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title

Efficacy and safety of boosted atazanavir in HIV-infected, ARV-naive patients – results from 48/96 weeks Castle study

authors

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summary

Antiretroviral regimens based on human immunodeficiency virus-1 protease inhibitors are the cornerstone of combination antiretroviral therapy because of their antiviral efficacy and high genetic barrier. Protease inhibitor – containing regimens are complicated by a number of side effects, mainly diarrhea, dyslipidemia, an increased risk of myocardial infarction, diabetes and lipodystrophy. Atazanavir (ReyatazTM) is the first, originally designed as once-daily HIV-1 protease inhibitor that offers a more convenient and safer PI-containing management of HIV infection. The antiviral efficacy of atazanavir has been proven in both treatment-experienced and treatment-naïve patients. In July 2008 boosted atazanavir has received registration for use in antiretroviral-naïve HIV-infected population. This specific registration was based on results from 48 weeks of the Castle (BMS AI424138) study.

key words

boosted atazanavir, atazanavir/ritonavir, HIV-1 protease inhibitor, antiretroviral therapy, ARV, HIV-1, once-daily regimen

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Introduction

Antiretroviral (ARV) regimens based on human immunodeficiency virus-1 (HIV-1) protease inhibitors (PI) are the cornerstone of combination antiretroviral therapy (cART) because of their antiviral efficacy and high genetic barrier. PI-containing regimens are complicated by a number of side effects, mainly diarrhea, dyslipidaemia, an increased risk of myocardial infarction, diabetes and lipodystrophy. ATV (ReyatazTM) is the first, originally designed as once-daily HIV-1 protease inhibitor that offers a convenient and safer PI-containing cART. The use of atazanavir has been associated with less hyperlipidaemia and diarrhea than other drugs in the same class (1). Atazanavir like the other PIs is a substrate of the subunit CYP3A4 of the P450 cytochromes and can be boosted with low dose of ritonavir to increase plasma concentration. In Poland atazanavir has been registered boosted with 100mg of ritonavir, once daily (2). However in USA it is also registered in unboosted dosing, therefore in clinical practice atazanavir is very often used as an ritonavir – sparing, PI-based therapeutic option (3).

In terms of antiviral activity *in vitro* and susceptibility ATV is one of the most potent drugs in HIV-1 protease inhibitor class, having EC50 (50% effective concentration) of 3-5 nM and an EC90 of 9-15 nM against a variety of HIV-1 isolates in different cell types. Atazanavir has activity against HIV-1 Group M subtype viruses A, B, C, D, AE, AG, F, G, and J isolates in cell culture. It has also activity against HIV-2 isolates (EC50 of 1.9 to 32 nM0 (2).

Due to very fast absorption ATV reaches the peak serum concentration 2.5 hours after dosing. Its bioavailability depends on gastric pH. Therefore in the presence of food, exposure measured as the area-under-the-curve (AUC) can be raised by 70% in comparison with the fasting state. Atazanavir should therefore be administered with food. (4). Atazanavir is 86% protein bound (5) and the trough plasma levels when ATV 300 mg is given in combination with ritonavir 100 mg in HIV-1-infected patients average 709 ng/mL (30-60 times the protein binding-adjusted EC50) (6). Metabolism of ATV in the liver leads to the production of three metabolites – none of them inhibits the P450 cytochrome system or has anti-HIV-1 activity. The plasma half-life of ritonavir boosted ATV is 11 hours. The Cmin and AUC are respectively 5- and 3-fold higher than when the drug is administrated boosted with ritonavir (in comparison to dose of 400 mg q.d., without boosting). The main way of elimination is biliary – 79% of the drug is recovered in the feces, therefore dose adjustment for renal insufficiency is unlikely to be required. In comparison with healthy subjects, a 42% increase in the AUC has been observed in patients with hepatic impairment (2). In subjects with severe hepatic impairment ATV/r has not been studied and therefore is not recommended (7). In antiretroviral treatment naive patients, the I50L substitution, sometimes in combination with an A71V change, is the signature resistance substitution for atazanavir. The N88S substitution has been rarely observed in patients with virologic failure on atazanavir treatment. In clinical studies N88S by itself does not lead to phenotypic resistance to atazanavir or have a consistent impact on clinical efficacy (2).

The antiviral efficacy of atazanavir has been proven in both treatment-experienced and treatment-naïve patients (3). In July 2008 boosted atazanavir has received registration for use in antiretroviral-naïve HIV-infected population. This specific registration was based on results from 48 weeks of the Castle (BMS AI424138) study (9).

Castle study – design and results

The aim of the CASTLE study was to compare the clinical efficacy of atazanavir/ritonavir once-daily and lopinavir/ritonavir twice-daily, given in combination with once-daily, fixed-dose tenofovir and emtricitabine, in treatment-naive HIV-1-infected patients. It was open-label, randomized, multicentre non-inferiority study (with non-inferiority margin Δ 10%, 95%CI). Patients participating in this study were recruited from 134 centers (29 countries in Euorpe, Asia, Africa, North and South America). The eligibility criteria for the participation in the study were: HIV-1 infection, age >18 years, no previous history of antiretroviral therapy (naïve), HIV-1 RNA ≥5000 copies/mL. Patients were randomized 1:1 to receive either atazanavir 300mg plus ritonavir 100 mg once daily, or lopinavir/ritonavir 400/100 mg, each with tenofovir/emtricitabine fixed dose (300/200 mg) once daily. Patients were also stratified by HIV RNA level at baseline: below 100 000 copies/mL or 100 000 copies/mL or greater and geographic region.

The primary endpoint used in this study was the proportion of patients with HIV RNA <50 copies/mL at week 48 of therapy. The principal analysis is based on confirmed virological response (CVR), non-completer equals failure (NC = F), intend–to–treat (ITT). Supportive analysis includes: time to loss of virologic response (TLOVR–ITT) and virologic response observed cases (VR-OC, OT – on treatment). Secondary endpoints were: 1/ the proportion of patients with HIV RNA <400 copies/mL at week 48; 2/ the proportion of patients with HIV RNA <50 copies/mL at week 96; 3/ changes from baseline in absolute CD4 count through weeks 48/96; 4/ HIV RNA reduction (log) by week 48; 4/ resistance profiles; 5/ virologic failures; 6/ genotypic and phenotypic testing; 7/ adverse events (AEs); 8/ changes in fasting lipids – fasting lipid National Cholesterol Education Program (NCEP) shifts and ratios (9,10).

In Castle study 883 HIV-infected, treatment-naive patients were randomised: 440 patients to ATV/ RTV group and 443 to LPV/r – treated arm. Selected baseline characteristics of patients is summarized in table 1. There were relatively high percent of women participating in the study (31% in both arms), patients were advanced in HIV infection: 48% had CD4 cell count <200 cells/mm^3, 51% had HIV RNA >100000 copies/mL. Study data show that antiviral efficacy of once-daily atazanavir boosted with ritonavir is non-inferior to twice-daily ritonavir-boosted lopinavir, both in combination with tenofovir/emtricitabine (FD, once-daily) for the treatment of antiretroviral-naive HIV-1-infected patients over 96 weeks. At weeks: 48 and 96 similar percent of patients in each arm had HIV RNA <50 copies/mL (principal ITT analysis, CVR, NC = F), confirmed by the supportive analyses (TLOVR ITT, VR-OC, OT). Detailed results of proportion of subjects achieving primary and secondary virologic endpoints are in table 2. Response rates achieved according to baseline HIV RNA (<100 000 and ≥100 000 copies/mL) are presented in table 3. The association between virologic response and baseline CD4 cell count was performed as *post hoc* analysis for both regimens. At week 48 lower virologic response was associated with lower baseline CD4 cell count in LPV/r treated patients (p = 0.0085), but not in ATV/RTV treated subjects. At week 96 the response rates for ATV/RTV were maintained across all CD4 strata. There was no specific trend in virologic response for either arm. For patients starting therapy with CD4 cell count bellow 50 cells/mL response rate was 78% in ATV/RTV arm compared to 58% in LPV/r group (Table 4). This reduced response rate in

LPV/r arm in patients with very low baseline CD4 cell count was mainly caused by high rate of discontinuations due to adverse events (2% in ATV/RTV arm and 12% LPV/r arm) (11). Virologic failures defined as 1/ rebound to HIV RNA >400 copies/mL without re-suppression, 2/ lack of (= never achieved) confirmed VL <400 copies/mL or 3/ discontinuation caused by lack of efficacy before week 48 were 6% and 7% in ATV/RTV and LPV/r arms respectively. In the ATV/RTV arm one patient had both major and minor substitutions, five patients had M184V, one K65R and one had TAMs. In LPV/r arm one patient had minor PI substitutions at virologic failure, seven had M 184V and three had TAMs.

