Prevalence and Risk Factors of HCV/HIV Co-Infection and HCV Genotype Distribution in North-Eastern Poland

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1. Background

Highly active antiretroviral treatment (HAART) has resulted in a shift in the causes of morbidity and mortality to non-HIV related causes (1, 2). Liver disease is now a leading cause of death in patients with HIV (PLHIV, people living with HIV), mainly due to chronic hepatitis C (2-4). The prevalence and incidence of both human immunodeficiency virus (HIV) and Hepatitis C virus (HCV) have increased in Poland in the recent years (5-10). There were 18646 officially registered HIV cases between 1985 and 31st December 2014 (11). HCV infection incidence was 5.58 per 100,000 in 2011, with a marked increase in deaths reported in 2011 (9). Shared transmission routes are responsible for the high rate of co-infection, increasing both the complexity of disease management and the public health burden (3).

The prevalence of HIV/HCV coinfection varies greatly across the world, from as low as 0.9% in Istanbul, Turkey up to above 90% in Russia, Bielarus, Ukraine, Latvia, Estonia (12, 13). Polish data regarding HIV/HCV coinfection prevalence and genotype distribution are scarce and fragmentary (14-17). No studies are available regarding the risk factors of HCV infection among people living with HIV (PLHIV).

2. Objectives

The aim of this study was to analyze the prevalence of HCV infection based on anti-HCV serology and HCV-RNA and HCV genotype distribution in a group of PLHIV from one of the Polish HIV/AIDS reference centers located in north-eastern Poland. Risk factors associated with HCV infection and causes of death in our cohort were also studied.

3. Patients and Methods

Study participants were recruited from adult, HIV-1 infected patients, treated in HIV/AIDS outpatient clinic of medical university teaching hospital in Bialystok, north-eastern Poland, (Table 1) one of 17 HIV/AIDS reference centers in the country. A total of 836 patients were eligible for the study and 457 were enrolled. The main inclusion criterion was at least one anti-HCV test result available. No exclusion criteria were applied. Prospective data collection was started from 2008 for all patients on initial attendance and retrospectively for those who had their first visit prior to 2008 and was conducted until the end of December 2013. The collected...
clinical and epidemiological parameters included age, gender, ethnicity, duration of HIV infection, mode of HIV transmission [sexual: hetero- or homosexual, injecting drug use (IDU), mixed-sexual and IDU or unknown], history of incarceration, mental disorders and alcohol abuse, HBs seropositivity, date and cause of death. All patients were Caucasian. No data regarding the length and numbers of incarcerations were analyzed. The nadir CD4 T lymphocyte count, measured by flow cytometry, was collected. The study was approved by Medical University of Białystok ethical committee.

3.1. Serological Analysis
Anti-HCV antibodies and HBs antigen were measured at the baseline evaluation of all HIV positive individuals with commercial serological assays (Architect, Abbott).

3.2. Molecular Tests
HCV-RNA was analyzed using RT PCR. Cobas Ampli Prep and Cobas Taqman (Roche Diagnostics) were used with lowest detection limit of 11 IU/mL. HCV genotypes were determined using Versant HCV (Bayer Diagn, Germany).

3.3. Deaths Analysis
The analysis of deaths was based on clinical and autopsy data, where available. Information for patients who died in our center is complete. Where patients died at home or at other medical institutions, their family was contacted and asked to provide all the available data regarding patient’s death.

3.4. Statistical Methods
The data was analyzed with Statistica PL software (Statsoft, USA), using Mann-Whitney, Fisher and chi² tests. In the multivariate model, the following factors were included; age at first positive HIV Western Blot, heterosexual route of HIV transmission, HBs seropositivity, history of incarceration, injecting drug use, alcohol misuse and psychiatric disorders.

4. Results
Four hundred and fifty seven adult patients with HIV infection attending for treatment and care at the outpatient clinic, medical university teaching hospital, Białystok, north-eastern Poland were included. The median age was 38 years (ranged 23 - 72 years); most were male, 350/457 (76.6%) Table 1. Most patients acquired HIV infection via intravenous drug use, 264/457 (57.8 %). Anti-HCV antibodies were detected in 325 (71.1%), who were significantly younger with a median age of 37 years [ranged 23 - 57] compared to anti-HCV negative patients; median age 41.0 years [ranged 23 - 72], P = 0.04 (Table 1); positivity varied across age groups (Table 2). Univariable analysis revealed that male sex, younger age at HIV diagnosis and at the study time, injecting drug use as route of HIV transmission, alcohol misuse and a history of imprisonment were all factors associated with anti-HCV seroprevalence (Table 2). The history of psychiatric disease was not associated with a higher risk of HCV seropositivity (P = 0.07589). In multivariable analysis only;
- Being injection drug user [OD 125.02; 95% CI 10.76-1453.62; P = 0.0001],
- History of imprisonment [OD 4.454; 95% CI 1.141-17.394; P = 0.310] and
- Younger age at the HIV diagnosis [OD 4.454; 95% CI 1.141-17.394; P = 0.310] and
- Older age at the HIV diagnosis [OD 4.454; 95% CI 0.749-0.981; P = 0.025] were identified as risk factors for HCV infection.

