

# hiv & aids review

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## title

## 2008 Nobel Prize for Medicine or Physiology for discovery of HPV and HIV viruses – short history of discovery of HIV

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## summary

In 2008 the Nobel Prize for Medicine or Physiology was divided and half of it awarded discovery of the human papilloma virus (HPV) and its correlation with women's cervical cancer, and the other half – discovery of the human immunodeficiency virus (HIV). The latter part raised many comments and controversies. As 25 years have passed since the HIV virus was identified, the short history of this discovery was recalled, as it is quite forgotten now.

## key words

**HIV, discovery, Nobel prize**

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On the 6<sup>th</sup> October 2008 the Nobel Committee announced that half of the Prize for *Medicine or Physiology* was granted to the German researcher Harald zur Hausen who had discovered the *human papilloma viruses* (HPV) causing cervical cancer and the other half to two French scientists – Françoise Barré-Sinoussi and Luc Montagnier for their discovery of *human immunodeficiency syndrome* (HIV).

The grounds of the Committee's decision indicated that Harald zur Hausen had abolished the former axioms by proving that the oncogenic human papilloma viruses (HPV) are responsible for cervical cancer – the most frequent neoplasm in women, he had also showed that HPV form a heterogeneous virus family and only some types cause the cancer. His discovery allowed for analysis of the HPV infection process, for understanding mechanisms of HPV-induced carcinogenesis and for creation of a vaccine preventing HPV infection. Françoise Barré-Sinoussi and Luc Montagnier discovered the HIV virus. They showed that the virus is produced in lymphocytes of patients with enlarged lymph nodes at early stages of immune deficiency and in blood of patients at advanced stages of the disease. They characterised HIV as the first known human lentivirus based on its morphological, biochemical and immunological features, they also proved that it destroyed the immunological system by massive replication and lymphocyte damage. This discovery was the basis of the current understanding of biology of this disease and of the antiretroviral therapy. The entire grounds and curriculums of the laureates can be found at the Nobel Committee's website: [http://nobelprize.org/nobel\\_prizes/medicine/laureates/2008](http://nobelprize.org/nobel_prizes/medicine/laureates/2008).

The Nobel Foundation's rules limit the number of laureates of the physiology or medicine prize to 3 persons. It is often controversial to omit someone. This year, the Committee didn't recognise Robert Gallo, the American virologist who had worked at the *National Cancer Institute* (NCI), Bethesda, USA, for many years before moving to the University of Maryland in Baltimore. Gallo told the *Associated Press* that he was "disappointed" that he was not awarded along with the French team. Anthony Fauci, head of the *National Institute of Allergy and Infectious Diseases* expressed his joy that the Frenchmen were recognised and he said he was convinced that if only the Nobel Foundation's rules allowed for awarding four researchers, Robert Gallo would certainly be included [1].

## SHORT HISTORY OF DISCOVERY OF HIV

Almost immediately after the acquired immunodeficiency syndrome (later called AIDS) was characterised, scientists started to search for its aetiology factor. In the first report describing the new acquired immunodeficiency syndrome, Gottlieb et al. mentioned that the cytomegalovirus (CMV) played a role in inducing immunodeficiency [2]. It was suggested that the virus affected homosexual men who used nitriles [3] or that it was connected with some types of sexual activities, such as "fisting" or "rimming" [4]. The syndrome was also believed to be caused by hepatitis B virus (HBV) [5]. In the early 1980s scientists thought that human T-cell leukaemia virus is especially attractive as an agent as it is a retrovirus with known tropism for T helper phenotype cells. In AIDS it could be causing cell destruction rather than malignant proliferation, an idea not without precedent [6].

In the early 1980s there were above all two big research teams working on the issue of aetiology of AIDS: the American and French ones.

The American team worked at the *National Cancer Institute* in Bethesda, USA and it was led by Robert Gallo, whose scientific output was already quite significant at the time. He was recognised for the discovery of *T cell growth (mitogenic) factor*, now called interleukin 2 (IL-2) [7], and of the *human T-cell leukaemia virus-1* (HTLV-1) [8]. In 1982 he obtained the *Albert Lasker Medical Research Award* [9], one of the most respected science prizes in the world. They often presage future recognition by the Nobel committee, so they have become popularly known as "America's Nobel" [10]. (He was awarded with this prize again in 1986, together with Luc Montagnier for discovery of HIV).

Establishment of the French team was initiated by physicians who took care of AIDS patients: Willy Rosenbaum, David Klatzman and Jean Claude Gluckman, who were joined by several other researchers from different medical schools in Paris. The doctors gathered at the nephrology department of Pitié-Salpêtrière Hospital and they held the first French epidemiological, immunological, and virological studies of AIDS. The exchange of ideas that took place in this study group was essential for the discovery of the disease's causal virus. Rosenbaum and virologist Françoise Brun-Vezinet contacted Luc Montagnier's group at the Institut Pasteur and brought them a lymph node specimen [11]. Montagnier, Barre-Sinoussi et al. had previously searched for neoplasm-inducing retroviruses and a milestone of their studies was the 1979 discovery that antibody against alpha interferon allows significant increase in mouse retrovirus production by infected cells [12].

In May 1983 the French research team reported that it had isolated a new *T-lymphotropic retrovirus* [13], then called shortly LAV – *lymphadenopathy associated virus*, from a lymph node of a young man with generalised lymphadenopathy and indicated that their isolate was "clearly distinct from each previous isolate". Their electron micrographs demonstrated a virus budding from the cell membrane which was distinct from HTLV but similar to lentiviruses. Simultaneously three articles by Gallo and his associates were published on the involvement of the HTLV in AIDS [14, 15, 16], a topic which was further amplified in the same issue of *Science* in an article entitled "*Human T-cell leukemia virus linked to AIDS*" [17]. In interviews for medical magazines, Gallo stressed that the most probably HTLV was the AIDS aetiology factor [18]. The American virus name evolved in time. At first, it was referred to as *human T-cell leukemia virus*, then – *human T-cell leukemia/lymphotropic virus* [19] and finally – *human T-cell lymphotropic virus*. The abbreviation HTLV remained.

During a Cold Spring Harbour (CSH) Laboratory meeting in 1983 Montagnier presented a paper on "A new human T-lymphotropic retrovirus: characterization and possible role in lymphadenopathy and acquired immune deficiency syndromes". This presentation provided evidence that their virus isolate, in contradiction to HTLV, belonged to lentivirus subfamily of retroviruses. It included extensive serological and immunological data, electron micrographs showing typical lentivirus morphology, and evidence that the viral isolate propagated in vitro and was cytopathic to the helper CD4 lymphocytes, causing cells to fuse with giant cell formation [20]. The authors acknowledged Robert Gallo for providing antibodies to HTLV and for HTLV-producing cells. In an interview for the *Bulletin of World Health Organization*, Barre-Sinoussi remembers his American colleague's reaction to the news about this discovery "He joked that I should throw it all in the trash because of what we would unleash" [21]. One month later, in June 1983, the French team submitted a second paper entitled "Selective tropism of lymphadenopathy as-

sociated virus (LAV) for helper-inducer T-lymphocytes” to the London office of *Nature*; the manuscript conclusively showed that the virus involved in AIDS belonged to a new group of human retroviruses that differ from human T-cell leukaemia virus (HTLV-1); it also made a most significant observation that the virus was cytopathic to helper T4 (CD4) cells, providing for the first time an explanation of how and why AIDS developed. Regrettably, the manuscript was rejected. The resulting delay before it was finally published in *Science* [22], meant that its medical and scientific audience has been denied crucial information for nearly a year [20].

The French scientists were surprised when on 23 April 1984 at an urgent press conference Margaret Heckler, secretary of the U.S. Department of Health and Human Services (DHHS) announced that Robert Gallo of the NCI discovered the cause of AIDS – the retrovirus called HTLV-III [23], and she declared that soon tests for presence of the virus in blood would be available. She expressed her hope that a vaccine against AIDS would be developed within 2 years. At that conference, the discovery by the French team was not mentioned [24].

In 1984 Jay Levy’s team also isolated a virus from an AIDS patient. The virus was called *AIDS related virus* (ARV) [25]. For the first time, authors have proved that there is an asymptomatic stage of infection, by isolating the virus from clinically healthy homosexual men as well.

Montagnier in 1984 recorded in a *Nature* letter that his laboratory “supplied Dr Gallo LAV first isolate on 17 July and 23 September 1983. According to Dr Gallo, the first sample failed to grow in his laboratory, but the second did”. The letter also states: “In our earlier investigations, we received from Dr Gallo only HTLV-1 reagents, which were useful to show that LAV was not related to HTLV-1” [26]. It appears that after the second shipment of LAV to Gallo’s laboratory, the Czech virologist Míclav Popovic succeeded in growing the French isolate in the Hut-78 T-cell line. On 12 December 1983 Gallo submitted another paper to *Science*, accepted on 12 March 1984 [27], regarding the involvement of HTLV in AIDS [20]. None of the works published in 1984 mentioned that isolates of the virus causing AIDS were obtained from the French researchers a year before or that the T-cell line used for growing the virus was produced in another laboratory [28]. Electron micrograph illustrating HTLV-III in one of the papers turned out to be LAV actually [29]. This fact was explained as an unintended mistake.