Immunologic response defined as mean increase from baseline to week 48/96 in CD4 cell count (203/268 cells/μL in ATV/RTV group and 219/290 cells/μL in the LPV/r group) were comparable and did not differ significantly.

Additionally efficacy analysis was performed for patients infected with non-B HIV clade. In both arms viral response was similar to clade B infected subjects. These information is important in Africa, Asia or South Africa where non-B clade infection is frequent (12).

In Castle study subanalysis of efficacy and safety of both regimens was also performed for group of HBV and/or HCV co-infected patients (48 weeks data).

Table 1. Selected parameters of baseline patient's characteristics

	ATV/RTV (n = 440)	LPV/r (n = 443)	Overall (n = 883)
Age – median, range, years	34 (19-72)	36 (19-71)	35 (19-72)
Gender – female	31%	31%	31%
HIV RNA – log10 copies/mL, median	5.01	4.96	4.98
HIV RNA ≥100 000 c/mL	51%	47%	49%
CD4 – median, cells/mL	205	204	205
HBV positive	5%	5%	5%
HCV positive	9%	9%	8%
HIV-subtape non-B	33%	35%	34%

Table 2. Proportion of patients achieving HIV RNA <50 copies/mL at week 48 and 96

HIV RNA < 50 copies /mL	Week 48		Week 96	
	ATV/RTV	LPV/r	ATV/RTV	LPV/r
CVR, NC = F*	78%	76%	74%	68%
Difference Estimate(95% CI; p-value) ATV/r - LPV/r	-2.9% (-7.5 to 1.6)		6.1% (0.3 to 12.0)	
TLOVR#, ITT	78%	76%	70%	63%
Difference Estimate (95% CI; p-value) ATV/r – LPV/r	1.9% (-3.6 to 7.4)		6.6% (0.4 to 12.7)	
VR-OC&, OT	84%	87%	89%	88%
Difference Estimate (95% CI; p-value) ATV/r – LPV/r	-3.5% (-8.7 to 1.8)		1.6% (-3.1 to 6.2)	

* Confirmed Virologic Response, Non completer = Failure; # Time to Loss of Viral Response, Intend to Treat; & Viral Response – Observed Cases, On treatment

Table 3. Response rates achieved according to baseline HIV RNA (<100 000 and ≥100 000 copies/mL, ITT, CVR, NC = F)

% of patients achieving HIV RNA <50 copies/mL	Week 48		Week 96	
	ATV/RTV	LPV/r	ATV/RTV	LPV/r
BL VL <100 000 c/mL	82%	81%	75%	70%
BL VL ≥100 000 c/mL	74%	72%	74%	66%

BL VL – baseline viral load

Table 4. Outcome in patients with advanced HIV infection (week 96)

n (%)	ATV/r n = 440 n (%)		LPV/r n = 443 n (%)	
	CD4 < 50 copies/mL n = 58	CD4 <100a & HIV RNA ≥100,000 c/mL n = 83	CD4 <50 copies/mL n = 48	CD4 <100a & HIV RNA ≥100,000 c/mL n = 64
Virologic Response CVR (NC = F)	45 (78)	59 (71)	28 (58)	39 (61)
Virologic Failure	4 (7)	11 (13)	4 (8)	10 (16)
Discontinuations due to:	9 (16)	13 (16)	16 (33)	15 (23)
• AE	1 (2)	1 (1)	6 (13)	5 (8)
• Death	2 (3)	3 (4)	2 (4)	1 (2)
• Withdrew consent	1 (2)	1 (1)	3 (6)	4 (6)
• Nonadherence	1 (2)	3 (4)	3 (6)	3 (5)
• Other	4 (7)	5 (6)	2 (4)	2 (3)

At weeks 48 and 96 respectively: 9% and 21% patients in the ATV/RTV group, 13% and 21% patients in the LPV/r group discontinued their therapy. Similar proportions of these discontinuations in each group were due to adverse events: 2% and 3% on ATV/RTV and 3% and 5% on LPV/r.

At week 96 treatment–related adverse events of grade 2-4 were diarrhea reported in 2% of patients on ATV/RTV and in 12% on LPV/r, nausea in 4% vs 8% for ATV/RTV and LPV/r respectively, jaundice 4% in ATV/RTV and 0% in LPV/r arm. 22% of subjects in LPV/r arm initiated anti-diarrhoeal therapy during the study period vs 9% in ATV/RTV group. The incidence of ALT/AST abnormalities were consistent between the regimens and the rate of hyperbilirubinaemia was predictably higher in ATV/RTV-treated group. Hyperbilirubinaemia and jaundice may be of concern because of their potential effect on patient quality of life, only 3 patients (<1%) discontinued treatment with atazanavir/ritonavir due to jaundice at week 48 and 96 (none patient interrupted therapy between week 48 and 96 due to HBR).

In the Castle study, there were statistically significant increase from baseline to 48/96 week in total fasting cholesterol, non-HDL-cholesterol and triglicerydes in LPV/r arm. 17% of patients on ATV/RTV (vs 23% at baseline) had a total cholesterol: HDL-cholesterol ratio of >5 in contrast to 27% in LPV/r group.

Summary

Data from Castle study data show that antiviral effect of once-daily ATV/RTV is non-inferior to twice-daily LPV/r, in combination with once-daily tenofovir/emtricitabine for the treatment of antiretroviral-naive HIV-1-infected patients over 96 weeks. This efficacy was maintained irrespective of baseline CD4 cell count; in LPV/r arm reduced viral response was seen for patients with lower baseline CD4 cell counts.

Long-term efficacy of cART is strongly related to good tolerability, safety profile of ARV drugs and their convenience (number of doses and pills of pills/day, size, taste). Gastrointestinal adverse effects: diarrhea and nausea are established risk factors for therapy failure (13). According to Castle data ATV/RTV use reflects with less gastrointestinal toxicity then LPV/r. The growing concern in choice of ARV therapy in treatment – naïve patients is long-term toxicity. In the context of recent data from D:A:D and FHDH cohorts the potential risk of long-term effects of PI-associated hyperlipidaemia and myocardial infarction strongly depends on the choice of protease inhibitor in the initial ARV regimen (14,15). The results of Castle study confirm favorable lipid profile of ATV/RTV. Additionally show for the first time in a large, controlled population of ARV-naïve patients that ATV/RTV has better lipid parameters compared to LPV/r. These findings are important when making therapy choices in an aging population or with other cardiovascular risk factors.

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title

Efficacy and safety of atazanavir-based regimens in routine management of HIV-infected adults

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summary

The aim of this retrospective cohort study was to evaluate safety and efficacy of atazanavir in routine clinical practice. Of 62 patients treated with atazanavir-based regimen, therapy was discontinued in 3 (4.8%) cases, one (1,6%) patient died, but the cause was not associated with treatment. The mean increased of CD4 cell count was 197 cells/mL. We found low rate of adverse events in analyzed population and favorable lipid profiles.

key words

atazanavir, HIV infection , lipid profile, PI

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Introduction

The treatment of HIV infection with potent combinations of antiretroviral drugs has transformed from a fatal disease to a chronic condition that is manageable. The evolution began in the mid-1990s with the introduction of protease inhibitors (PI). The long-term success of many boosted protease inhibitor-based treatments is compromised by metabolic disorders. There are some evidence that PI-related hyperlipidaemia my increase risk of cardiovascular disease in HIV-infected patients (1, 7, 8).

Atazanavir is an azapeptide protease inhibitor approved by the FDA (Food and Drug Administration) on June 20, 2003 for the treatment of HIV infection in combination with other antiretroviral drugs. In 2004 Reyataz become available in Poland. Atazanavir has a resistance profile distinct from than in other protease inhibitors. Treatment – naïve patient develop a I50L mutation and increased susceptibility to other drugs in its class. Boosting atazanavir has the potential to increase antiretroviral potency (6, 14).

Atazanavir boosted with ritonavir taken once daily with food is nowadays one of preferred combinations recommended by the DHHS and EACS as component of first line antiretroviral therapy in treatment naïve patients (4, 11). This recommendation is associated with the results from the Castle study which demonstrated similar efficacy of once-daily atazanavir boosted with ritonavir to twice-daily lopinavir/ritonavir (Kaletra) each with combination with emtricitabine/tenofovir in treatment-naïve HIV infected patients. In the Castle study the atazanavir/ritonavir was associated with better lipid profile and better tolerability then lopinavir/ritonavir (9-10).