4.1. Time Trends in HCV Infection
We analyzed the prevalence of HCV infection in two groups of PLHIV: those diagnosed before 2005 and those diagnosed during or after 2005. There was a significant decrease in HCV seroprevalence from 85.2% (218/256) to 53.2% (107/201) in the whole group analyzed (P = 0.0001). However, differences among patients who acquired HIV via different routes of exposure were not significant. Trends of decrease were observed in IDUs and IDUs/heterosexualy infected. HCV seroprevalence increased in MSM (men who have sex with men) and unknown way of HIV transmission, Table 3.

Table 1. Characteristics of the Study Participants

| Variables                  | Study Group | HIV/HCV Coinfection | HIV Monoinfection | P Value |
|----------------------------|-------------|----------------------|-------------------|---------|
| Number of patients         | 457         | 325 (71.1)           | 132 (29.9)        | 0.04    |
| Age, y                     | 38.0 (23 - 72) | 37.0 (23 - 57)       | 41.0 (23 - 72)    | 0.04    |
| Gender, male               | 350 (76.6)  | 264 (81.2)           | 86 (65.1)         | 0.0002  |
| Age at HIV diagnosis, y    | 29.1 (14 - 64) | 26.0 (14 - 51)       | 33.5 (17 - 64)    | < 0.0001|
| Length of HIV infection, y | 10 (0 - 26)  | 11.3 (1 - 26)        | 7.0 (0 - 21)      | < 0.0001|
| Nadir CD4, cells/µL        | 199 (4 - 1176) | 199 (4 - 1174)       | 199.5 (4 - 886)   | 0.2826  |

a Data are presented as No. (%) or median (range).
### Table 2. Prevalence, Co-Morbidities and Univariate Analysis of Risk Factors for Anti-HCV Seropositivity Among HIV Infected Individuals, North-Eastern Poland

| Variables                                      | Study Group Total | HIV/HCV co-Infection | HIV Monoinfection | P Value |
|------------------------------------------------|-------------------|----------------------|-------------------|---------|
| **Age groups at HIV Western Blot, y**          |                   |                      |                   |         |
| < 20                                           | 52                | 7 (13.5)             | 45 (86.5)         | < 0.0001|
| 20 - 29                                        | 224               | 178 (79.5)           | 46 (20.5)         |         |
| 30 - 39                                        | 127               | 87 (68.5)            | 40 (31.5)         |         |
| ≥ 40                                          | 54                | 39 (72.2)            | 15 (13.5)         |         |
| **Current age groups, y**                      |                   |                      |                   |         |
| < 30                                           | 41                | 20 (48.9)            | 21 (51.2)         | < 0.0001|
| 30 - 39                                        | 210               | 170 (81.0)           | 40 (19.1)         |         |
| 40 - 49                                        | 154               | 116 (75.3)           | 38 (24.7)         |         |
| ≥ 50                                          | 52                | 19 (36.9)            | 33 (63.5)         |         |
| **Gender**                                     |                   |                      |                   | 0.0002  |
| Male                                           | 350 (76.6)        | 264 (81.2)           | 86 (65.1)         |         |
| Female                                         | 107 (23.4)        | 61 (18.8)            | 64 (34.8)         |         |
| **HIV transmission**                           |                   |                      |                   | < 0.0001|
| IDU                                            | 264               | 258 (97.7)           | 6 (2.3)           |         |
| Sexual                                         | 151               | 112 (74.4)           | 39 (25.6)         |         |
| **HIV transmission detailed**                  |                   |                      |                   |         |
| IDU                                            | 264               | 258 (97.7)           | 6 (2.3)           |         |
| Heterosexual                                   | 111               | 28 (25.3)            | 83 (74.7)         |         |
| Homosexual                                     | 40                | 3 (7.5)              | 37 (92.5)         |         |
| IDU/heterosexual                               | 21                | 20 (95.2)            | 1 (4.8)           | < 0.0001|
| Unknown                                        | 21                | 16 (76.2)            | 5 (23.8)          |         |
| **Imprisonment**                               |                   |                      |                   |         |
| Yes                                            | 107               | 100 (93.5)           | 7 (6.5)           |         |
| No                                             | 345               | 222 (64.4)           | 123 (35.7)        | < 0.0001|
| **Alcohol abuse**                              |                   |                      |                   |         |
| Yes                                            | 62                | 52 (83.9)            | 10 (16.1)         |         |
| No                                             | 389               | 269 (62.2)           | 120 (37.8)        | 0.01748 |
| **Psychiatric disease**                        |                   |                      |                   |         |
| Yes                                            | 34                | 25 (73.5)            | 9 (26.5)          |         |
| No                                             | 418               | 297 (71.1)           | 121 (28.9)        | 0.07589 |