In March 1985 the FDA (*Food and Drug Administration* – USA) registered the first test (ELISA) [30] detecting anti-HTLV-III/LAV antibodies, and produced based on a preparation obtained from Robert Gallo’s laboratory [31]. DHHS decided to transfer the technology developed at the National Cancer Institute to the private sector, five companies (Abbot Laboratories; North Chicago, Illinois; E. I. DuPont de Nemours and Company, Inc., Wilmington, Delaware; Electro-Nucleonics Ind., Fairfield, New Jersey; Travonol/Genentech Diagnostics, Cambridge, Massachusetts and Litton Industries, Sunnyvale, California) were awarded nonexclusive, royalty-bearing licenses to produce commercial antibody tests [32].

In 1985 there were reports that LAV and HTLV-III are identical [33, 34]. Gallo’s group reported the “First isolation of HTLV-III”, stating that they had evidence for the presence of a new retrovirus in AIDS and ARC (AIDS-related complex) patients long before the LAV particles were sent to Gallo’s laboratory and even before the publication of the results by Barré-Sinoussi et al in 1983 [35]. However, it was later confirmed that LAV and HTLV-III are the same virus [36, 37, 38].

In 1986 the International Committee on Taxonomy of Viruses called it HIV (*human immunodeficiency virus*) [39]. Prior to this time, numerous publications refer to HTLV-III as the causative agent of AIDS or use the dual designation LAV/HTLV-III or HTLV-II/LAV.

Patents for tests to detect presence of anti-HIV-1 antibodies became a profitable undertaking. The research team of the Institut Pasteur in Paris believed they the first to discover the causative factor of AIDS and demanded a right to participate in the revenues. Dispute was resolved in 1987 by an agreement between President Reagan and French premier Chirac that scientific credit and royalties be equally shared by the two countries: each country keeps 20% of the royalties from its tests before pooling the rest of the remaining 80%, 25% has gone to the World AIDS Foundation, which funds AIDS research and education in the developing world; the rest has been split evenly between the two sides. Until 1994 United States had received \$ 20 million from its HIV blood-test patent; the Pasteur had taken \$ 14 million. The reason for the imbalance was that the U. S. test sells better than French one. In 1994 director of NIH announced that the royalties would be relocated to “equalize” the amounts by the two countries by giving the Pasteur 50% of the pooled money and cutting the U.S. share to 25%, with 25% still going to the World AIDS Foundation [40]. One of the points of the agreement provided that the chronology of research should be presented jointly by Gallo and Montagnier [41]. But in November 1989 the Chicago Tribune published an extraordinary article by John Crewdson suggesting that Gallo had robbed the French of their virus and rightful credit, though is cautiously concluded that Gallo’s claims of discovery were based on “either an accident or a theft” [42]. NIH ordered an investigation by the *Office of Scientific Integrity* (OSI), recently established in response to suspicious allegations [43].

It seems no coincidence that during the investigation by OSI, Gallo admitted that his cultures were incidentally contaminated with the French virus [44]. His letter to *Nature* ends with an appeal: “It is now time for this period of controversy to come to an end and for us all to focus our efforts on ending the pandemic”. In September 1991 the final report by OSI found that Gallo deserves only to be charged with insufficient supervision of his subordinates. In the early 1990s two of his close collaborators were dismissed and he himself assured that he knew nothing of his deputy laboratory chief’s misconduct and that these two separate criminal cases involving his laboratory scientists were unfortunate coincidences.

In March 1992 the US Health Department and subcommittee of the Congress resolved to renew the investigation and entrusted the *Office of Research Integrity* (ORI) with the task.

It turned out also that two subjects described in an article in the *Lancet* co-authored by Gallo and French researcher Daniel Zagury had died, but Gallo had failed to report these deaths to the NIH as was required by grant regulations and had erroneously reported in the *Lancet* that he had observed no adverse reactions in the human subjects [45, 46]. Gallo again explained that the statement in the *Lancet* was an inadvertent error and that his failure to comply with NIH procedure was a result of unfamiliarity with the regulations – this despite some 20 years of employment at the NIH [47].

Referring to controversies concerning the anti-HIV antibodies test, Dr. Gallo first stated that the virus he used was definitely different from that used by the competing French team. When genetic sequencing proved that the vi-

ruses were identical he suggested that the French must have taken his virus. When that claim was challenged, Dr. Gallo explained that there must have been an inadvertent contamination in his laboratory [45].

In December 1993 the ORI report ascertained that Gallo had used the French preparation and had purposely claimed discovery of the virus, dishonestly reviews papers concerning LAV signed by Montagnier, including a modification of the French text suggesting precedence of discoveries at his own laboratory, careless preparation of his own papers and covering unethical actions of his collaborators, disorder in lab documentation, making their appropriate examination impossible [48]. The case lasted many years [49], but finally Gallo and his team were cleared of charges of wrongdoing [50].

The dispute who was the first to discover the virus caused France's decision to reject the American offer of tests in March 1985 and to wait for tests produced by the Institut Pasteur, which were made available in August the same year [51]. This seemingly short delay resulted in HIV infection of 4,000 persons, including 1,000 haemophilia patients [51]. The dispute contributed also to a thesis by some researchers, including a virologist Peter Duesberg who stated that the conclusion that HIV causes AIDS was rash. Duesberg proposed his hypothesis that AIDS is caused by long-term consumption of recreational drugs and/or antiretroviral drugs [52]. Duesberg's denial of HIV/AIDS science is cited as a major influence on the public health policies of South Africa under the administration of Thabo Mbeki. Duesberg also served on an advisory panel to Mbeki, convened in 2000. The consequent failure of South Africa to provide antiretroviral drugs in a timely manner is thought to be responsible for hundreds of thousands of excess AIDS deaths and HIV infections [53].

Former scientific adversaries finished their disputes a long time ago. After the governments' agreement signed in 1987, they wrote together the history of AIDS studies, and then they described it again in separate papers published in the same magazine in 2002 [54, 24]. Montagnier wrote "Over the past 20 years, the scientific and legal controversies between our team and Gallo's group have faded". The essays were seen by some as a way to prepare the ground for shared, controversy-free Nobel award. Yet "the protagonists don't get to write history themselves" says Pasteur researcher Simon Wain-Hobson [50]. In an interview given for *The Wall Street Journal* after obtaining the Nobel Prize, Luc Montagnier said that several months after his team's discoveries, "Dr. Robert Gallo and his colleagues at the National Cancer Institute in Bethesda, Md, confirmed and extended our findings" [55]. He said also that "it is certain that he deserved his as much as us two". Gallo, meanwhile, was also magnanimous "I congratulate this year's Nobel Prize winners" [56]. In many medical magazines, comments after the Nobel Prize awarded to the French team only, it was reminded that many other scientists contributed to discovery of HIV as well, such as Jean-Claude Chermann, Jay Levy, and Robert Gallo [57]. In *Science* more than 100 researchers from all over the world published a letter stressing Robert Gallo's merits [58]. Few articles mentioned Willy Rosenbaum, AIDS patients therapist who persuaded his patient in an early stage of AIDS with generalized lymphadenopathy to undergo lymph node biopsy and who supplied the tissue to the laboratory where scientists could study it [59, 60]. His contribution to identification of aetiology of AIDS and the future Nobel Prize cannot be overestimated.

As the British researcher Abraham Karpas wrote: "*The history of AIDS research involves huge rewards, unscrupu-*

*lous ambition, disregard for common principles of scientific conduct, battles over priority leaving injustice uncorrected, and terrible consequences in the wired world. It is not an exaggeration to say that AIDS research was squandered for the best part of a year, delaying the development of an acceptable test for HIV, a year in which thousands of individuals contracted an infection that they may otherwise have avoided*" [20].

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# Healthcare and antiretroviral treatment in HIV-infected detained persons at the penitentiary units

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summary

There has been an increase rate of HIV prevalence among prison population in Poland. The prevalence of HIV infection in Polish prisons is 1,54 percent out of detained population. Total number of HIV/AIDS was 1145 prisoners in 2007, and 81 new cases was detected during imprisoning. HIV-positive injection drug users (IDU's) are a special category of patients whose access to treatment is limited by economic and addiction barriers, out of the prison walls. Recent studies in Central and Eastern Europe show that even with the wide availability of antiretroviral (ARV) medications, only 40 percent of IDU's received HAART. The situation is more alarming in Russia and other FSU, where less than 1 percent of HIV-positive drug users receiving ARV treatment. In Poland HIV-infected prisoners have been regularly monitored on the specialist visits, and they could voluntarily opt out of HIV tested, as well as HCV, HBV, syphilis, etc. Design of antiretroviral regimen in prison can be arrange precisely for long-term period. Directly administrated antiretroviral therapy is the best method for non-adherent patients, especially for IDU's in prison.

key words

**HIV infection, prisons, antiretroviral therapy, healthcare in prison**

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## INTRODUCTION

The widespread recognition of HIV epidemics and healthcare in prisons must be integral part of the public health policy. It is the principle of prisoners have received the same healthcare standard that people outside of prison. Furthermore, inmates who have participated in the antiretroviral therapy and have success of viral response, and comply with the prison rules, have a good opportunity to continue their treatment outside the prison.

Intravenous drug users (IDU's) detained has risen dramatically in Central and Eastern Europe, as well as in Poland. So, the number of drug dependent people with HIV/AIDS has been growing among arrested population recent years. Almost 70% of HIV-positive prisoners were intravenous drug users in Poland. Special offer for both; HIV infection treatment and drug addiction treatment is the principle mission for justice and penitentiary healthcare policy [1].

*Dublin Declaration on HIV/AIDS in Prison, 2004* was being initiated the first inter – ministerial efforts on HIV treatment in prison in Europe and Central Asia. The statement of both; the rights of people imprisoning to proper AIDS care, and the responsibility of governments of HIV healthcare in prisons, was described by representatives from 55 countries [2]. *The Consensus Statement on Prisons, Drugs and Society* had first been produced by the WHO and Council of Europe (Pompidou Group) in 2002 [3].