For patients who are unable to tolerate ritonavir, according to clinical data and common practice, atazanavir 400 mg can be taken with food once daily (3, 10).

The aim of the study was to evaluate the efficacy and safety of atazanavir in the antiretroviral treatment with two NRTI drugs in the routine clinical practice.

Materials and methods

This retrospective cohort study included all HIV infected adults who attended to the outpatient clinic at the Department of Infectious Diseases and Hepatology in Bydgoszcz from March 2004 to April 2008, for whom atazanavir was prescribed as a part of antiretroviral treatment. All patients had started antiretroviral treatment during chronic HIV infection and had been taking atazanavir as the part of the first regimen or after switch the other regimens due to toxicity or insufficient efficacy.

All patients were analyzed to ascertain demographic characteristics, HIV risk factors, AIDS history, history of antiretroviral treatment and causes of switch or death.

Assessment of virologic and immunologic efficacy was performed for all patients. Plasma HIV RNA levels, CD4 cell counts, adverse events, metabolic parameters, bilirubin and liver tests were analyzed in all patients prior and during treatment with atazanavir-based regimens. Plasma HIV RNA levels were measured by using the Amplicor Monitor Kit (Roche) with limit of detection of 40 copies/ml. Lymphocyte subset were determined using flew cytometry on freshly isolated cells. In routine practice patients were evaluated in 3 month intervals. CD4 cell count were analyzed after 12-24 month of therapy. Efficacy was defined as levels of HIV-RNA <50 copies/mL in last observation point. Assessment of safety included all treated with atazanavir patients.

Mean percent changes from baseline for lipid parameters were, analyzed.

Results

Of the 62 patients included to the analysis, 28 were treatment naïve, in 10 cases atazanavir was prescribed as a part of new regimen due to virological failure and in 24 due to adverse event occurred in previous regimens. In 14 cases stable antiretroviral therapy (HIV-RNA <50 copies/mL) was changed due to gastrointestinal problems, in one case due to erectile problems and in 9 patients due to metabolic abnormalities. Demographic and clinical characteristics of the patients was presented in table 1.

Table 1. Baseline demographic and clinical characteristics of the patients

Variable	
Gender (male), %	67,4
Mean age (range), years	37,5 (25-60)
Duration of HIV infection, (mean), years	7
AIDS N., (%)	25 (40,3)
Median CD4 cell count, cells/µL	257
HIV-RNA N (%), copies/mL • <50 • >100 000	 20 (32,5) 8 (12,9)
Treatment-naïve N (%)	28 (45,2)
Treatment-experienced N(%)	34 (54,8)
Prior antiretroviral use (median, years)	4,42
Switch N (%): • Due to virological failure • Due to adverse event	 10 (16,1) 24 (38,7)
HCV-coinfection N (%)	47 (75,8)
HIV-exposure N (%) • MSM • Heterosexual • I DU	 7 (11,3) 13 (21) 42 (67,7)

Treatment-naïve patients were in advanced stage of HIV disease with mean HIV-RNA viral load 147 604 copies per mL and baseline CD4 cell count 151 cells/mL (ranged 10-357 cells/mL), 12 of 28 (42.8%) treatment-naïve patients had have the history of AIDS-defining events.

The mean increase of CD4 cell count was 197.3/mL, and in 1 (1.6%) patient therapy was discontinued due to insufficient virologic efficacy.

In 3 (4.8%) patients treatment with atazanavir was interrupted: in the one case due to jaundice, in one case due to peptic ulcer, in one due to lost to follow up. 27 of 62 (43.5%) patients have been treated since 2004. In the 5 years of observation treatment was well tolerated and highly effective.

Total cholesterol and triglyceride levels decreased in subjects treated with atazanavir based regimens. In month 12 the mean decrease in total cholesterol and triglycerides were 14.4 mg/dL and 36.2 mg/dL respectively (p <0,05).

According to the US NCEP–ATP III guidelines [5] the percentage of patients with total cholesterol ≥240 mg/dL decreased from baseline to 12 months of therapy from 14.5% to 1.61%. In month 12 the mean increase in HDL cholesterol was 8.5 mg/dL and the mean decrease in LDL cholesterol was 14.4 mg/dL ($p < 0.05$). The percentage of patients with LDL ≥160 mg/dL decreased from 6.45% to 3.2% after 12 month treatment and the percentage of patients with HDL ≥40 mg/dL increased from baseline (38.4%) compared with month 12 (67%).

The percentage of patients with hypertriglicerydemia >200 mg/dL decreased from 29.03% to 19.4%, very high levels >500 mg/dL were noticed in 3 cases (4,8%) in pretreatment evaluation and in 1 (1.61%) at month 12.

The elevation of bilirubin in 3-4 grade levels were noted in 30 (48.4%) patients and it was not connected with increases of hepatic transaminase levels. Only in one patient discontinuation and switch to new antiretroviral regimen was due to jaudince without clinical or laboratory findings of liver injury. In the another case switch from boosted atazanavir to atazanavir 400mg had have positive influence on sustained lower bilirubin concentration.

The increased transaminase activity were noted in 10 patients and in all of them abnormal liver tests were present in the pretreatment evaluation.

One of the analyzed patients died due to substance abuse.

Conclusion

The study provided the opportunity to determine the efficacy and safety of atazanavir in routine clinical practice. Our findings are generally consistent with the result of clinical trials. The study shows that atazanawir was generally well tolerated with virologic efficacy during 5 years. The most common laboratory abnormality associated with use of atazanavir is increased bilirubin concentration. This abnormality is due to the inhibition of UDP-glucurnosyl transferase 1A1, an enzyme responsible for glucuronidation of bilirubin (14). Hyperbilirubinemia in those cases is reversible with discontinuation of atazanavir and is not associated with hepatic injury or inflammation.

We have found in our study that increased hepatic transaminase levels were noted only in patients with increased hepatic transaminase levels in pretreatment evaluation, and therapy did not negatively influence on the liver injury.

We have noted that mean level lipid's concentrations generally decreased on atazanavir treatment. The differences in total cholesterol, LDL-cholesterol and triglycerides levels between the pretreatment and on treatment evaluations were statistically significant. The percentage of patients who were within the NCEP ATP III desirable for lipid parameters increased from the pretreatment to on treatment evaluation. We have found however that patients with clinically significant hypertriglyceridaemia in pretreatment evaluation did not improve. In those cases lipid lowering agents were started.

In summary our study shows that atazanavir is an effective, well tolerated, dosing convenient and safe in antiretroviral treatment. Favorable lipid profiles may result in a reduced risk of cardiovascular events and reduced indications to the treatment with lipid lowering medications in these population.

If decision is made to start antiretroviral treatment with a boosted protease inhibitor, atazanavir seems to be the very attractive choice.

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title

Changes in the trends of the HIV/AIDS epidemic, based on surveillance data of Warsaw cohort

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summary

HIV infection remains one of the major public health concern, with evidence of increasing, even in several developed countries. The article provides an overview of HIV surveillance data of patients from outpatient clinic in Warsaw.

In Poland the first HIV infection was detected in 1985, and the first case of AIDS one year later. In the period between 1990-2000y among HIV infected patients approximately 70% were intravenous drug users. In the next decade the shift of predominant mode of transmission for HIV infection is observed. From 2001 onward, the increasing number of persons infected through sexual contacts, without the past history of intravenous drug using has been noticed. Since 2005, among newly reported HIV infected adolescents the sexual contact between men followed by hetero-sexual contact has been the main route of transmission. The significant increase of this mode of transmission was noticed in 2008. The deaths rate remains relatively low, even decreases.

key words

HIV epidemiology, HIV trends, route of infection

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Background

The first case of HIV infection was detected in Poland in 1985 and the first case of AIDS was recognized, a one year later. In Poland, during the first years of registration, the main route of HIV transmission was injecting drug use. The total number of diagnosed HIV infected patients till the end of 2008 stands about 12014, including 2177 AIDS cases and 961 deaths. [1,2] The outpatient clinic [Poradnia Profilaktyczno-Lecznicza (PPL)] in Warsaw was established in 1990 and since then provides care, treatment and diagnosis for patients with HIV/AIDS from the nearest region and other parts of Poland.

Aim of the study

To present the epidemiological assessment of patients registered in PPL (the main Polish center for adult patients with HIV/AIDS) in years between 1990 and 2008.

