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title

Perfect adherence in taking antiretroviral drugs – role of the doctors

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summary

Adherence to antiretroviral medications is essential to therapeutic success. The health care professional represents an essential element of care that should be evaluated and optimized in order to maximize adherence and therefore success in HIV clinical care.

key words

antiretroviral drugs, adherence, monitoring

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The introduction of highly active antiretroviral therapy (HAART) in 1996 has radically modified the management and care of HIV positive patients (1, 2), and soon adherence to HAART has been shown to play a crucial role in determining virological response. Common types of non-adherence with medication include not filling prescriptions, taking an incorrect dose (too little or to much), taking a dose at the incorrect time, missing doses of one or more drugs from a regimen, stopping all treatment and taking treatment prescribed for others (3). Several factors are related to non-adherence, especially patient-related factors such as depression, abuse, but also regimen complexity, patient's lack of trust in the treatment, their attitudes about medication-taking and disease, and poor patient-physician relations.

How important is adherence to success of antiretroviral therapy?

Paterson et al. (4) observed adherence of patients taking protease inhibitor (nelfinavir) who neither used a medication organizer nor received their medication in an observed setting, such as jail or nursing house. Adherence was significantly associated with successful virologic outcome and increase in CD4 lymphocyte count. Virologic failure was documented in 22% of patients with adherence of 95% or greater, 61% of those with 80,0% to 94,9% adherence, and 80% of those with less than 80% adherence. While treatment with unboosted protease inhibitors (PI) requires near perfect adherence for virologic suppression, the introduction of more potent non-nucleoside reverse transcriptase inhibitors (NNRTI) and ritonavir boosted PI therapy has lead to reliable virologic suppression at moderate levels of adherence for most, but not all patients (5). Maggiolo et al. (6) followed up a large cohort of patients who were receiving a steady (duration > 6 months) and effective (viral load achieved, < 50 HIV RNA copies/ml) HAART. The main conclusion that could by drawn from the study were that patients who were receiving NNRTI reported greater adherence that did those who were receiving protease inhibitors (PI). But the risk of virologic failure associated with suboptimal adherence was greater for patients who were receiving PI-based regimens than for patients who were receiving NNRTI-based regimens. For NNRTI adherence window is 2 – 70% (7). Moderate levels of adherence (range: 23,5% – 53,5%) can lead to virologic suppression in most patients taking lopinavir/ritonavir-based HAART (8).

The main mechanism involved in the association between adherence and virologic failure is development of drug resistance, which is the product of 2 necessary conditions: subtherapeutic drug levels and persistence of viral replication. For some regimens, drug resistance may be more likely to develop in patients with better adherence, for the other regimens, the opposite may be true (5). Current understanding of the relationships between adherence and viral resistance suggest that the risk of the development of resistance varies by class of antiretroviral drugs and that there is no single cutoff below which the risk of resistance clearly outweighs the potential drug benefit (9). Patterns of adherence may be more critical than overall level of adherence. Patient reported treatment discontinuation of more than 48h is an independent risk factor for non-nucleoside reverse transcriptase inhibitor resistance, even controlling for average adherence over time (10).

When perfect adherence is most important?

For antiretroviral-naive individuals, simulated and observed results both suggests that the likelihood of accumulating new mutations will increase sharply with even small departures from perfect adherence, with a rise to 1.9 times higher for individuals with 90% adherence and to 2.4 times higher for individuals with 80% adherence. Indeed, the maximum likelihoods of accumulating mutations occur at some of the most commonly observed adherence rates – 60-80%(11). This implies that many antiretroviral-naïve individuals may benefit substantially from adherence interventions not only because of the short-term benefit that accrues from greater viral load suppression, but also because a long-term benefit would accrue due to preservation of future drug options. Carrieri et al. (12) showed the need for strict initial adherence (up to 4 months) to maintain prolonged viral suppression. In the first 4 months of HAART, the patients who were moderately adherent did not significantly differ from non-adherent patients in terms of prolonged viral suppression at months 36. If viral replication is not drastically reduced early in treatment, the remaining replication may favor the later emergence of resistant strains.

Miller et al. (13) suggested that patients' knowledge of antiretroviral therapy was often suboptimal at regimen initiation but improved over time. Poor knowledge 8 weeks after regimen initiation was associated with lower adherence. Patients' knowledge of their HIV condition and its treatment, which influences adherence to antiretroviral therapy, can be improved through educational programs and should be initiated early in therapy (14).