Regularly updated *The National AIDS Program in Poland – 2006-2011*, provide access to antiretroviral therapy for all patients with HIV/AIDS, including imprisoning individuals in Poland [4].

## CHARACTERISTICS OF HIV-POSITIVE POPULATION IN PRISON

Remaining in detention, a sentenced person has right to obtain regularly proper diet, clothes, living conditions and free of charge medical care and medicines.

Besides of AIDS disease, prisoners have many concomitant diseases, e.g. hepatitis, cirrhosis, malignancies, tuberculosis, syphilis, as well as drug-related illness and psychiatric disorders. A medical surveillance of prisoners infected by HIV show the great prevalence of co-infections HCV, HBV.

In penitentiary population psychosis, depressions or characteropathy have occurred very often, so adherence to various therapies are poor and antiretroviral treatment discontinuation have been observed among this patients frequent. Sometimes patients refused their medicines and stopped therapy themselves due to behavior abnormalities in prison. The closed population in detention also makes for infection HIV spread quickly through sex, violence and needles share inside the prison walls.

## ANTIRETROVIRAL THERAPY IN PRISON AND PENITENTIARY MEDICAL CARE

Antiretroviral treatment in prison is not easy. In penitentiary ambulatories and hospitals there were observed patients strongly experienced of ARV therapies due to many ARV regimens in their history, willfully drug discon-

tinuation and drug resistance in consequence. Furthermore access to antiretrovirals in prison sometimes is limited. According to the guidelines, it is necessary to regular monitoring for PCR HIV-1 RNA, CD4 count, genotyping test, other laboratory parameters, as well as drug resistance, drug interactions and side effects. This parameters makes for increase total costs of medical care for HIV-infected prisoners.

Including criteria to ARV, drug regimen and monitoring process are identical as in freedom patients. Good adherence, drug doses strongly comply and special diet recommendations have been required over an antiretroviral therapy. Because of poor diet choice and various daily activities prisoners e.g. work, transportation to the Court, education lessons etc., this regimen can not be undertake in prison precisely.

Penitentiary healthcare workers are engage insufficiently on the antiretroviral treatment in prison units. To improve this situation, it is necessary to enforce the education penitentiary staff and develop of substitution programs for opiate addicts [5].

## HIV EPIDEMICS IN PRISONS IN EASTERN EUROPE COUNTRIES

Violence between prisoners is well-known and difficult to keep it under control. It appears that the risk and incidence of HIV infection is higher in prison, than in general population. In Ukraine, which has one of the highest HIV growth rates, 7% of prisoners are infected HIV, according to The Nikolaev Charity Foundation [6]. The "Medicins Sans Frontieres" discovered that in seven Russian prisons 43% of the inmates had permanently illegal drugs injections during detention, and 13,5% out of this group started heroin addiction in prison [6]. The Pskovian Anti-AIDS Initiative (Russia) registered five fold over of drug addicted individuals imprisoned recent years.

The AIDS Prevention Center in Latvia demonstrate well, how HIV and drug use magnify each other in prison. The data from Latvia has shown that one fifth of the total HIV cases were in prisons, and half of the newly diagnosed infections are coming from the penitentiary units [7].

Many people with criminal history, have turns to the drug trade. A newest study in Tajikistan has shown that women enter the drug trade because of the poor economic situation and unemployment. Among of all women in prison in Tajikistan, 59% are there for drug-related crimes [6,7].

## PENITENTIARY HEALTHCARE SYSTEM FOR HIV-INFECTED PRISONERS IN POLAND

In 90-ties many difficulties were relating to the HIV/AIDS tolerance in prisons. At this ages prisoners who have confirmed HIV-seropositive, were isolated and separated of the penitentiary units. It has caused protest of both; the local community in prison and penitentiary staff. Since 1994 testing for HIV has been implemented in penitentiary medical care by voluntary.

After providing the education and information on HIV issues for all penitentiary workers, the segregation and isolation because of HIV seropositive status was discontinue

totally. Now, in all arrests and prison units, HIV-positive prisoners have been lived with other in the same cell. Education contained the information for penitentiary staff about health and safety at work, drugs, addiction issues, infectious diseases and the services required. The main objectives of education was to raise awareness of health problems in prison and encourage a positive attitude towards risk behavior reduction by both inmates and personnel.

Detained persons living with HIV, has been registered in Poland since 1989 and their number is continuously increasing. According to statistical data of the prison surveillance report, total prison population was 90 714 people, who were detained in 155 penitentiary units (32 – on high security) in 2007. Within the administrative structure in 15 regional inspectorates, healthcare centers providing health services in 157 operating ambulatories and 13 penitentiary hospitals on various profile, with 1287 hospital beds. Since 2000 prisoners have gained an access to the specialist consultation on HIV, as well as providing the antiretroviral therapy. In April 2004 the Regional Director of Prison Healthcare Service, opened methadone maintenance substitution in Warsaw (3 units) for imprisoned in Warsaw Penitentiary Department [5,8]. Methadone substitution enable to contact with opiate dependent prisoner, improve of psychological status stabilization, and ARV treatment as well as HIV infection management. Methadone program participation has given also the chance of diagnosis, and treatment of opiate – related illness, e.g. HCV, HBV, bacterial infections, thrombotic vein inflammation, tuberculosis and sexually transmitted diseases. Fourteen Methadone programs in Polish prison units has enabled to access to the large medical offer for drug addicted people who were deprived of freedom [9,10]. Prisoners may voluntarily opt out of HIV tested, as well as HCV, HBV, syphilis and other diseases diagnostics.

Total number of HIV/AIDS was 1145 prisoners in 2007 (in 2006 it was 1244) [6,8]. It was also 81 new detected cases in prison this year. The prevalence of HIV infection in Polish prisons is 1,54% out of detained population [8]. Every month almost 400-600 prisoners HIV-infected regularly have been resided in all prisons in Poland. Antiretroviral procedures there were realized in 220 patients in 2007.

HIV-infected patients have been regularly monitored within the specialist visits. When there is a need to hospitalization, they are sent to one of the three internal hospital wards.

Design of antiretroviral regimen in prison can be arrange precisely for long-term period and actually the Directly Observed Treatment (DOT) and Directly Administration of Antiretroviral Treatment (DAART) has to be adaptable in Poland.

DOT model of ARV therapy is the best means to success among non-adherent patients.

## CONCLUSION

Mostly, individuals in prison are severely affected by HIV/AIDS, owing to the high-risk behavior that they engage in prior to incarceration. Stress and side effects were the most frequently stated factors for interruption treatment; usually for short period of time. Therefore, it is important to identify and understand them before starting the therapy.

A variety factors affect adherence to antiretroviral therapy in detained patients. It is also important to understand individual patient's disease history. Drug users usually do not adhere to therapy, as a consequence of marginalization, domestic violence, psychiatric disorders and the poor doctor-patient relationship in the lives outside prison wall. Non-adherence to ARV regimen is the most important determinant of the virologic and immunologic failure. Barriers reduction to medical care during detention has improved adherence to difficult, long-term antiretroviral regimens. Directly administered antiretroviral therapy (DAART) is the best method to improve therapy results, and prison offers an ideal opportunity for its realization. Many patients on the DAART program in prison, have achieved undetectable HIV-1 viremia at 24 week of therapy.

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## title

# Efficacy of antiretroviral therapy among HIV-infected prisoners treated with Directly Administration of Antiretroviral Treatment (DAART) method in Warsaw Penitentiary Department

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## summary

The prevalence of HIV infection among the Polish detained population is 1,54%, therefore since 2000 prisoners have gained an access to the HIV-specialist consultations at penitentiary medical clinics. In Poland, prisoner may voluntary opt out of HIV tested as well as HCV, HBV, syphilis and other. An antiretroviral therapy is offer for people deprived freedom. More than 81% of HIV-infected individuals in prison units are intravenous drug users. The aim of this paper is evaluation of antiretroviral therapy efficacy at 24 week of treatment, among prisoners treated with the Directly Administration of Antiretroviral Treatment (DAART). According to DAART, tablets are administrated under healthcare and penitentiary staff control. In Warsaw Penitentiary Department data base there were 528 individuals HIV-positive, and 244 people out of this community there were included to ART. Among ARV-treated patients on DAART method, viral response (VR) <50 copies/mL were achieved in 83,6% prisoners. Patients with low HIV-1 viremia at baseline, have undetectable HIV-1 viremia at 24 week in 82% out of treated individuals. DAART system in prison can be useful for long-term ARV monitoring, especially for non-adherent drug users.

## key words

directly administration of antiretroviral therapy, HIV in prison, antiretroviral therapy

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## INTRODUCTION

The prevalence of HIV infection among prison population in Poland depends on penitentiary region and imprisoning intravenous drug users, as well as the risk behavior patterns in the prison community. Drug using patterns have changed over time in Poland, so HIV-risky behaviours inside prison also changed. HIV presence among prisoners has been registered since 1989 in Poland (1,3,6,7).