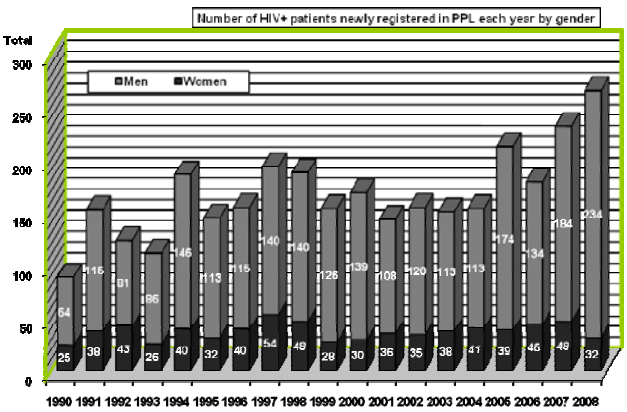
Material and methods

The analysis includes reviewed medical records of all patients diagnosed and treated in PPL in every year. The age at HIV diagnosis (based on the date of Western blot test), gender, probable route of infection and deaths in the observation period were analyzed (absolute number and frequency).

Results

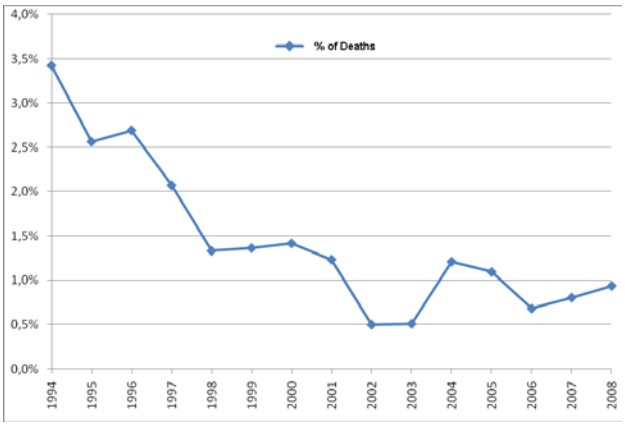
Since 1990 till 2008, 3163 persons with HIV/AIDS aged between 18 and 81 years were diagnosed and treated. Among them there were 718 (22.7%) women and 2445 (77.3%) men. The number of newly infected patients each year ranged between 89 and 266 cases (in 1990 and 2008 respectively). Figure 1 presents the total group of patients registered in each year by gender.

Figure 1. Number of newly registered HIV+ patients in PPL each year by gender



The registration of deaths of patients treated in PPL has been reported since 1994. The highest proportion of deaths (i.e. 3.4%) has been noted in the first year of registration. Within the next years this proportion has become lower and ranged from 2.56% to 0.51% with slightly decreasing trend. However, the marginal increase of deaths rate was observed recently. It seems to be connected with more precise data collection.

Figure 2. Proportion of deaths in PPL by year



The main group of patients were intravenous drug users, infected through intravenous use of psychoactive substances contaminated with HIV infected blood. Out of all registered patients 1663 persons were infected through this route – 52.6%. Among them, 446 (26.8%) were women and 1217 (73.2%) men. Not all persons were active drug users at the time of testing. Some of them were taking drugs sporadically or did not use drugs for years, while others still were active drug users. Among the patients registered in PPL, 610 (19.3%) persons were infected through homosexual contacts and 123 (3.9%) through bisexual contacts. In total, men who had sexual contacts with men constituted 23.2% of study population. Through heterosexual contacts were infected 650 (20.5%) persons, among them 237 (36.4%) women and 413 (63.6%) men. Infection through parenteral route during infusion of blood derived products was noted sporadically – in 3 persons infected before 1987 (before introduction of routine HIV tests in blood donation facilities in whole country). Only 3.7% persons were unwilling or unable to disclose the route of infection.

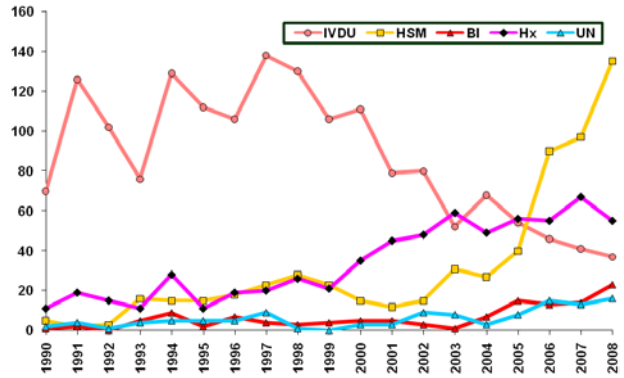


Figure 3. Number of patients in PPL by route of infection
IVDU – intravenous drug users, HSM – infection through homosexual contacts, Bi – persons who had both homo- and heterosexual contacts, Hx – infection through heterosexual contacts, UN – other route or unknown

From 2001 onward the shift in epidemic trends is observed in PPL. More and more persons are infected through sexual contacts, including homosexual, without history of intravenous drug use. From 2005 onward among patients newly registered in PPL persons infected through homosexual contacts are prevailing with significant increase in 2008.

Table 1. Shift in route of infection in new patients between years 2000 and 2008

Route of infection	Year 2000	Year 2008
IVDU	111 (65.7%)	37 (13.9%)
HX	35 (20.7%)	55 (20.7%)
HSM	15 (8.9%)	135 (50.7%)
Bi	5 (2.9%)	23 (8.7%)
UN	3 (1.8%)	16 (6%)

Young persons up to 30 years of age are slightly prevailing among the patients diagnosed in PPL. HIV infection was diagnosed in 1441 (45.5%) persons in the age group 21-30 years, 144 (4.6%) persons below 20 years and 1578 (49.9%) patients above 30 years of age. Young people up to 30 years of age were predominant among infected IVDU, with significant majority of men. However, patients infected through sexual route were mostly men in over 30 years age group. At the time of diagnosis the highest proportion of women (57%) was in the group below 30 years of age.

Table 2. Number of patients in PPL by age group, route of infection and gender

Route of infection	Age group								
	< 20 years		21-30 years		> 30 years		Total		
	Man	Woman	Man	Woman	Man	Woman	Man	Woman	Man & Woman
IVDU	61	45	272	598	113	574	446	1217	1663
HSM	-	13	-	248	-	349	-	610	610
Hx	13	7	121	127	103	279	237	413	650
Bi	-	3	-	40	-	80	-	123	123
Transfusions	-	-	-	1	-	2	-	3	3
UN	1	1	20	14	14	64	35	79	114
Total	75	69	413	1028	230	1348	718	2445	3163

IVDU – intravenous drug users, MSM – infection through homosexual contacts, Hx – infection through heterosexual contacts, Bi – persons who had both homo- and heterosexual contacts, Transfusions – iatrogenic infections through infusion of blood derived products, UN – route unknown

Discussion

Aspect of current epidemiological trends in HIV infection is very diverse. Visible variations apply not only to continents, regions of the world, but also specific countries, provinces or population groups.

HIV infection still is one of important issues of the public health in Europe. Since year 2000 almost twofold increase in new HIV infections per 1,000,000 inhabitants has been observed in Europe. Particularly distressing trends are present in eastern region of Europe (WHO European Region East) with the highest rate of new infections in Estonia – 472 cases/mln, Ukraine 285/mln and Moldova – 204/mln, as well as Portugal 217/mln (2007). [3]

In Russian Federation the HIV prevalence is variable, from low (1-50 cases per 100 000 population) in 31 regions, medium (51-150/100 000) in 26 regions to high (151-300/100 000) in 16 regions. There is above high prevalence (301-620/100 000) in 15 regions. With an estimation of HIV seropositivity rate of 0.6-1.0% among adult population (age group 15-49), the Russian Federation still has a concentrated HIV epidemic. [3]

Since 1997 the gradual decrease of infections rate among intravenous drug users has been observed in Western Europe (WHO European Region West) and Central Europe (WHO European Region Center). In 2007 infection through this route was observed only in 8-13% of patients in this region. [6]

Poland was an exception among countries of the Central Europe with nearly 95% share of intravenous drug use in routes of infection in years 1990-1997. Currently with 13.9% the model of infection is approaching models in other regions of Western and Central Europe. [5]

Among persons infected with HIV in Eastern Europe still the main group are intravenous drug users. It should be assumed that also in this region the reversing of infection trends from intravenous route to hetero and homosexual contacts will take place. [4]

In Europe women constitute on average 33% of all infected persons. Approximately 1/3 of them is in the age range of 15-29 years. Among patients in PPL women constitute 20-25%, with the markedly decreasing trend since 2006. It is probably caused by increasing number of young men with HIV infection registered in this period. [5]

Since year 2000 the decrease in deaths rate due to AIDS has been observed, especially in the region of Central and Western Europe, caused by the good accessibility and effectiveness of antiretroviral treatment (HAART). Increase in deaths due to AIDS were noted only in Belarus and Moldova. Among patients in PPL we observe a relatively low deaths rate what reflects the National Institute of Hygiene data for the whole Poland. It is also related to the good accessibility of antiretroviral drugs to all in need.

