Bivariable analysis		Multivariable analysis ^b	
		OR (95% CI)	P-value	OR (95% CI)	P-value
Living in Zagreb					
Yes	256	ref.	< 0.001	ref.	0.002
No	353	1.90 (1.37-2.63)		1.70 (1.21-2.40)	
Transmission					
MSM	547	ref.	< 0.001	ref.	0.021
Heterosexual	62	3.13 (1.67-5.81)		2.18 (1.13-4.22)	
Age (per 10 years)	609	1.90 (1.58-2.28)	< 0.001	1.85 (1.53-2.23)	< 0.001

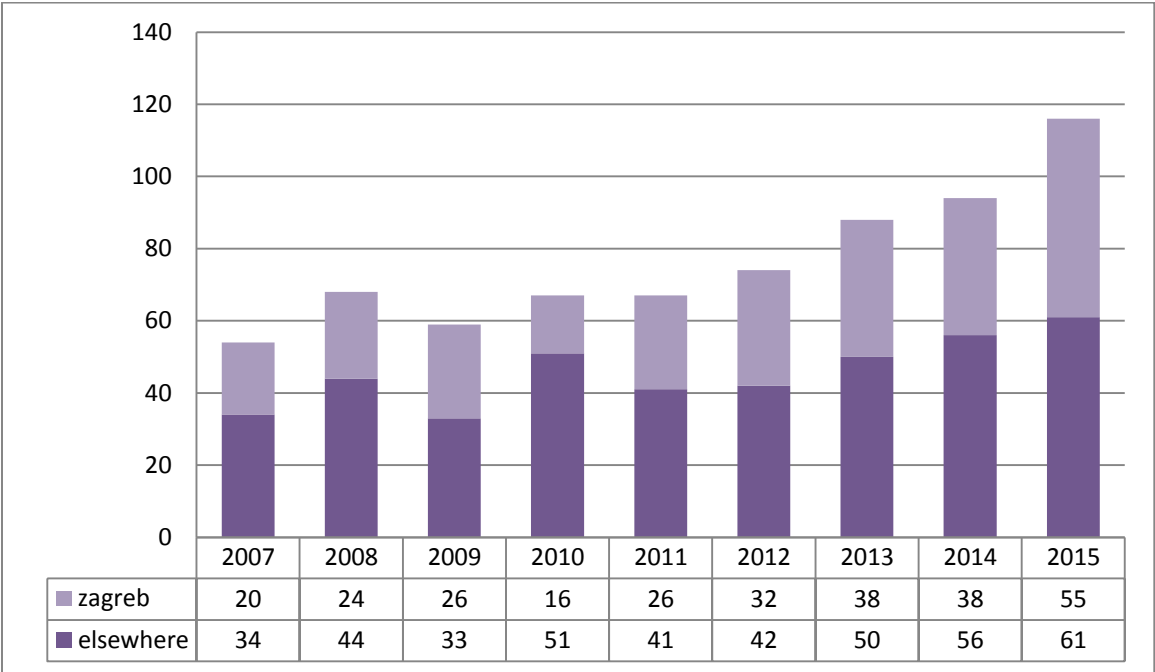
^aIncluded were persons who acquired HIV through male to male sex and those with heterosexual mode of transmission.

^bThe analysis was also adjusted for the calendar year (nonsignificant). MSM, men who have sex with men.

Proportion of people Living in capital Zagreb for first presentation to care from 2007 to 2015 (figure 17)

About 25% of the Croatian population live in Zagreb [9], we can expect there a lowest percentage of HIV diagnosed patients, confirmed by our data's: from 2007 to 2015 Zagreb

has always been the place where there was the lowest proportion of HIV diagnosed persons (for first presentation to care). These last years, we can also notice a slight increase in the proportion of patients entering care living in Zagreb.



	2007	2008	2009	2010	2011	2012	2013	2014	2015
Zagreb	37 %	35,3%	44,1%	23,9%	38,8%	43,3%	43,2%	40,4%	47,4%

Figure 17: Number of persons entering care compared by residence (Zagreb versus elsewhere).

Discussion

By analysing the number of persons entering care between 2007-2015, it was interesting to notice that the number of new HIV cases was slowly increasing till 2011 with a more pronounced increase afterwards (figure 7). This increase is predominately found among men who have sex with men. The increase may also be attributed to more testing in community-based centres which opened in 2013 and the development for STI services for MSM.