The penitentiary medical care service offer voluntarily opt out of HIV testing at the beginning of incarceration whereas first visit in medical room (2,3). Since 2000, prisoners have gained an access to a consultation of HIV specialist doctors at penitentiary units or HIV clinics

Epidemiological data shown, that total 1145 HIV(+) prisoners were registered in 2007 in all Polish prison units. This is interesting, 81 new cases detected in prison in the same year. Since 2000, there were diagnosed inside the prison wall 204 (39%) prisoners. The prevalence of HIV-infection among inmate population was 1,54 % . Patients with HIV/AIDS in prison units have been regularly monitored on the clinical visits and antiretroviral therapy is providing if it is necessary. The pattern of antiretroviral treatment (ARV) can be precisely determine for long-term therapy and control permanently. The Directly Observed Therapy (DOT) and the Directly Administrated of Antiretroviral Treatment (DAART) is the best method of treatment control for non-adherent patients, especially for drug users. The DAART system can be realize in prison ideally.

## OBJECTIVE

There were 10 stationary prison units and 5 pre-trial detainees with almost 7500 inmates in Warsaw Penitentiary Department. For eight years antiretroviral treatment has offered to HIV/AIDS prisoners. The DAART program have realized among all treated patients. It means, that each patient takes his tablets under control doctor or nurse. Regular physical examinations as well as biochemical parameters control is available during long-term therapy. HIV viremia level and CD4/CD8 count can be assess at precise moment of treatment. Viral failure, adverse events and intolerance reactions have been observed in prison unit on the spot.

## AIM

The aim of this paper is evaluation of ARV efficacy at 24 week, among patients – inmates treated with Directly Administrated of Antiretroviral Therapy. Additionally, the reasons of viral failure (VF), causes of discontinuation therapy and serious adverse events were analyzed.

## MATERIAL AND METHOD

The DAART system was available for prisoners within the Medical Consulting Clinic in Warsaw – Mokotow Prison, where patients with HIV/AIDS have been diagnosed and treated. Within DAART program, patient has administered tablets under healthcare and penitentiary personnel control on the purpose of adherence improvement. For 1st

January 2000 to 31th December 2007 there were provided of antiretroviral treatment for 244 prisoners at this center. Lymphocyte CD4 and CD8 count and HIV-1 RNA have measured at the baseline visit, then at 24 week of treatment process. Two groups of treated individuals were compared – one group with high HIV viral load (>100 000 copies/ml) and with low viremia (<100 000 copies/ml) prior to initiation therapy. The outcomes were analyzed through the statistics Chi<sup>2</sup> test with Pearson modification. Treated with ARV prisoners have been examined physically by doctor every month at the regular medical visit. Penitentiary nurses have registered everyday each taking tablet and behaviour observations.

The second endpoint this study there were analysis of the reasons of discontinuation therapy and side effects appearance.

## RESULTS

Among detained population in Warsaw – Mokotow Prison was 528 individuals with HIV/AIDS, registered in clinical data base between 2000 and 2007 (F-57, M-471). In this community 81% there were intravenous drug users, and 61% out of them have co-infection HIV+HCV/HBV. Antiretroviral treatment included in 244 (46%) patients, on DAART method during 24 weeks observation. There were 157 naïve and 87 experienced patients treated with antiretrovirals. The new ARV initiation regimen provided for 131 prisoners, but in 26 people antiretrovirals have started in external AIDS – clinic, thus in prison has been continued it. Among population who started with ARV treatment (n = 244) in detention, 67 prisoners did not continue therapy due to abandonment prison before 24 week (Court Sentence changing during medical observation [5]). In the total remaining ARV-treated group (n = 177), viral response <50 copies/ml were achieved in 148 (83,6%) individuals at 24 week. The first study group was 77 out of DAART – treated individuals with low level of HIV-1 viremia, and with high PCR HIV-1 RNA in second group was 71, prior to initiation therapy. Viral response < 50 copies/mL has obtained more frequent (82%) in the group with low HIV-1 viremia vs among patients with high viremia level(52,7% %), at 24 week. It was statistically significant p<0,05.

Average CD4 lymphocytes level before treatment was 188 cell/mL in total group. At 24 week ΔCD4 was av. 77 cell/mL ,but major CD4 count increase was registered among patients with high HIV-1 viremia.

Despite of everyday treatment controlling on DAART method, in 29 (16,5%) cases observed viral failure (VF). The reasons of VF were analyzed in this research also. In 4 cases, the Antiretroviral Drug Resistance Test was made, and confirmed drug resistance against to almost all NRTI class , therefore drug resistance was probably the main cause of viral failure in this cases. Nine patients refused ARV therapy and stoped treatment themselves due to behavioural abnormalities in prison, in 12 individuals discontinuation of ARV treatment have caused due to psycho disorders and/or psychiatric diseases advanced and 1 patient the suicide accomplished in prison.

The mostly observed adverse events among treated with antiretrovirals, there were: diarrhoea – in 56 cases, ALT, AST elevation in 31, triglycerides and cholesterol level rising in 30 individuals, rash in 9, and myalgia, fatigue, appetizing loss etc. were occurred rare.

## CONCLUSION

Antiretroviral treatment in prison with Directly Administered of Antiretroviral Therapy (DAART) proved useful method for non-adherent patients, especially for drug addicted [4,7]. In Warsaw Penitentiary Department, among individuals treated with DAART, in 83% achieved PRC HIV-1 RNA <50 copies/mL at 24 week since ARV initiation. Statistically significant HIV-1 viremia suppression occurred in patient group with low viremia on baseline ( $p < 0,05$ ). There were many factors influence on the viral failure in this population. The refusal of long-term therapy due to various factors, is the most frequent cause of viral failure in prison. Among treated penitentiary population, did not observed serious side effects, but psychiatric disorders, depression, irritation, sleeplessness etc. occurred in detention very often, that led to therapy discontinuation frequently than in patients outside the prison walls.

It seems, that DAART is a good method of ARV therapy in prison to promise realization of long-term therapy perfectly and safety.

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title

# Opinions and attitudes of students before completion of medical studies toward men who have sex with men (MSMs) and injection drug users (IDUs) living with HIV/AIDS

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summary

In 2000 National AIDS Centre organised studies about knowledge, attitudes and opinions of students at Polish medical universities related to HIV and AIDS. Among other results they showed that more than 60% of respondents revealed fear of AIDS, almost 60% of students agreed with the statement that HIV/AIDS is a disease of injection drug users (IDUs) and men who have sex with men (MSMs). Between 2004 and 2006 the same questionnaire was applied to students of the 6<sup>th</sup> year of the medical studies at the Medical University of Białystok, who should have already obtained information on HIV/AIDS in their education programme. The study's objective was to check whether the attitude of future doctors to HIV/AIDS, MSMs and IDUs has changed.

More than a half – 123 (52.8%) of students before completion of medical studies feel that there is a risk of getting infected with HIV while performing their professional duties and as many as 34.9% of the respondents admit that they fear AIDS. The study revealed homophobic attitudes as well as resentment against addicts.

The obtained results show that in the process of educating future doctors more attention should be paid to the issues of human sexuality, as well as addictions. This may lead to reduction of discrimination experienced or felt frequently by HIV-positive patients. This is especially important as the life-span of HIV-positive persons is getting much longer.

key words

HIV, medical students, knowledge, attitudes

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## BACKGROUND

The first report about a new syndrome, later to be called AIDS was published in the USA on the 10<sup>th</sup> December 1981. [1]. Three days later in Poland the martial law was declared, hampering information flow from the world, including medical data.

The first case of HIV infection in Poland was diagnosed in 1985, one year later there was the first diagnosis of AIDS, in a homosexual man, re-emigrant from the USA [2]. From the beginning of the HIV/AIDS epidemics, in the mass media in Poland it was almost exclusively stressed that men who have sex with men (MSMs) and injection drug users (IDUs) play a significant role in the spreading of the infection.

In the education programmes of the Polish universities where future doctors are taught, issues related to human sexuality are rarely touched on and not much attention is paid to addictions either. Attitudes and prejudices learned before the beginning of medical studies are often enhanced by the media and political campaigns.

Regardless of their HIV serological status, MSMs and IDUs are discriminated against and in the era of AIDS this discrimination became even stronger. At the early stage of the epidemics, there were there many studies on potential prejudices of medical care staff against both MSMs and IDUs. Research made in the early 1990s in Canada, France and the USA among residents in the last year of internal medicine or family medicine revealed that although majority of the respondents regarded treatment of HIV/AIDS patients as their ethical obligation, but 4% in France, 14% in Canada and 23% in the United States indicated that they would not take care of persons with HIV/AIDS if they had a choice (3). In the same period studies in the USA showed that homophobia, resentment against IDUs, fear of AIDS, futility of AIDS care, and clinical difficulty of AIDS care were strong independent predictors of willingness to care for persons with AIDS (4). However, recent years have brought significant progress in treatment of HIV-infected patients, prognoses for persons living with HIV/AIDS improved markedly, and the existing anti-retroviral drugs, it is possible to make the life span of persons with HIV/AIDS much longer (5), also in the case of IDUs (6). Much more frequently HIV infection is described as a chronic disorder which cannot be cured (it is impossible to eradicate the virus), and yet can be controlled during many years with the existing anti-retroviral drugs. Patients with HIV/AIDS live much longer now and more and more often they will seek aid of other specialists and HIV infection therapists.

In 2000 National AIDS Centre organised studies about knowledge, attitudes and opinions of students at Polish medical universities related to HIV and AIDS (7). Among other results they showed that more than 60% of respondents revealed fear of AIDS, almost 60% of students agreed with the statement that HIV/AIDS is a disease of IDUs and MSMs. Between 2004 and 2006 the same questionnaire was applied to students of the 6<sup>th</sup> year of the medical studies at the Medical University of Białystok, who should have already obtained information on HIV/AIDS in their education programme. The study's objective was to check whether the attitude of future doctors to HIV/AIDS, MSMs and IDUs has changed.