Central Europe, including Poland, remains the region with the stable low dynamic of the HIV/AIDS epidemic where the slight increase of number of cases with the incidence of 0.3-0.47 per 100,000 inhabitants has been noted since 1993. In PPL each year a slight increase of number of newly registered patients has been observed since 2003, what reflects the trends in Europe and in whole Poland. This phenomenon may be paradoxically explained by availability of effective antiretroviral therapy and increasing survival resulting in lessened fear of HIV and unsafe sexual behaviors.

Since 2001 the shift of epidemiological trends in high risk groups has been observed with more and more persons infected through sexual contacts, similar to trends in countries of the Western Europe.

Conclusions

Decidedly the profile of patients in PPL is changing. In the years 1990-2000 nearly 70% of all infected patients were persons addicted to intravenous psychoactive substances. From 2001 onward the reversal of infection trend from the intravenous route to the homo and bisexual contacts is observed. In the last 5 years the young men in the age between 21-30 years who were infected through homosexual contacts prevail.

The decreasing and relatively low deaths rate is observed among the patients of PPL clinic (comparable to data from the Western Europe).

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title

The transition of HIV within and between affected populations in Poland

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summary

Background. The aim of this paper is the estimation of the probabilities that describe the transition of HIV within and between the following three populations: homosexual and bisexual men, injecting drug users and heterosexual persons in Poland in the years 1995-2006.

Material and methods. The data on the routes of HIV infections come from "HIV/AIDS Surveillance in Europe". The restricted maximum likelihood method is applied for the estimation of underlying Markov chain.

Results. HIV infections are more probable within analysed populations than between them. The scale of HIV mobility is small. The estimated Markov chain predicts radical changes of the routes of HIV infection in the future. However, the evolution of the HIV epidemic in Poland is still far from equilibrium.

key words

HIV epidemic, routes of infection, Markov chains, transition probabilities, estimation, surveillance reports.

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Introduction

The analysis of HIV epidemic in a country requires, among others, the knowledge about the routes of HIV infection. Routinely collected surveillance reports provide data on the number of HIV infections diagnosed in selected populations "at risk", e.g. homosexual and bisexual men (HBM), injecting drug users (IDU) and heterosexual persons (HP) (In this paper we will omit other routes of HIV infection (vertical infections, blood transfusion etc.). Epidemiologists observe the trends of HIV infections in each of these populations. The inference about the future structure of HIV epidemic bases on extrapolations of observed trends for every route of HIV infection separately, i.e. as if these routes were "HIV-independent" (4).

The mentioned above independency of the dynamics of HIV infections can be questioned because of possible transmission of HIV between analysed populations. Therefore searching for interactions between HIV infections in analysed populations is necessary.

The other reason for this research is that the probabilities of HIV transmission between affected populations appear in many theoretical models of the HIV epidemic (2, 9, 11,12,13). Even simple simulation studies require some type of parameter estimation procedure, since almost all epidemic models contain some parameters, which cannot be, measured directly (1).

In this paper, we apply a method that enables the assessment of possible interactions between the dynamics of HIV infections. This method consists in estimation of the transition probabilities of a stationary Markov chain when only data from routinely collected surveillance reports are disposable.

The rest of this paper is organised as follows:

- formulation of Markov chain with states relating to the three populations (HBM, IDU, and HP);
- presentation of statistical data sources and transition probabilities estimation method;
- empirical results;
- final remarks and conclusions.

Material and methods

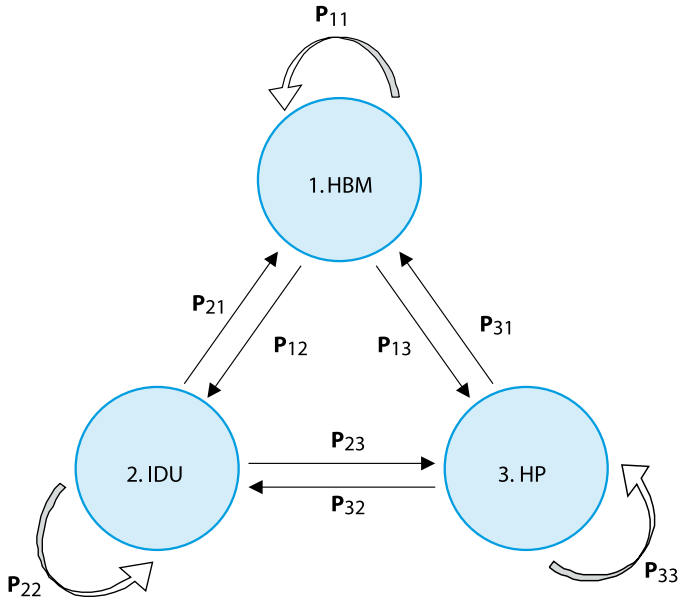
The source data concern the number of newly diagnosed HIV infections in analysed populations. The data for Poland come from EuroHIV reports: "HIV/AIDS Surveillance in Europe' the years 1995-2006 (3).

For every year *t,* we calculated the fractions (shares) $y_1(t)$, $y_2(t)$, $y_3(t)$ of HIV diagnoses in each of affected populations. We assume that a stationary Markov chain has generated these fractions.

Let the Markov chain states s_1, s_2, and s_3 denote the populations of HBM, IDU, HP, respectively. The HIV epidemic will occur if the HIV virus is transferred from one person to another, either within a population or between populations. The statistical data used in this paper only allow us to consider one year as a time unit. Therefore $P(X_t = s_i) = p_i(t)$ is the probability that a new HIV infection will be diagnosed in s_i population in year t. The vector $\boldsymbol{p}(t) = (p_1(t), p_2(t), p_3(t))$ will be called the 'theoretical' structure of HIV infection routes in year t, whereas the vector $y(t) = (y_1(t), y_2(t), y_3(t))$ will be called the observed structure in year t. The conditional probability $p_{ij}=P(X_t = s_i|X_{t-1}=s_j)$ describes the transition of HIV between populations during one year, i.e. the probability that an HIV-positive carrier belonging to the *i*th population in *t-1* will infect in *t* a person belonging to the *j*th population. The symbol p_{ii} denotes the conditional probability of HIV infection between two persons belonging to the same *i*th group. The *KxK* matrix $\boldsymbol{P}$ with elements p_{ij} is called the transition matrix.

Figure 1. shows the mechanism of HIV transition between states s_1, s_2, and s_3 over time.

Figure 1. The scheme of HIV transition



The estimation of the transition probabilities usually requires "micro-data", i.e. the observed sequences of Markov states in consecutive steps (e.g. years), for instance: s_1,s_1,s_2,s_3,s_3,s_1,...etc. Such data can be obtained from specially designed surveys. However, the transition probabilities can be also estimated from the 'macro-data", i.e. from empirical structures $y_1(t),y_2(t), y_3(t)$, thanks to the following relationship:

$$p_j(t) = p_{1j} \cdot p_1(t\text{-}1) + p_{2j} \cdot p_2(t\text{-}1) + \ldots + p_{Kj} \cdot p_K(t\text{-}1) \qquad (1)$$

for $j=1,2,\ldots,K$, and $t=1,2,,\ldots.$, where K is the number of states.

Equation (1) resembles a regression model with dependent variable $p_j(t)$, independent variables $p_1(t\text{-}1)$, $p_2(t\text{-}1)$, …, $p_K(t\text{-}1)$, and the K conditional probabilities p_{1j}, $p_{2j},\ldots,p_{Kj}$ as the coefficients of regression. If we substitute theoretical structures with empirical ones and add disturbing term Z_j with zero mean and variance σ^2, the regression model (1) will take the following form: (7)

$$y_j(t) = \sum_{i=1}^{K} p_j \, y_i(t-1) + Z_j \,, j=1,2,\ldots,K \qquad (2)$$

Unfortunately, the application of the least squares method (LSM) does not provide correct estimates of unknown transition probabilities in general (the LSM may give negative probabilities). Lee et al (6) overcome this inconvenience developing the restricted maximum likelihood estimators. However, the distribution of such estimators is unknown, except for the case $K = 2$. Therefore the statistical significance of such estimates cannot be tested.