* Data are presented as No. (%) or number.

### Table 3. HCV Seropositivity Among PLHIV Diagnosed Before the Year 2005 or in the Year 2005 and Later

| HIV Mode of Transmission | Number of Anti-HCV, Positive/Total Number (%) | P Value |
|--------------------------|-----------------------------------------------|---------|
|                          | HIV WB Before Year 2005 | HIV WB Year 2005 and Later | |
| IDU                      | 183/185 (98.9) | 75/79 (94.9) | 0.0676 |
| Heterosexual             | 11/37 (29.7)  | 17/74 (23.0)  | 0.2914 |
| Homosexual (MSM)         | 0/6 (0)       | 3/34 (2.8)    | 0.6057 |
| IDU/heterosexual         | 12/13 (92.3) | 4/6 (66.7)    | 0.2219 |
| Unknown                  | 12/15 (80.0) | 8/8 (100)     | 0.2567 |
| Total                    | 218/256 (85.2)| 107/201 (53.2)| < 0.0001|

* Abbreviation: PLHIV, people living with HIV.

* Fisher exact test.
4.2. HCV-RNA Detection and HCV Genotypes Analysis

HCV-RNA and/or genotyping was performed in 233 patients being potential candidates for treatment; HCV RNA was detected in 207 (88%). Among 13 patients seronegative for HCV tested for HCV RNA and/or HCV genotype, only two had positive HCV-RNA results (occult HCV infection). The genotype results were available for 193 patients. Regarding the HCV genotype (GT) distribution, our analysis showed almost equal GT1, GT3 and GT4 distribution, with slight GT1 domination, which was found in 72 persons (37.3%), mainly GT1b, followed by GT3 detected in 62 PLHIV (32.1%) and GT4 in 59 PLHIV (30.6%). No significant differences in HCV genotypes distribution were found between patients who had different HIV acquisition routes.

4.3. Deaths

Sixty three deaths were registered in the study group, 17 among HCV seronegative patients and 46 in seropositive ones, P = 0.773. In 13 cases, the cause of death was unknown. Further analysis of the causes of death, including comparing liver-related versus other causes showed no significant differences between HCV seropositive and seronegative individuals, P = 0.390.

5. Discussion

Four hundred and fifty seven patients, with a median age of 38 years [range 23 - 72], predominantly males, 76.6% were studied. Anti-HCV antibodies were detected in most, 325/457 (71.1%). The highest seroprevalence was found in the 30 - 40 year old group as 81%. Our study group can be considered as an example of an "old" HIV cohort with IDU as the predominant means of HIV acquisition, 264/457 (57.8%). However, the proportion of MSM among new HIV diagnoses increases each year, consistent with an earlier study of IDUs in the community (26). The dynamics of blood borne infections, HBV , HCV and HIV, the history of illicit drug use and imprisonment are closely intertwined. Several European studies have recently been found in Warsaw, the capital and Krakow [unpublished, personal communications - Dr. E. Firlag-Burkacka, Dr. M. Bociaga-Jasik].

A recent analysis of 14651 HCV genotypes in the general population in Poland between 2003 - 2012 revealed a predominance of GT1 as 79.4%, followed by GT3 as 11.8% and GT4 as 4.9% (14). Locally in north-eastern Poland, the proportion of GT3 and GT4 were significantly higher as 27% and 8.6%, respectively (14). However, the proportions of GT3 and GT4 were even higher in earlier analysis, conducted between 2002 and 2006, reaching 34.1% and 15.5%, respectively (15, 24). HCV G3 was the major genotype seen among Polish prisoners (16). International EuroSIDA analysis, comprising eastern European countries, including Poland also reported higher proportions of HCV GT3 as 40%, GT4 19% and GT1 as 40% (25). The percentage of patients with replicating HCV in our study was higher than that seen in the EuroSIDA survey as 88.8% versus 77% (25).