## MATERIAL AND METHODS

Between 2004 and 2006 a study on knowledge about HIV/AIDS was held among students of the 6<sup>th</sup>, final years of doctors' studies at the Medical University of Białystok. The questionnaire was prepared by the National AIDS Centre and the company *RUN Badania Rynkowe i Społeczne* (RUN Market and Social Studies). The questions concerned mainly medical knowledge about HIV/AIDS, but there were also questions on attitudes and opinions about MSMs and IDUs.

Two hundred thirty five students participated in the study. This group is characterised in the Table 1.

Table 1. Characteristics of the respondent students (n = 235)

<b>Age:</b> average 25 years (from 24 to 39),	
<b>Sex:</b> female – 156 (72.2%), male – 79 (27.8%),	
<b>Permanence residing place:</b>	
village, locality of less than 10,000 inhabitants	33 (14.0%),
locality of 10,001 to 50,000 inhabitants	54 (23.0%),
town of 50,001 to 200,000 inhabitants	39 (16.6%),
town of 200,001 to 500,000 inhabitants	96 (40.9%),
city above 500,001 inhabitants	3 (1.3%),
no reply	10 (4.2%).
<b>Reason for choosing medical studies</b> (an option to tick more than 1 answer):	
will to help people	158 (67.2%),
will to develop one's interests	82 (34.9%),
will to achieve a good social status	28 (11.9%),
continuation of family traditions	14 (6.0%),
suggestions of friends and relations	8 (3.4%).
<b>Attitudes to religion:</b>	
deep believers	29 (12.3%),
believers	178 (75.7%),
uncertain	0 (0.0%),
non-believers	9 (3.8%),
positive non-believers	6 (2.6%),
no reply	13 (5.5%).
<b>Attendance at religious services:</b>	
regular attendance	97 (41.3%),
irregular attendance	94 (40.0%),
attendance at unique services (baptism, wedding etc.)	23 (9.8%),
non-attendance	13 (5.5%),
no reply	8 (3.4%).

The statistical analysis was performed with the Statistica 7.0.Pl software.

## RESULTS

The future doctors were asked to assess their own knowledge about HIV/AIDS. More than a half of them assessed it as good – 129 students (54.5%), but only 5 declared that it is very good, 106 respondents (45.1%) assessed it as poor and 2 persons wrote it was very poor and 3 respondents declared that they know nothing on the subject. However, when a question was asked whether their previous studies brought sufficient information about HIV/AIDS, 115 (48.9%) respondents answered yes and only 8 declared that there was positively much information and 120 respondents (51.5%) denied that they were well prepared during their studies, while 27 students (11.5%) wrote that their studies gave them no preparation on the issue.

The insufficient preparation of students to the issues related to HIV/AIDS was confirmed by answers to the question whether feel at risk of getting infected while performing their professional duties. More than half of them – 123 (52.8%) feel that there is a risk of getting infected with HIV while performing their professional duties, 112 (47.7%) felt no risk and only 18 students among them (7.7%) believe that the infection risk at a doctor's professional duties is very low. As much as 34.9% of respondents admit that they fear AIDS. The Table 2 presents the students' replies to the questions concerning their attitudes toward HIV/AIDS.

The students were asked about their willingness to take care of seropositive patients. Significant majority of the 232 persons who answered this question (200 students – 86.2%) would like to work both with the HIV-infected and non-infected patients and only 5 respondents (2.2%) chose working with people who live with HIV, and 27 (11.7%) would like to work exclusively with HIV-negative persons.

Considering that the future doctors very frequently declared that they are believers and attend religious services, we have analysed the relation between religious attitudes and regarding HIV/AIDS as a disease of MSMs. The results are presented in Table 3. The correlation coefficient between the attitude to religion and opinion that HIV/AIDS is a disease affecting MSMs is 0.0691 and it is statistically irrelevant ( $p = 0.305$ ). However, after dividing the respondents into believers and non believers, we found that the deeper faith declared, the more strongly the students agree with such an opinion ( $r = 0.009$ ,  $p = 0.009$ ). No such correlation was found in the case of persons who declared themselves as non-believers ( $r = -0.786$ ,  $p = 0.785$ ). The percentage of persons who stated that HIV/AIDS is a disease of MSMs was higher among men ( $p = 0.0489$ ), and men also expressed no opinion on the subject more frequently ( $p = 0,0291$ ), although women make the more religious group ( $r = 0.197$ ,  $p = 0.003$ ) and they attend religious services more often ( $r = 0.212$ ,  $p = 0.001$ ).

Table 2. The medical students' opinions and attitudes toward HIV/AIDS, MSMs and IDUs

	Is HIV/AIDS a disease of MSMs?			Is HIV/AIDS a disease of IDUs?			HIV-positive persons bear some responsibility for their infection?			I fear AIDS			IDUs should be punished and not treated		
	n	%	n (%)	n	%	n (%)	n	%	n (%)	n	%	n (%)	n	%	n (%)
Positively yes	9	3.8	46	27	11.5	86	9	3.8	71	38	16.2	82	73	31.1	110
Probably yes	37	15.8	(19.6)	59	25.1	(36.6)	62	26.4	(30.2)	44	18.7	(34.9)	37	15.7	(46.8)
Probably no	68	28.9	183	79	33.6	133	121	51.5	137	103	43.8	150	28	11.9	119
Positively no	115	48.9	(77.8)	54	23.0	(56.6)	16	6.8	(58.3)	47	20.0	(63.8)	91	38.7	(50.6)
I don't know	6	2.6	6 (2.6)	16	6.8	16 (6.8)	27	11.5	27 (11.5)	3	1.3	3 (1.3)	6	2.6	6 (2.6)

Table 3. Attitude to religion versus treatment of HIV/AIDS as a disease of MSMs

Attitude to religion	Is HIV/AIDS a disease of homosexuals?					
		Positively yes	Probably yes	Probably no	Positively no	I don't know
Deep believers	n	1	10	9	9	0
	%	3.5	34.5	31.0	31.0	0,0
	n (%)	11 (38.0)			18 (62.0)	
Believers	n	6	24	52	93	3
	%	3.4	13.5	29.2	52.2	1,7
	n (%)	30 (16.9)			145 (81.4)	
Uncertain	n	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0,0
	n (%)	0 (0.0)			0 (0.0)	
Non-believers	n	1	0	3	5	0
	%	11.1	0.0	33.3	55.6	0,0
	n (%)	1 (11.0)			8 (88.9)	
Positive non-believers	n	1	1	0	4	0
	%	16.7	16.7	0.0	66.6	0,0
	n (%)	2 (33.4)			5 (66.6)	

Students were asked about their attitudes to MSM relationships. Out of the 235 respondents, 5 (2.1%) replied that such relationship should have legal status including a right to adopt children and according to 71 of them (30.2%) MSM relationships should have legal status without a right to adopt children, while 140 (59.6%) respondents declared that such relationships should be tolerated without any legal regulations and 19 of them (8.1%) wrote that they should be forbidden and punished.

Another question asked concerned the issue whether avoiding any private, not only sexual, contact with MSMs reduces HIV infection risk by 90%. Ten students (4.3%) replied positively yes, 37 (15.7%) – probably yes, 78 (33.2%) – probably no, 103 (43.8%) – positively no and 7 students (3.0%) had no opinion on the issue. If an acquaintance revealed being homosexual, 8 students (3.4%) would terminate any contacts with this person, 14 (6.0%) would limit them significantly, 32 (13.6%) would limit the contacts slightly, 103 persons (43.8%) declared that nothing would be changed and 7 respondents (3.0%) did not know how they would react in such a situation.

When asked whether during a professional training trip they would agree to share a room with a homosexual person of the same sex, more than a half (53.4%) of the respondents asked that they would agree (41 – 17.4% declared a positive yes, 108 – 46.0% said that probably yes), but 36.2% would not agree (36 – 15.3% probably would not agree, 49 – 20.9% would refuse positively).

The same persons who believed that avoiding contact with homosexuals reduces the risk of getting infected declared more frequently willingness to terminate any contacts with an acquaintance admitted to be homosexual ( $r = 0.2180$ ,  $p = 0.01$ ), such persons would not like to share a room with a homosexual of the same sex ( $r = -0.1575$ ,  $p = 0.018$ ). And the persons who declared they would limit contact with homosexuals would not like to with them ( $r = -0.443$ ,  $p = 0.000$ ).

The attitude toward religion did not either affect opinion concerning avoiding social contacts with homosexuals as a means to reduce HIV-infection risk ( $r = 0.1154$ ,  $p = 0.084$ ), or potential maintaining contacts with an acquaintance who would admit being homosexual ( $r = 0.1267$ ;  $p = 0.058$ ). However, the persons who declared deep faith would more frequently refuse to share a room with a person of such orientation ( $r = -0.1405$ ,  $p = 0.035$ ).

It was revealed that there is a significant correlation between regarding HIV/AIDS as a disease of both MSMs and IDUs ( $r = 0.3477$ ,  $p = 0.000$ ). In the respondents' opinion the problem of HIV/AIDS affects both these groups to the same extent.

## DISCUSSION

Punishments for homosexual orientation was abolished from the Polish penal code as early as in 1932, earlier than in many other European countries and yet the society's attitude to other orientations than heterosexual has always been and still is inconsistent and controversial. After 2005 the issue of homosexuality was referred to by many politicians, who stressed resentment and hostility against sexual minorities. Human Rights Watch has recently drawn the authorities' attention to the phenomenon of intolerance of homosexuals and the European Parliament has passed resolutions on homophobia in Europe and in Poland.