It immediately follows from equation (1) that transition matrix $\boldsymbol{P}$ enables the forecasting of future HIV epidemic

structures. In matrix notation, the structure $\boldsymbol{p}(t+h)$ for h steps ahead is equal to:

$$\boldsymbol{p}(t+h) = \boldsymbol{p}(t)\,\boldsymbol{P}^{h} \quad (3)$$

For regular Markow chains, $\boldsymbol{p}(t+h)$ approaches the steady-state probability vector $\boldsymbol{p}_0$ (equilibrium state vector) if h approaches infinity (5). The steady-state transition matrix $\boldsymbol{P}_0$ contains identical rows $\boldsymbol{p}_0$.

Shorrocks (10) proposes the index which summarises mobility of HIV between Markov chain states:

$$I_s = \frac{K - tr\,\mathbf{P}}{K - 1} \quad (4)$$

where trP is the trace of $\boldsymbol{P}$ matrix, i.e., the sum of elements p_{ii} on main diagonal.

$Is = 0$ in the case of *perfect immobility*, i.e. when $\boldsymbol{P}$ is identity matrix. (with 1 on the main diagonal and 0 otherwise). $I_s = 1$ in the case of *perfect mobility*, i.e. when $\boldsymbol{P} = \boldsymbol{P}_0$ is the steady-state matrix, so the probability of moving to any state is independent of that originally occupied.

Results

For every year t, the $y_j(t)$ fractions in the jth population are calculated, j = 1,2,3. These fractions are presented in Table 1.

In this table, each row shows the year-end structure of the HIV epidemic with respect to the mode of HIV transmission (For known origins only. The cases with unknown origins are treated as missing data.). The last column shows the total number of HIV infections, whereas the second from last column shows the total number of infections with known origins.

The HIV epidemic pattern in Poland is typical for Central and Eastern Europe, with a very high proportion of HIV infections among IDU and low proportions for HBM and HP. The fraction of new HIV infections among injecting drug users declined remarkably in the years 2004-2006. On the other hand, in that same period one can see an increase of the fraction of new HIV infections among the HP and HBM populations.

The results of the transition probabilities estimation are presented in Table 2.

Table 1. Fractions of HIV infections newly diagnosed in Poland, in the years 1995-2006, by the mode of transmission

Year	The mode of transmission*			No. of cases with known origin	Total No. of cases
	HBM	IDU	HP		
1995	0.072193	0.860963	0.066845	374	539
1996	0.100985	0.847291	0.051724	406	551
1997	0.090659	0.865385	0.043956	364	579
1998	0.087805	0.860976	0.051220	410	637
1999	0.105960	0.847682	0.046358	302	527
2000	0.066313	0.872679	0.061008	377	630
2001	0.074919	0.859935	0.065147	307	564
2002	0.123348	0.788546	0.088106	227	574
2003	0.062745	0.831373	0.105882	255	610
2004	0.087866	0.769875	0.142259	239	656
2005	0.139013	0.618834	0.242153	223	652
2006	0.177515	0.538462	0.284023	169	750

* Abbreviations: HBM: homo/bisexual men; IDU: injecting drug users; HP: heterosexual persons.

Source: Authors' calculations using data from 'HIV/AIDS Surveillance in Europe' reports.

Table 2. The estimated probabilities of the transition of HIV between the populations (states) of: 1. Homo/bisexual men (*HBM*), 2. Injecting drug users (*IDU*), 3. Heterosexual persons (*HP*) for Poland in the years 1995-2006

State at t-1	State at t			Shorrocks' Is Mean Squared Error MSQE
	1 HBM	2 IDU	3 HP	
1 HBM	0.69969	0.03152	0.26879	Is = 0.19778
2 IDU	0.03722	0.96278	0.00000	
3 HP	0.05803	0.00000	0.94197	MSQE = 0.001677

Source: Authors' calculations using data from Table 1.

The estimates of probabilities on the main diagonal, i.e. p_{11}, p_{22}, and p_{33} in each of the transition matrices presented in table 2, show the scale of "intra-group infection', i.e. the transition of HIV between persons in the same population. The elements outside the main diagonal reflect the inter-group transmission of HIV. The last column of Table 2 contains Shorrocks' mobility index and the mean squared error of estimation.

High probability values on the main diagonal of the transition matrix ***P*** suggest that the HIV epidemic in Poland spreads mainly inside the selected groups. The IDU and HP groups seem to be quite separate from each other. The probability of HIV transmission between these groups within one year is nil. Although homosexual/bisexual men mainly infect other men from the same group, they can also infect injecting drug users with a probability of 0.03 and heterosexual women with a probability of 0.27. In turn, homosexual/bisexual men can contract HIV from injecting drug users with a probability of 0.04 and from heterosexual women with a probability of 0.06. The transmission of the virus between HBM and IDU seems to be symmetric. On the other hand, an asymmetry exists in the HIV flow between HBM and HP.

The probability of infection within the IDU group is very large (0.96). This could be a reflection of inadequacies in Poland's needle exchange and/or methadone therapy programmes.

The Shorrocks' index for Poland is 0.19778. This means low HIV mobility between considered populations in Poland.

The next table shows HIV epidemic forecasts for the next 10 years. The last row of each table contains the steady-state probabilities.

Table 3 predicts radical changes in the future structure of the HIV epidemic in Poland.

One can expect that a new structure with a prevailing share of HIV infections among heterosexual persons will eventually replace the recent, typically East-European pattern of infections being more prevalent in the IDU group. However, reaching a steady-state structure within one decade does not seem likely. We can see in Table 3 that even 10-year forecasts are still very far from the equilibrium probabilities. Therefore the proclamation of the 'near end of HIV infection among injecting drug users' in Poland seems to be premature.

Table 3. The *h*-year ahead forecasts of the HIV epidemic in Poland by the mode of transmission* and steady-state probabilities p_0

h	Year	HBM	IDU	HP
1	2007	0.16073	0.52402	0.31526
2	2008	0.15026	0.50958	0.34016
3	2009	0.14384	0.49535	0.36081
4	2010	0.14002	0.48144	0.37854
5	2011	0.13786	0.46794	0.39421
6	2012	0.13675	0.45487	0.40838
7	2013	0.13631	0.44225	0.42144
8	2014	0.13629	0.43008	0.43362
9	2015	0.13653	0.41837	0.44510
10	2016	0.13693	0.40710	0.45597
∞	Steady-state probabilities p_0	0.15435	0.13071	0.71494

* Abbreviations: HBM: homo/bisexual men; IDU: injecting drug users; HP: heterosexual persons.

Source: Authors' calculations using data from Table 2.

FINAL REMARKS AND CONCLUSIONS

Empirical findings show that HIV infections are more probable within analysed populations than between them. However, the scale of HIV mobility is small.

The estimated Markov chain predicts radical changes of the routes of HIV infection in the future: the HIV infections among the HP population will dominate the infections among the IDU group and the HBM group. However, the evolution of the HIV epidemic in Poland is still far from equilibrium.

The possibility of estimating the transition probabilities using routinely collected data extends the set of HIV epidemic analysis tools. The knowledge of the conditional and unconditional probabilities can also be helpful as Bayesian prior information to the modelling of HIV infection (1).

The empirical results presented in this paper should be interpreted with caution. We cannot test the significance of the estimated transition probabilities because the distribution of restricted estimators are unknown. Also one year seems to be too large as a time unit in the Markov chain. Pilcher et al (8) have found transmissions occurring less than six months after infection. Although half-yearly data can be retrieved from mid-year surveillance reports, such data are not reliable.

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title

A suspicion of aspergillosis in a child with AIDS – a case report

authors

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summary

We are presenting the case of a 10-year-old girl with late AIDS diagnosis and a suspicion of invasive aspergillosis with liver involvement who showed a good response to voriconazole treatment.

key words

AIDS, aspergillosis, child

address

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Background

HIV infection is rarely considered to be the potential cause of severe or recurrent bacterial and fungal infections in children. Until now, screening for HIV infection during pregnancy has not been carried out in Poland. The diagnosis of a child is thus often made late, when the disease is already at the advanced stage (1,2).

Severe immunodeficiency leads to opportunistic infections, including TB, PCP, CMV, invasive candidiasis, MAC, cryptococcosis. Although aspergillosis, a fungal infection, is rare among people with HIV infection, it is often a life-threatening disease with detrimental outcomes. The estimated incidence of invasive aspergillosis in pediatric AIDS patients was 1.5-3.0% prior to HAART era (3). Specific risk factors include low CD4 count, neutropenia, corticosteroid use, broad spectrum antibiotic exposure, previous pneumonia, concurrent malignancy with chemotherapy, respiratory opportunistic infections and HIV-related phagocytic impairment. Pulmonary and central nervous system (CNS) infections are the most common, hepatitis is a rare manifestation.