From 2007 to 2015, 44 people were coming from abroad to be treated in care, meaning that foreigners account for more than 6,5% people who entered care. From those people about 63% were coming from Europe and less than 18% from African countries. Most people were

coming from Germany, Spain and USA. Most of them were Croatians, who worked in the abovementioned countries before returning permanently to Croatia.

Concerning age distribution of people entering in care, all the age groups were showing an increasing of number of people diagnosed, except the one below 18, we can guess that this is partly due to the good MTC prevention and young people are also less likely to be detected: acceptance of homosexuality at this age is harder and first sexual contact would more likely be after 15. The most at risk age group is the one between 18 to 39 with peak prevalence for those 30 to 39. People older than 50 are also rarely diagnosed.

Concerning the gender (figure 9) results are not surprising, giving the type of epidemic in Croatia: 7,4% of infected persons during the period 2007 to 2015 were women while in other developed countries, the percentage is more likely to be between 15-40%. The low number of HIV infected women is explained by the low prevalence of immigrants from Africa, where the incidence of infected women is the highest. For comparison in France in 2013: 23% of 6200 people infected were women born from abroad and 15% women from France so in total 38% of infected person were women [20].

From figure 10, it is interesting to see an evolution in transmission mode: MSM transmission was found to be rising since 2011. The dominant mode of transmission was sex between men, reaching 80%, so almost two times more than for the period 1985-2007 which was 48%: it reveals probably a better acceptance of homosexuality in the country in correlation with its evolution as well that the reason mentioned above: a better screening of MSM.

Infected blood products and haemophiliacs way of transmission completely disappeared, showing the great efficiency of the testing of blood products performed since 1987. There are also only a few new HIV infections among people who inject drugs probably because of the needle exchange programs as well as opioid substitution programs.

MTC transmission was found in only 3 children his last 9 years, showing a good control of HIV in pregnant women even though there is no systematic HIV screening in pregnant women.

From the results of figure 12, 13, 14, 15 we saw that 56% of patients included in care for the first time had late presentation. 2011 was the year with the most people presenting with late presentation (69%) and 2015 with the least (50%). From all these 4 curves we can ask ourselves why from 2007 to 2011 the curve of cdc at presentation was dropping constantly and what, in 2011, made the tendency to reverse. We can ask ourselves why the late presentation rate was so high and CDC count were so low for the years 2010-2012.

From the logistic regression analysis about risk factors of late presentation we found that “Not living in Zagreb” was also a risk factor for late presentation, which is easily explained by a better access to primary prevention, screening centers and access to care in the capital. Older age was associated with low CD4 at screening..This might be due to greater perceived risk of HIV infection by younger, thanks to the influence of the media and sexual education. In contrast, older patients might consider themselves less at risk of HIV infection with perhaps a lack of access to knowledge about STDs. Also heterosexual transmission was associated with greater odds for late presentation. This might be explained by the low perceived risk of heterosexual men and women for acquiring HIV. This study has several limitations and a limited number of explanatory variables that should be considered when interpreting the results. First, although most of our results are consistent with previous reports on late presentation to care, some potential risk factors such as educational level, knowledge/attitudes towards HIV, concept of religious practice and professional status, have not been studied. Second, the number of newly diagnosed HIV infections is relatively small so one should be cautious in making firm conclusions.

Conclusion

It is not necessary to remind that HIV is an exchange disease, so wider the border will open, wider the prevalence of HIV will be. It was useful to make a review of HIV in Croatia for these last 9 years, as a proof, the data for HIV are evolving toward those of other European countries: more people diagnosed in parallel with a earlier diagnosis, probably due to a better primary and secondary prevention.

Efforts for primary and secondary prevention should continue as good as clinical care and follow up of patients. This study is suggesting a positive involvement of prevention programs in earlier diagnosis of HIV. The prevention is focusing on screening targeted population (like testing in STDs center, or LGBT centers), extending screening tools to community hospitals and referring patients to UHID later on. The prevention in high school is also progressing, giving sexual education classes to the students, despite some religious and political pressure. Another important point is fighting stigma in order that people would seek for testing and declare their serological status without feeling ashamed.

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