The Polish legal regulations are harder on drug users. In 2000 the act on drug addiction prevention introduced punishment for possession of even small quantities of ille-

gal substances, ranking manufacturers, dealers and drug users, i.e. addicts all as criminals. Public discussion held during the process of tightening the regulations and subsequent attempts to liberalise it revealed opinions of a significant part of the society supporting punishments for persons addicted to illegal substances.

Previous attitudes and prejudices originating from the social environment where future doctors were raised are often enhanced as a result of political and media campaigns. Important role is played also by opinions expressed by ordinaries of the dominant in Poland Catholic Church hierarchs, especially as currently they get more and more often involved in discussing modification of the Polish law and 88.0% of our respondents declared themselves as believers.

As a result of the HIV/AIDS epidemic more attention is paid to sexual orientations. Among people living with HIV there are a lot of persons openly admitting their homosexual orientation, more than among patients with other disorders. Many HIV-positive persons got infected as a result of using drug injections. Because of the improved prognosis for persons with HIV/AIDS, they will be treated also by other physicians, not only anti-retroviral therapy specialists. Earlier studies show that many doctors who graduated in the pre-AIDS era discriminate against patients living with HIV [8]. This is why we studied opinions and attitudes of future doctors toward HIV/AIDS, MSMs and IDUs.

More than a half (54.5%) of the respondents assessed their knowledge about HIV/AIDS as good or very good and yet only 48.9% of them declared that previous studies gave them enough information on this subject. More than a half (52.8%) of the future physicians felt that they are at risk of getting infected with HIV while performing their professional duties. More than 30% of the respondents fear AIDS.

In a 1986 evaluation at the University of Mississippi School of Medicine a hypothetical homosexual patient was viewed as being more responsible for his illness, more dangerous to others, and suffering less pain than a hypothetical heterosexual patient [9]. Kopacz et al. studied students of the 2<sup>nd</sup> year of medical studies before the beginning of their education on human sexuality and found that 62% of the respondents expressed concern that working with HIV/AIDS patients may be hazardous, only 16% feared that during the education process they would not obtain sufficient information to work safely with HIV-positive persons and AIDS-phobia was significantly associated with homophobia. [10].

At the behavioural level significant majority of the students who answered our questionnaire does not see an connection between social contacts and risk of HIV-infection, although every fifth future physician believes that avoiding personal contact with homosexuals markedly reduces HIV infection risk. For more than ¾ of the respondents an information that an acquaintance is homosexual would not affect their mutual relations, but 54 respondents (23.4%) would terminate or limit their relationship with such a person. Arnold et al. found in their study performed in Vienna that students of medicine expressed negative attitudes starting from reluctance to interact with lesbian and gays, even in a casual manner [11].

Among students of medicine there are also MSMs. In the questionnaire 1 man wrote that he was gay himself but he also added that he had had a HIV test and was not infected. However, during the discussions concerning results of the questionnaire no-one referred to his own sexual orientation. Regarding frequent homophobic statements of

his colleagues, both male and female, this has to be regarded as a self-protection attitude. In a study by Canadian scientists it was revealed that homosexual medical students and residents reported using considerable energy constantly assessing their environments, trying to find a balance between self-protection and self-disclosure, and that those who were coping with their first awareness of themselves as gay or lesbian during their medical training were especially vulnerable [12].

Prejudices against homosexuality are not rare among medical students and medical staff in many countries [11, 13, 14]. IDUs are also frequently marginalised, deprived of access to medical care and in the case of HIV-positive persons this may contribute to significant reduction of chances to commence anti-retroviral therapy, improvement of quality of life and longer life span.

The British scientists who made a research in mid-1980s among students of beginner years of medical studies found slight correlation between prejudices against homosexuals and knowledge about AIDS, there was a higher correlation with the confession [15]. It was also shown that teaching and promoting acceptance of MSMs and IDUs can bring about change [16].

Our study concerned students of two subsequent years, graduating from only one medical university in Poland and therefore they cannot be generalised as concerning all future physicians. But at the Medical University of Białystok there are students from all over Poland.

The obtained results suggest that in the process of educating future doctors, more attention should be paid to issues related to human sexuality and addictions, which may lead to reduction of the discriminative behaviours often experienced or felt by persons living with HIV. This is especially important now that HIV-positive persons live much longer.

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## title

# HIV infection in ageing population Case report of three patients over 75 years old

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## summary

Epidemiological data shows, that among HIV infected patients population of persons older then 50 years is steadily growing. This group consists of patients treated successfully with ART and growing older on treatment, and of patients diagnosed with HIV in older age. Data shows, that older age is connected with faster progression to AIDS, faster decline in CD4 cell count and that response to ART is poorer in this group when compare with younger population. Age is a risk factor of developing cardiovascular disease, liver, kidneys and bone disorders. It become apparent, that medical standard of care for older HIV patients needs adjustment. This paper describes three cases of patients age 75 years or more, the oldest patients under care in the clinic in the year 2008.

## key words

**HIV infection, age, antiretroviral therapy**

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## BACKGROUND

HIV infection was always regarded as a disease of youth. Epidemiologic data, however, demonstrate that the prevalence of HIV and AIDS among persons 50 years of age or older is increasing. (1) This population consists of two groups. In one, there are people infected in older age. Data presented by CDC (2) shows, that cases of newly diagnosed patients in age over 50 is stable, about 10% of all new infections. It means, that with increasing number of new HIV infections, number of new cases among older people is also growing. Prevention programs are usually addressing young population. People in age over 50 don't consider themselves to be in risk group. New and effective ways of impotence treatments facilitate sexual activity among older people. Taking those facts under consideration, it can be expected that the number of new infections among older people will increase also in future. Second group of patients over 50 years old are those treated successfully with ARV. Improvements in the efficacy of ART have led to increased survival among HIV-infected. Number of people infected 20 years ago or more is growing. This is the main source of increasing number of patients over 50 years of age.

Impact of patients age on natural course of HIV infection was investigated in cohort studies from pre-HAART era. (3,4,5) It shows that the ability of the immune system to fight pathogens decreases with age. In consequence, older HIV-infected individuals may have poorer prognoses than the younger persons. Older age at seroconversion was associated with faster progression to AIDS or death and with a more rapid decline in CD4+ cell count. Introduction of antiretroviral treatment changed those prognosis.

In studies comparing immunological response to treatment in age groups, older patients had smaller median CD4 cell increase vs young people (1,2,3,4). Although old age was connected with faster immune system deterioration and smaller increase of CD4 cell count during treatment, older patients achieved superior virologic responses following HAART initiation compared with younger patients (5,6,7). This may be due to better adherence to antiretroviral treatment among older patients.

Age is well known risk factor of cardiovascular diseases in general population. Data from many HIV cohorts confirm that age is an independent factor of CVD among HIV infected persons (1,2,3). Similar findings are connected with metabolic syndrome. A prospective, cross-sectional studies, as well as cohort studies like D:A:D shows connection between age and increased risk of hypercholesterolemia and diabetes mellitus (1,2,3). Creatinine clearance decreases with age in general population as well as among HIV infected people. Multivariate analysis shows that age was a strong predictor of chronic renal failure (1,2). Age has also been linked with bone disease among HIV infected persons. Observational case control analysis shows association between low mineral density or osteoporosis and older age in HIV infected individuals (1).

## MATERIAL AND METHODS

Outpatients clinic for HIV infected persons at Hospital for Infectious Diseases in Warsaw operates since 1990. Over 3000 patients are in medical care in this clinic. Some individuals for 19 years. Population that was infected in late 80s and was cared for in outpatients clinic in early 90s is now 20 years older, approaching 50 years of age or more. Advanced age is connected with specific health problems, especially in HIV infected population. In this paper cases of three oldest patients in the clinic are presented. Those are three males age 75 years or more.

### Case 1

**Male, born 1933. HIV infection confirmed with WB test in 2001.**

- Time of infection unknown.
- Way of transmission unknown.
- HBV negative, HCV negative
- Single, never married
- Not smoking, no history of alcohol or narcotics use.

#### At the time of HIV diagnosis:

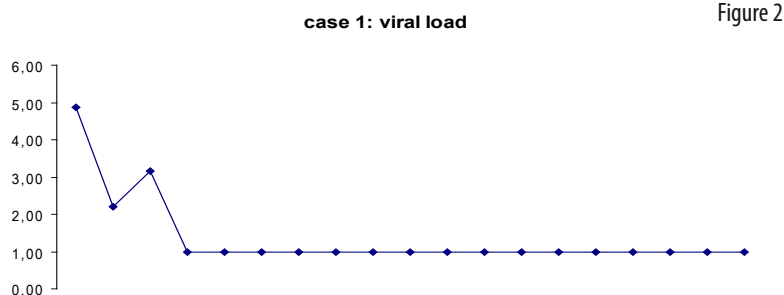
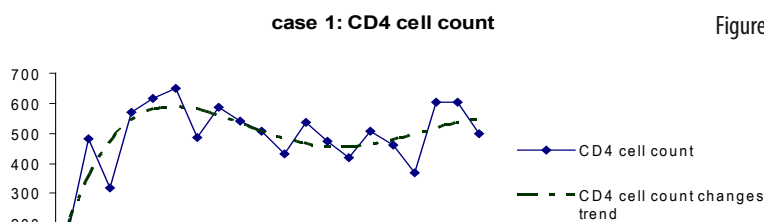
- CD4 153 cell/mm<sup>3</sup>, VL >75 000 copies/ml
- Diagnosed with esophageal candidosis confirmed in gastroscopy
- Treated with metoprolol, due to blood hypertension

#### Antiretroviral treatment

- Zidovudine/lamivudine + efavirenz started 30.08.2001
- Changed to zidovudine/lamivudine + nevirapine 14.12.2004 due to hypercholesterolemia.
- Patient continues stable ART.