The aim of the paper was to present the case of a child with late AIDS diagnosis and a suspicion of aspergillosis.

Case presentation

A 10-year-old girl with newly diagnosed HIV infection (most probably vertical infection) was admitted to the Department of Children's Infectious Diseases, Medical University of Warsaw.

Past medical history. The patient was born full-term to a 32 year-old mother by a cesarean section (because of the mother's urinary tract defect). Her weight was 2900 grams and she was given 7 points on the Apgar scale. She was breastfed for 18 months.

Family history. Her mother had been hospitalized on numerous occassions before she died of unknown reasons, when the child was 8 years old. She was not checked for HIV at all.

A retrospective review, based on medical documentation and information obtained from the father, stated that the child had been suffering from recurrent respiratory tract infections, supposedly due to asthma, since her early childhood. Later cystic fibrosis was also suspected. Growth deficiency was observed. She was hospitalized on numerous occasions.

When she was 9.5 years old, she started to complain about leg aches, fatigue, vomiting, refusing to eat, failure to thrive. She was suspected of having cystic fibrosis, but the diagnosis was not fully confirmed. At the age of 10 years she was hospitalized due to worsening of general condition, refusing to eat, vomiting, cough, stomach aches. On physical examination, candidiasis of digestive tract, hepato and splenomegaly and rhonchi on lung auscultation were observed. Laboratory abnormalities included: neutropenia (WBC 0,94 $\times 10^3/mm^3$, neutrophils 0,24 $\times 10^3/mm^3$), thrombocytopenia (platelets 67 G/l), hepatitis: alanine transaminase (ALT – 303 U/l: normal range 10-70), aspartate transaminase (AST – 776 U/l: normal range 10-59), gammaglutamylotranspeptidase (GGTP – 177 U/l: normal range 15-73). In abdominal USG partial fibrosis of pancreas was observed. She received amoxicillin with clavulanic acid, azithromycin and fluconazole.

She was moved to a hematological ward, because of pancytopenia (WBC 1,72 $10^3/mm^3$, platelets 55 G/l, RBC 3,64 T/l) and bone narrow examination was done to exclude leucaemia. Hepatitis with cholecystitis and pancreatitis was diagnosed: ALT 384 U/l, AST 1300 U/l, bilirubin 251 μmol/l (normal range 3-22), amylase in serum 837,9 U/l (normal range 30-110), amylase in urine 7221 U/ml (normal range 32-641). It was confirmed by abdominal USG and CT scans. *Aspergillus* antigen in serum was positive and passive haemaglutination test for *Aspergillus fumigatus* was also positive (1:160, normal range 1:80). Immunological examinations find extremely low CD4 count, and this finding resulted in HIV testing. Positive HIV Western blot was obtained. CT examination of thorax demonstrated patchy infiltrate in the middle right lobe and in the posterior segments of left lower lobe. MRI examination of brain showed an evidence of cortical atrophy, suspicion of degenerative changes of white matter, enlargement of cerebrospinal fluid spaces, swelling of mucous membrane of both maxillary sinus, sphenoid sinus and ethmoid cells. Findings on brain MR imaging, chest CT and abdominal USG were non-specific to any particular pathogen.

She received wide spectrum antibiotics (ceftazidime, amikacin, piperacillin + tazobactam), fluconazole and supportive treatment with partial improvement – she recovered from pancreatitis, but not from hepatitis. Co-trimoxazole was started for pneumocystodosis (PCP) primary prophylaxis.

She was moved to our Department with AIDS diagnosis and a suspicion of aspergillosis.

On admission. Physical examination revealed wasting syndrome, jaundice, hepato and splenomegaly. She complained about abdominal pain.

Laboratory investigations showed neutropenia (WBC 2,0 $\times 10^3/mm^3$, neutrophils 0,55), anaemia (HGB 8,5 g/dl, RBC 3,23 T/l), aminotransferases level elevation with aspartate predominance (ALT 131 U/l, AST 574 U/l), hyperbilirubinemia (bilirubin 192,5 μmol/l) with conjugated bilirubin predominance and the highest GGTP level of 763 U/l.

The patient had CD4 count of 33 cells/ml (9%) and HIV RNA VL of 505 526 copies/ml (5,7 log).

PCR DNA *Aspergillus* from gastric lavage was positive. PCR DNA *Candida glabrata and parapsilosis* from gastric lavage was also positive. Other opportunistic infections (TB, MAC, PCP, cryptococcosis) were excluded. HCV and HBV infection were excluded (PCR HCV RNA negative and HBsAg negative, respectively). Cultures for bacterial and fungal infections from blood and CNS fluid were negative. Other agents, which may cause hepatitis with cholestasis were excluded (CMV, HSV, EBV, HAV, toxoplasmosis).

Soon after admission she was switched from fluconazole to voriconazole (7 mg/kg intravenously twice daily) to treat presumptive invasive aspergillosis. Wide spectrum antibiotics were continuated for one more week. She also received immunoglobulins. Co-trimoxazole for primary PCP prophylaxis and azithromycin for primary MAC prophylaxis were administered. Rapid clinical improvement was observed (general condition improvement, no abdominal pain, proper food intake). After 10 days she started combined antiretroviral therapy (cART) consisting of emtricitabine, tenofovir, nevirapine.

Follow up

After 8 weeks of voriconazole treatment the bilirubin and aminotransferases levels were normal, GGTP decreased to 221 U/L. Heamatological parameters were within normal ranges. Seven weeks lasting cART resulted in 3 log decrease in HIV RNAVL – to 641 copies (2,81 log), but no improvement in CD4 count was observed. She remained on voriconazole therapy for the next 3 months (7 weeks of intravenous induction with oral maintenance).

Four months after cART initiation she was admitted to the hospital due to clinical manifestations of pneumonia. For the first time there was no radiological changes in the chest X-ray. She received standard treatment (cefuroxime) with a good clinical response. Aminotransferases levels were normal, GGTP remained slightly elevated – 85 U/L. No anaemia, neutropenia or thrombocytopenia were observed. HIV RNA VL was still detectable – 416 copies (2,6 log), and for the first time improvement in CD4 count was observed – 117 cells/ml (8%).

Discussion

There are about 150 HIV-infected children in Poland, 90% of them got vertically infected (4). Before 2009 there were no recommendations for routine offering testing for HIV in pregnant women (5). Vertical transmission prophylaxis relays on a women's knowledge of their HIV status. It reduces the risk of HIV infection in a child from 30 to 1%.

In the patient described here, it was not possible to determine for sure whether the route of infection was vertical, but some factors (growth and weight deficiency, recurrent bacterial infections from early infancy, early death of the mother) have made it the most probable. Infection with HIV in children may be attended by nonspecific clinical findings, including mild failure to thrive, non-specific intermittent diarrhea, fever and chronic skin diseases, recurrent or chronic bacterial infections, hepatosplenomegaly, parotitis, generalized lymphadenopathy. Disease progression leads to anaemia, low platelets count, severe bacterial infections (pneumonia, meningitis, sepsis), fungal and viral infections. These clinical signs and symptoms are shared by other pediatric disease processes and can cause a delay in diagnosis. In Poland the diagnosis of vertically acquired HIV is established late, often at AIDS stage, with severe immunodeficiency.

The case discussed shows how important it is to test for HIV those children characterised with growth deficiency, recurrent bacterial and fungal infections or haematological abnormalities. When two or more signs or symptoms from those mentioned above are present, one should look for immunodeficiency, including HIV infection.

The clinical features of AIDS include opportunistic infections e.g. TB, MAC, PCP, fungal infections. *Aspergillosis* is rare in HIV-infected individuals (6). *A. fumigatus* is the most common species recovered from cases of invasive aspergillosis. Predisposing risk factors include: neutropenia, severe immunodeficiency and antibiotic use, previous pneumonia and recurrent respiratory infections, which all were present in the reported case. Pulmonary infection by *Aspergillus* is the most common. Other manifestations include CNS involvement, cutaneous, sinus, middle ear and mastoid process (7). Up to our knowledge, hepatic involvement has been documented once (8). Voriconazole is the recommended treatment, which was given to our patient and yielded a good clinical response.

A definitive diagnosis of aspergillosis requires the histopathologic demonstration of an organism in biopsy specimens obtained from involved sites and a positive result of culture of a specimen from a normally sterile site. Our study has limitations: liver biopsy and bronchoscopy were not performed. The definition of probable aspergillosis requires the fulfillment of criteria within 3 categories: host factors, clinical manifestations and microbiological evidence (in some cases non-culture-based method i.e. a positive galactomannan is sufficient) (9). In our patient, apart from positive *Aspergillus* antigen assay in serum and passive hemaglutination test, PCR DNA *Aspergillus* from gastric lavage was positive. However, PCR system has not been standardized and remains investigational.