Our study identified a history of imprisonment as an independent risk factor for HCV infection among PLHIV, consistent with an earlier study of IDUs in the community (26). The dynamics of blood borne infections, HBV, HCV and HIV, the history of illicit drug use and imprisonment are closely intertwined. Several European studies have identified a history of imprisonment as an independent risk factor for HCV infection among PLHIV, consistent with an earlier study of IDUs in the community (26). The dynamics of blood borne infections, HBV, HCV and HIV, the history of illicit drug use and imprisonment are closely intertwined. Several European studies
reported higher HIV and HCV prevalence and incidence in prisons (26-30). Polish data are summarized in Table 4. A cross-sectional study in French prison inmates showed 2.9% HIV and 4.8% HCV prevalence, which was six times higher than the general population, with 2.5% of inmates having viremic hepatitis C (27). In Spain, among 237 prisoners, 117 HCV seroconversions were detected, giving an incidence of 1.17/100 patient-years (29, 30). The incidence was higher among cases with HIV co-infection (8.34/100 patient-years (py)) and IDUs without methadone replacement treatment during follow-up (6.66/100 py) (29). All potential routes of HCV transmission can occur in prison such as sharing of contaminated injection equipment, unsafe sexual contacts, unsafe skin penetrations (piercing, tattooing, sharing razors and blood-sharing rituals); however, this period of obligatory isolation may provide conditions for optimal adherence during chronic hepatitis C treatment.

Recent studies indicated that the prevalence and total number of patients with anti-HCV has increased from 2.3% (95% uncertainty interval [UI]: 2.1% - 2.5%) to 2.8% (95% UI: 2.6% - 3.1%) and from more than 122 million to more than 185 million between 1990 and 2005 (31, 32). In the general population in Poland, HIV antibodies were detected in 1.9% of over 26000 adults; HCV-RNA was detectable in 31% of seropositive individuals (33).

Our study results showed a decrease in HCV prevalence in HIV infected individuals from 8.5% to 53.2% in those diagnosed before 2005 compared to those diagnosed in 2005 or later. This is in line with other European observations (17, 34, 35). In the Swiss HIV cohort, HCV incidence has decreased among IDUs, remained stable amongst heterosexuals and increased 18 fold in MSM between 1998 and 2011. In MSM, a history of inconsistent condom use and a history of syphilis predicted HCV seroconversion (33). Similar observations were made in the French national survey, demonstrating a decrease in the overall prevalence of HIV-HCV co-infection from 22 - 24% to 16 - 18%. This prevalence decreased from 93% to 87% among injecting drug users, while it increased from 4% to 6% among MSM during 2003 - 2012 (34).

We did not observe any difference of mortality rate between HCV seropositive and seronegative patients. However, the total number of deaths recorded was 63 and in 13 the cause of death was not determined. Data shows that HCV serostatus does not affect HIV disease progression; however, liver related deaths are more frequent among co-infected patients (13, 36). Besides the accelerated progression of liver damage caused by HCV replication in HIV infected individuals, HCV increases liver-related mortality and risk of renal insufficiency in HIV infected individuals (19, 37, 38).

Study limitations include its cross-sectional design and single center data analysis. However, our results complement the scarce information currently reported on the Eastern Europe HIV/HCV epidemics. In conclusion, HIV/HCV co-infection is an important medical problem in North-Eastern Poland, requiring relevant attention and curative and preventive measures.

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Authors' Contributions

Study concept and design: Anna Grzeszczuk; acquisition of data: Anna Grzeszczuk, Alicja Danuta Wandaowicz; analysis and interpretation of data: Jerzy Jaroszewicz, Anna Grzeszczuk, Alicja Danuta Wandaowicz; drafting of the manuscript: Anna Grzeszczuk, Jerzy Jaroszewicz, Robert Flisiak; critical revision of the manuscript for important intellectual content: Anna Grzeszczuk, Jerzy Jaroszewicz, Robert Flisiak; statistical analysis: Jerzy Jaroszewicz, Anna Grzeszczuk; the study supervision: Anna Grzeszczuk, Robert Flisiak.

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