#### Immunological response

- Patient started treatment with CD4 153 cell/mm<sup>3</sup> and VL > 75 000 copies/ml.
- From 5.10.2001 CD4 > 200 cell/mm<sup>3</sup>. CD4 cell count reached 400-600 cell/mm<sup>3</sup>, and remains on this stable level. CD4 cells count changes are presented in Figure 1.
- Viral load reached undetectable level on 13.08.2002, and remains undetectable (Figure 2).



**Cardiovascular disease:** Patient was diagnosed with hypertension before HIV infection. Treated with metoprolol, enalapril, indapamid. No symptoms of CVD disease.

**Metabolic syndrome:** Patients weight is stable, between 78 and 83 kg, BMI is 30,8. There is visible abdominal fat accumulation. From Feb 2002 elevated glucose level was observed. In 2007 diabetes was diagnosed, patient started treatment with oral antidiabetic drugs. From Feb 2002 elevated lipids level was observed. Patient started treatment with atorvastatin in Feb 2004. Patient fulfils all criteria of metabolic syndrome.

**Kidney function:** From Sep 2002 mild elevation of creatinine level is intermittently observed. GFR within normal limits.

**Bone disorders:** In chest X-ray done in April 2004 additional finding was possible decrease of bone density. DEXXA scan was not done.

**Other:** In October 2006 arterial stenosis in lower extremities was diagnosed. Claudication distance is about 300 m. From the year 2005 patient shows symptoms of depression and memory loss.

## Case 2

### Male, born 1933. HIV infection confirmed with WB test Feb 1999

- Time of infection probably 1998/1999. First EIA test January 1999 uncertain.
- Way of transmission unknown.
- HBV negative, HCV negative
- Married, has children
- Smoking, no history of alcohol or narcotics use.

#### At the time of HIV diagnosis:

- CD4 627 cell/mm<sup>3</sup>, VL 4546 copies.
- Recurrent pneumonia, chronic bronchitis, depression

#### Antiretroviral treatment

- Started with combivir + nevirapine in June 1999, when CD4 cell count was 481 cells/mm<sup>3</sup>

In February 2001 change of AZT to d4t due to diarrhea and muscle pain in legs.

In March 2001 returned to previous combination, combivir + nevirapine due to polineuropathy.

In October 2002 change to ziagen + nevirapine + nelfinavir due to myalgia and hematologic disorders.

In December 2002 change of nelfinavir to kaletra due to diarrhea

In November 2003 change of ziagen to 3TC due to hypersensitivity

In June 2004 kaletra changed to tenofovir due to hypercholesterolemia

In September 2004 nevirapine changed to atazanavir due to headaches

In July 2006 intensification of treatment to 3TC + tenofovir + atazanavir + ritonavir.

Patient remains on this combination till now.

#### Immunological response

Patient was changing therapy 8 times in 7 years, in all cases due to side effects and toxicity. Between July and October 2002 patient stopped therapy due to severe myalgia and polineuropathy. It resulted in short elevation of HIV replication. Except of this episode viral load remains undetectable. From the beginning of ART, CD4 cell count is high. CD4 cell count changes trend remains slowly raising.

CD4 cell count changes are presented in Figure 3 and viral load in Figure 4.

In June 2003 esophageal candidosis was confirmed in gastroscopy.

**Cardiovascular disease:** In February 2001 patient was hospitalized in Internal Diseases Ward due to supraventricular arrhythmia. Complex cardiological diagnostic was performed. ECG, Holter and echocardiography. No symptoms of ischemia were found. Supplementation with potassium, magnesium and beta-blocker treatment improved patients status. He remained under permanent care of cardiologist, with no new symptoms of cardiovascular disease.

**Metabolic syndrome:** Patients weight remains stable, about 80 kg. BMI 23,3 Mild abdominal fat accumulation was observed. No symptoms of diabetes. Lipid levels was normal or slightly elevated.

**Kidney function:** within normal range.

**Bone disorders:** In October 2007 osteopenia was found in DEXXA scan. No treatment was administered.

**Other:** From May 1999 patient was diagnosed and treated for depression.

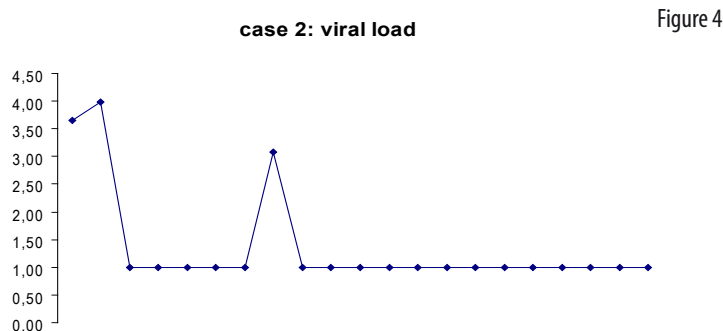
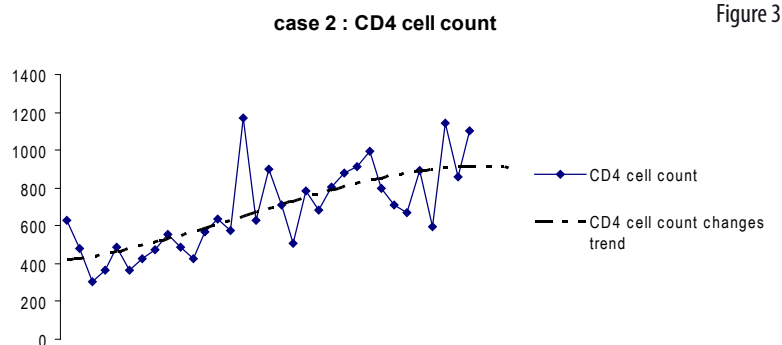
Chronic bronchitis, recurrent pneumonia were diagnosed before HIV infection. X-ray shows symptoms of pulmonary emphysema.

In Feb 2008 arthritis with elevated uric acid was diagnosed. Treatment with colchicines was administered, with recovery.

Patient suffered from severe polineuropathy, connected with ARV treatment. Symptoms decreased after change of treatment.

In April 2008 arterial stenosis in lower extremities was diagnosed.

From 2005 increasing feet edema and problems with movement due to pain in lower extremities are seen. Calcaneal spur and bone atrophy of feet were diagnosed.



**Case 3****Male, born 1927. HIV infection confirmed with WB test, in May 2008**

- Last negative HIV test May 2007
- Way of transmission – bisexual
- HBV negative, HCV negative

**At the time of HIV diagnosis:**

- CD4 363 cell/mm<sup>3</sup> VL >100 000 copies
- Hypertension diagnosed before HIV infection
- Carcinoma prostate diagnosed in July 2007

**Other**

- Patient has deep depression. After initial diagnosis of HIV infection, he refused treatment or any contact with the Clinic.

## DISCUSSION

This paper presents three oldest patients treated in out-patient clinic for HIV positive patients in Warsaw. It can be expected, that problems connected with ageing of HIV infected population will be expressed especially in those patients.

In the first case, patient was diagnosed in the late stage of infection, at the time of opportunistic infection. It represents the situation when older patients don't consider themselves in risk of HIV infection. Second patient was diagnosed at the beginning of HIV infection. Early diagnosis was possible due to exacerbation of chronic respiratory tract disease, that might be connected with HIV. The third case represents a person aware of risk behavior and checking HIV status regularly. Patients were diagnosed with HIV in age 68, 66 and 81 respectively. All represent a group of patients diagnosed in age over 50. Way of transmission in first two cases remains unknown. All three patients were reluctant to discuss possible source of infection, nor risk behaviors that could be connected with HIV infection. Aversion to talk about this issues can be related to depression observed later in all cases.

Analyzing first measured CD4 cell count, it appears that results corresponded with suspected stage of infection. In the first case CD4 was low, 153 cells/mm<sup>3</sup>. In the second and third case high, 627 and 363 cells/mm<sup>3</sup> respectively. Viral load results doesn't show such coincidence. In published data advanced age was connected with rapid progression to AIDS. It is not confirmed in presented cases, because in the first case no data are available when patient was infected and for how long HIV was damaging immune system. In the second and third case, patients were diagnosed in early stage of the disease. The first patient started treatment immediately after diagnosis, second patient started treatment soon after diagnosis, when CD4 cell count was 481 cells/mm<sup>3</sup>. ARV treatment changes the natural course of disease and no influence of age on the disease can be seen. Both patients continue treatment with good results: undetectable viral load and high CD4 cell count. Good immunological response is reflected also by only one case of new opportunistic infection, esophageal candidosis diagnosed in second patient. This infection was connected mostly with long treatment with antibiotics due to recurrent bronchitis. All changes of ARV drugs in case one and two were connected with side effects, intolerance or toxicities. Part of those findings are in accordance with observation that older patients are more compliant in comparison with younger population. Good adherence results in undetectable viral load achieved soon after start of ART, and that was confirmed in cases 1 and 2. Poorer immuno-

logical response to treatment connected with age is hard to confirm in presented cases. Both patients who received treatment have good immunological response, high CD4 cell count and stable CD4 change trends.