Voriconazole treatment was crucial: the patient recovered from hepatitis and cholecystitis, no haematological abnormalities were noted after treatment. The previous treatment, consisting of wide spectrum antibiotics and fluconazole (because of suspicion of fungal infection) was ineffective. Voriconazole treatment resulted in rapid clinical response and normalization of laboratory abnormalities. After 4 months of ART initiation CD4 count increased slightly and significantly decreased HIV RNA VL.

In summation, we presented a rare manifestation of aspergillosis in the child with AIDS. Invasive aspergillosis, is said to have detrimental outcomes in general so early diagnosis and treatment are imperative to survival. Good response to voriconazole confirmed the diagnosis of invasive aspergillosis with liver involvement in the presented case despite lack of histopathologic or cultures positive results.

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title

Atazanavir, a promising option in therapy in HIV infected patients with liver injury and hyperbilirubinemia – a case report

authors

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summary

The prevalence of liver disease among individuals infected with HIV is more frequent then in general population. The most common causes of clinical overt and subclinical hepatitis are infections with HCV, HBV, opportunistic pathogens, neoplasmas and drug related hepatotoxicity. All HIV infected individuals with symptoms of liver injury are in need of detailed diagnostic procedures in establishment of exact diagnosis. Treatment of HIV infection in those cases poses difficulties. This paper prescribe a case of HCV infected patient with advanced stage of HIV disease and hepatobiliary diseases.

key words

Atazanavir, liver injury, HIV

address

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Introduction

The prevalence of liver diseases among HIV infected patients is more frequent then in general population. Among the most common causes of liver injury in the HIV infected patients are viral hepatitis, opportunistic infection, hepatotoxicity of many drugs and alcohol (2,6). All currently approved drugs for the treatment of HIV infection are potentially hepatotoxic. Patients with concomitant liver injury are at increased risk of hepatotoxicity from antiretroviral drugs (2,6,8). At present it is recommended that therapy of HIV treatment-naïve patients should include boosted with ritonavir protease inhibitor or non-nucleoside reverse transcriptase inhibitor in combination with two nucleoside reverse transcriptase inhibitor (3,9).

The aim of this paper is to describe a case of HIV and HCV infected patient with cholecystitis and cholangitis of unknown origin in advanced stage of HIV disease for whom antiretroviral treatment was prescribed in the time of active hepatitis.

Case Report

A 31-year old man was admitted to the Department of Infectious Diseases and Hepatology in Bydgoszcz due to hepatitis. He was diagnosed as HIV and HCV positive in the time of hepatitis onset. He reported with three month history of intermittent, severe pain in the epigastric region and progressive jaundice. Those symptoms were accompanied with progressive general malaise, loss of appetite and a 10 kg loss of weight. He denied vomiting, but admitted to having had dark urine and episodes of watery diarrhea. He had taken an analgestic to alleviate the pain and denied any fever. On history taking the patient reported that he had been generally unwell, with recurring oral candidiasis and episodes of diarrhea over the past 2 years. He denied alcohol and drug abuse.

On the physical examination the patient was in general bad condition. He was significantly undernourished, icteric, his blood pressure was 90/60, heart rate was 90/min. Abdominal examination revealed considerable tenderness on palpation without muscle guarding or rebound tenderness. The liver was palpable 5 cm under the right costal margin. The remainder of physical examination was normal.

Diagnostic investigations were performed. Laboratory results showed moderate anemia with slightly reduced number of platelets and white blood cells: haematocrit – 29,8%, haemoglobin – 10,9 mg/dL, white blood cells – 3,2 $\times 10^9$/mL and platelets – 107 $\times 10^3$/mL , C-reactive protein was low – 0.5 mg/dL, total bilirubin was 9.41 mg/dL, direct bilirubin – 7.0 mg/dL, ALT – 213U/l, AST – 1088 U/l, GTP – 245 U/l, alkaline phosphatase – 245 U/l, serum bile acid 145 μg/l, triglycerides 419 mg/dL. Serum protein electrophoresis revealed hypergammaglobulinemia and reduced concentration of albumin. Microbiology revealed a negative stool, blood and urine culture. In the work-up for hepatitis the following results were obtain: positive serology and positive viral load for hepatitis C (postitve anti-HCV and HCV-RNA), negative serology for HBV (negative hepatitis B surface antigen, total core antibody- negative), CMV (anti-CMV IgM negative), EBV (anti-EBV IgM negative).

The patient demonstrated negative test for antimitochondrial antibodies and autoimmune markers. Opportunistic infections were excluded; serology for *Toxoplasma gondii* was negative (anti-Toxo IgM and IgG-negative), the sputum was negative for *Pneumocystis jeroveci*, and Mycobacterium tuberuculosis, and blood culture was negative for *Mycobacterium avium comlex*. The chest radiography was normal. Abdominal ultrasonography exhibited hepatomegaly, no concretions in gallbladder, intrahepatic and extrahepatic bile ducts were normal. Patient underwent gastroscopy which excluded malignant lesions. Abdominal computer tomography (CT) revealed consistent with cholescystitis and cholangitis. According to clinical findings diagnosis of cholangiohepatitis was established. The treatment was started with antibiotics (Fortum, Metronidazol, followed by Meronem) and ursodeoxycholic acid. Due to advanced stage of HIV disease the antiretroviral therapy was extremely needed.

His CD4 T cell count was 20 cell/μL and HIV viral load 901 000 copies/μl. He was started on sulfamethoazole/trimetoprim and received an antiretroviral regimen of not boosted atazanavir, abacavir and lamivudine. The HAART pretreatment evaluation show: bilirubin – 11.4 mg/dL, ALT – 153U/L, AST – 797 U/l, GTP – 309 U/l. The patient respond well to the therapy. After 4 weeks of treatment CD4+ cell count was 150 cell/μl and HIV viral load was 2410 copies/mL. Liver tests were normal except for bilirubin which was slightly elevated – 2.33 mg/dl. After 12 months of therapy there was no progression of liver disease, liver tests, bilirubin concentration and lipid profile were normal. Treatment was well tolerated and reported by patient as convenient. After achieving the sustained normalization of liver tests treatment ursodeoxycholic acid was stopped. Liver tests are still in normal range. CD4+cell count was 441 cell/μl and his HIV viral load below 50 copies/ml on the last follow up point.

Discussion

Patients with underlying liver diseases are still problematic in concern of antiretroviral treatment. For the individuals with CD4 cell count warranting HIV should be treated as soon as possible, as untreated can lead to rapidly progressive immune dysfunction, and development of opportunistic infections or other AIDS defining events (3,9). At this time antiretroviral choices should be made in accordance with current guidelines for HIV therapy, irrespective of liver diseases. All protease inhibitors have been associated with significant hepatotoxicity, especially in those with underling preexisting liver disease (2,7). At present all guidelines recommend that if we are going to treat HIV infection in treatment naïve patients with protease inhibitors it should be boosted with low dose of ritonavir (3,9). In presented case the choice of treatment with boosted PI was problematic. Most of available data are connected with safety of antiretroviral treatment in coinfected individuals, but there no data with other underling liver diseases. The data suggest the relative safety of boosted PI therapy in terms of hepatotoxicity, although variations may exist (2).

In some clinical situations for example for patients who are unable to tolerate ritonavir, according to clinical data and common practice, atazanavir 400 mg can be taken with food once daily. The unboosted atazanavir was chosen due to its hepatic safety which was observed in clinical trials and in our clinical experience. The most common laboratory abnormality associated with use of atazanavir is increased bilirubin concentration (1,4,5,7,8,12). This abnormality is due to the inhibition of UDP-glucurnosyl trans-

ferase 1A1, an enzyme responsible for glucuronidation of bilirubin (11). Hyperbilirubinemia in those cases is reversible with discontinuation of atazanavir and is not associated with hepatic injury or inflammation (10,11).

Presented in this paper case is an example of a necessity of very detailed process in establishment of correct diagnosis of liver lesion in patients with underlying advanced HIV disease. In those cases very important is to find effective and safe antiretroviral regimen. Although it seems to be controversial to introduce therapy with unboosted protease inhibitor and abacabivir for patient with very high viral load and CD4 count below 50 cells/μl in our case this regimen was not only extremely effective but also safe (3,9). In conclusion in patient with coexisting liver injury atayanavir-based regimen seems to an safe and effective choice.

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