Symptoms connected with older age like increased risk of cardiovascular diseases, metabolic syndrome, bone diseases or renal impairment were found in cases one and two. First patient presented all symptoms of metabolic syndrome, hypertension, osteopenia, and decrease of renal function. Second patient was diagnosed with supraventricular arrhythmia, hypertension, and osteopenia. Both were diagnosed with arterial stenosis in lower extremities. Third patient was treated for hypertension, but no additional data about this patient is available. Those findings confirm already published data, about age related symptoms in HIV positive population. It indicates the importance of performing scrupulous diagnostic procedures to detect early symptoms of cardiovascular disease, metabolic syndrome or other diseases connected with age, especially in patients aged more than 50 years. The same health problems that apply to general population, also apply to HIV infected patients. Problems for HIV positive persons increase with start of ART, because treatment is often connected with appearance of risk factors like dyslipidemia, elevated glucose and other symptoms. Population 50 + should be aware of possible health problems and advised about changes in the life style, diet and prophylaxis to avoid diseases mentioned above.

In all three presented cases severe depression was the dominating symptom. First patient was taking small doses of antidepressants, but refused to visit psychiatrist. Depression in his case was connected with memory loss and cognitive function impairment. As a result any changes in treatment, diet or daily routine, was very difficult to introduce. Second patient was diagnosed with depression and is under permanent care of psychiatrist. Patient takes antidepressants but it is not improving his mental state. In third case depression in time of HIV diagnosis led to refusal of treatment or any contact with the clinic.

Severe depression in older persons, symptom seen in all presented cases, should be approached with special attention. Epidemiologic data from pre-HAART era, as well as actual data shows an increased rate of HIV-associated dementia among older patients (1,2). Depression and dementia have a deep impact on both diagnostic and treatment process. Those findings confirm importance of complex, multispecialist approach to HIV patients, with particular consideration of psychiatrist and psychologist. Regular assessment of neuropsychological impairment and depression is especially important in older patients.

## CONCLUSION

Analysis of patients over 75 years of age confirms that diseases like cardiovascular disorders, metabolic syndrome, osteoporosis and kidney disorders can be expected in ageing HIV infected persons. Regular screening is particularly important in this group. Evaluation of cardiovascular risk, monitoring of fasting lipid and glucose levels, renal function, and markers of bone disease should be undertaken within routine follow-up.

Antiretroviral therapy could be safely administered to elderly patients, and results of treatment are good. Differences in natural course of HIV disease and immune restoration after HAART between young and old population lead to suggestion, that perhaps older patients should start treatment earlier.



Older patients especially need multispecialist medical care. Psychiatrist and psychologist help is very important. There is need for regular monitoring of neurocognitive disorders and care of specialist.

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title

**A heavily pre-treated HIV positive patient with limited treatment options and multiple concomitant diseases treated successfully with raltegravir – the first case in Poland**

authors

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summary

We present a case of a heavily antiretrovirally pre-treated 38-year old male patient with numerous concomitant diseases and no or very few treatment options available who was started on raltegravir regimen, as part of early access programme, with optimized background. The patient's previous regimes all have finally failed and he accumulated numerous drug mutations. He also had developed a chronic disseminated MAC infection, which probably was responsible for the failure of his antiretroviral therapy. After changing the regimen to raltegravir in March 2008, CD4 cell count rose and HIV viremia became undetectable. Now the patient is still taking the new regimen without any side effects and is in good medical condition. No signs of HIV infection or concomitant diseases progression are present so far.

key words

**raltegravir, heavily antiretrovirally pre-treated patients**

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## BACKGROUND

In recent years new antiretroviral drugs and new drug groups became available giving hope to patients infected with multiple resistant HIV. Such resistance can be either primary or acquired. As the rate of new infections with primary resistant HIV in Poland exceeds 10% (confirmed in SPREAD study) each new patient should have a genotypic assay performed as soon after diagnosis as possible or at least blood specimen preserved. Genotypic assay should also be performed if viral escape occurs and before regimen change but due to mutation archiving HIV resistance genotype alone can sometimes be misleading and careful analysis of drug history is essential (1,2).

## CASE PRESENTATION

A 38-year-old Caucasian man diagnosed with HIV-1 and HCV infection in 1997 (most probably intravenous drug use) started combined antiretroviral therapy (cART) for the first time in March 1997 with zidovudine, lamivudine and saquinavir. At the beginning of treatment CD4 T cell count was 37 cells/ $\mu$ l and HIV RNA viral load 150.000 copies/ml. In the course of cART the patient was questionably adherent at times, once stopping the treatment altogether. In the beginning of treatment history (1999) he was hospitalized due to Pneumocystis pneumonia (PCP) and later on because of disseminated atypical mycobacteriosis. The mycobacteriosis became his main medical problem complicating the course of treatment on many occasions with anemia, renal insufficiency in the course of mycobacterial sepsis, hepatosplenomegaly, pneumonia, cervical lymphadenitis with abscess formation and finally subphrenic and left pleural abscesses in 2007. Due to this infection his antiretroviral treatment had to be changed on a few occasions. In 2001 the patient was also diagnosed with necrotic pancreatitis but we could not ascertain whether it was caused by mycobacterial infection itself or drug toxicity. In the course of treatment the patient received ethambutol together with azitromycin or ciprofloxacin for over 2 years and occasionally steroids during disease exacerbations. During one episode of mycobacterial disease exacerbation bacterial resistance assay was performed revealing resistance to all tested drugs namely ethambutol, rifampicin, isoniazide and streptomycin. The patient received cycloserin and etonamide and the symptoms subsided.

During 11 years of antiretroviral treatment the patient had received 9 different drug regimens but HIV viremia was always detectable apart from efavirenz-based regimen (1999-2001). However, after 18 months of this treatment the patient developed resistance to efavirenz, confirmed by breakthrough viremia but not by resistance test done in 2007. Other resistance mutations in this test included for reverse transcriptase M41L, M184V and T215Y and for protease L10F, V32I, M46I, I47V, I50V, I62V, L63P, A71V and V82A leaving only tipranavir as one fully active drug. Even though there were no obvious mutations for NNRTIs present we decided not to re-introduce them taking the patient's cART history into account. The patient was receiving suboptimal treatment continually and we waited for new potent drugs to become available. CD4 cell count was oscillating around 150-200/ $\mu$ l and HIV viremia around 800-40.000 copies/ml.

Because of the severe recurrent disseminated atypical

mycobacterial infection, the antiretroviral treatment being unsuccessful and the patient's clinical condition deteriorating (facial lipoatrophy, peripheral neuropathy, AIDS dementia complex, hepatomegaly, thrombocytopenia of 50.000 cells/ $\mu$ l and weight loss), when raltegravir became available under early access programme, we decided to compose a new regimen of raltegravir one tablet twice daily in combination with optimized background of tipranavir 2 tablets twice daily boosted with ritonavir 100 mg tablets twice daily and abacavir/lamivudine co-formulated tablet once daily. During the first 2-3 months of treatment the patient's neuropathy exacerbated but the symptoms were relieved after substitution of 2 tablets of thiamine 3 times daily. Difficulties with sleeping also became more pronounced but we attributed them to patient's anxiousness. Additionally papulo-pustular rash on the patient's chest and back appeared with no accompanying itching or pain. It seemed to have been the result of immune reconstitution and it suddenly disappeared after 3 months of cART and numerous unsuccessful topical therapies.

Five months into treatment CD4 cell count lymphocytes rose to 274/ $\mu$ l and HIV-RNA became undetectable using an ultrasensitive assay by QIAGEN-ARTUS. The patient started to feel well and most of the previous symptoms subsided almost completely (neuropathy, insomnia, rash). He also regained weight (facial lipoatrophy became much less pronounced, the patient had more energy and strength). However, hepatomegaly was still present. During treatment all major laboratory results were stable including complete blood count and morphology, aminotransferases and prothrombin complex activities, bilirubin and creatinine concentrations.

In February 2009 the patient was admitted to hospital due to left-sided tension sensation in his chest and for a general check-up. All results came back normal, no further pleural effusion or abscesses were present and the tension sensation in his chest was most probably attributable to post-inflammatory (mycobacterial pleural effusion in 2007) fibrous tissue seen on chest x-ray spanning his left lung and pleural space. Now the CD4 cell count is 289/ $\mu$ l and HIV-RNA is still undetectable using the same ultrasensitive assay.

## CONCLUSIONS

The history of this patient is an example of difficulties, which may distort the antiretroviral treatment plan. In this case the possible causes for multiple treatment failures are patient's low adherence, at least on few occasions, and recurrent infections. It has been accepted that both chronic and acute inflammation can accelerate HIV's replication rate and shorten time to progression to AIDS. It seems probable that chronic mycobacterial infection has the same effect and should be treated accordingly. Quick metabolism of antiretroviral drugs also may have contributed to the poor clinical outcome but we were unable to perform drug concentration monitoring.

Multiple treatment failures in this patient point to yet another factor in treatment strategy i.e. resistance assays. Because access to them has been very difficult in Poland, there has been a tendency to rely very often on treatment history alone and resistance assays are performed only as the last resort. None-the-less, reliable treatment history should be accompanied by reliable resistance assays at diagnosis, treatment beginning and treatment failure.

However, as it has turned out with this patient, new and potent drug classes with optimized background offer a good chance of getting HIV replication under control even after numerous treatment failures. The patient requires further clinical monitoring to make sure that these effects will be long-term and that the mycobacterial infection does not exacerbate again.

### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

Bartosz Szetela and Jacek Gasiorowski took care of the patient during treatment. Bartosz Szetela prepared the manuscript and all authors read and approved the its final version. Malgorzata Zalewska performed virological assays.

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