Whether doctors can exactly estimate adherence of their patients

Physicians estimate their patients' adherence to medications, and base decisions about treatment on these estimates. In HIV, misjudgment of patients adherence can have adverse consequences, including withholding of therapy, unnecessary changes in therapy, or unnecessary laboratory testing. A review of literature demonstrates that physicians' are often inaccurate in estimating patient adherence with HAART. Gilbert et al. (15) evaluated the adherence estimates made by 10 primary physicians of patients taking digoxin. Adherence was also assessed through pill count and measurement of serum digoxin levels. The sensivity of clinical judgment for detecting nonadherence was 10%. Similar results were found for patients with whom physicians had relationship >5 years. According to Paterson et al. (4) physicians predicted adherence incorrectly for 41% of patients, and clinic nurses predicted it incorrectly for 30% patients. In a study by Haubrich et al. (16), in 173 patients for whom adherence was assessed by self-report, there were discordance between patients' and physicians' assessments in 45% of cases. Hugen et al. (17) compared multiple methods of assessing medication adherence. They found that the correlation of the physician's estimate with Medication Event Monitoring System (MEMS) was lower that other methods, including self report, therapeutic drug monitoring (TDM), and estimation by a clinical nurse specialist. In comparison of adherence

measures in homeless or marginally housed persons receiving HAART Bangsberg et al. (18) demonstrated that provider estimate of adherence was inaccurate whereas structured patient report was more closely related to pill count.

There are several possible explanations for the inaccuracy of physicians' estimates. Physician may pay more attention to objective clinical findings than to patient subjective reports. They may lack the expertise or time to assess adherence; and patient may be reluctant to disclose nonadherence because of concerns about social desirability, reluctance to disappoint the physician, or fears of having medications withheld.

Benefits of perfect adherence

Paterson et al. (4) found that patients with adherence of 95% or greater had fewer days in the hospital (2,6 days per 1000 days of follow-up) than those with less than 95% adherence (12,9 days per 1000 days of follow-up). No opportunistic infections or deaths occurred in patients with 95% or greater adherence. Prior to the introduction of HAART most of the expenditures for HIV care were spent on hospitalizations and the treatment of opportunistic infections and neoplasm's (19). After the introduction of HAART, the need for hospitalization and the incidence of opportunistic illness decreased considerably (1, 2). It is now estimated that 54 – 64% of healthcare expenditures in HIV-infected populations in resource-rich settings are attributed to the cost of combination antiretroviral therapy (20, 21). Despite the expense, antiretroviral therapy is cost effective for HIV-infected individuals in resource-rich (and resource-limited) settings (22, 23). Gardner et al. (24) hypothesize, that, as antiretroviral drugs become available as generic preparations in the US, excellent adherence will likely become cost saving, not just cost effective.

Patient-provider relationship, and adherence to HAART

A good patient-provider relationship appears to be strongly associated with better adherence to HAART (25). The quality of this relationship is generally measured in terms of the support, trust, and caring the patient perceives. It has been found, in numerous studies, that outcomes are better for patients whose providers have greater experience caring for HIV-infected patients and such patients also have better adherence to HAART (26, 27).

At the physician level, increasing awareness about patients adherence is crucial. It may be helpful for physicians to simply accept the fact that it is difficult to know whether a patient is or will be adherent. This can help to justify the initial step of asking about the patients' lives and potential barriers to adherence. After the patient has begun treatment it also helps to justify the importance of asking about adherence at every patient visit. After therapy has begun, the physician may be an important actor of other interventions to improve adherence, such as the use of reminders and psychoeducational strategies.

At the interpersonal level, the quality of communication has been found to be an essential component of adherence. Confident, collaborative, and effective communication between patients and physicians has been shown to positively influence patients' health behaviours, satisfaction, and adherence, and, consequently, the effectiveness of treatments (28). But practitioners spend little time teaching their patients ways to take pills – which would help patients stay on their medications. Even though studies have demonstrated that interactions between physicians and patients are key to patients' adherence to therapies, medical educators have largely neglected a focus on fostering partnerships between physicians and their chronically treated patients. Physicians, who see patients on regular basis and who are trusted by those patients, are the logical interventionists (29). HIV clinicians must be also aware that their own personal belief system, biases, cultural sensivity, and communication skills can impact adherence (30).

There is a broad array of strategies that providers can use to enhance their patients' adherence to HAART. It is important for each provider to have an adherence strategy that consists of core interventions for all patients and optional components that are based on the needs of individual patients. Routinely interviewing to enhance the adherence of all patients before problems develop will increase the likelihood of treatment success for patients who receive HAART.

Monitoring adherence to HAART

There is no standard approach to adherence assessment in routine practice. Various methods are used to measure adherence (31), but the straightest is patient self-report. Self-report has several advantages, including low cost, ease of administration and timing of assessment, and the potential to yield specific information regarding dosing behavior, but has also many limitations. While self reported adherence is significantly associated with other measures, it remains a coarse measure of adherence and suffers from a ceiling effect (32). There are strategies to reduce this ceiling effect. There include asking about adherence over several intervals (33), asking about the last time when the dose of the drug was missed. Also exist the possibility to identify specific questions that are both sensitive and specific to patterns of adherence that put patients at risk for resistance. Physicians usually asked about adherence if they perceived a patient adherence to be low and they perceived adherence to be an important issue. However, if physicians perceived the specific patient's adherence to be good, or if they generally did not consider it a very important issue, they often felt that it was not necessary to ask. An important barrier to in-depth adherence communication is that some physicians felt it is awkward to explore the possibility of non-adherence if there are no objective signs of treatment failure, because patients could be "accused" (34). Barfod et al. (34) proposed model of physicians' communication with patients about adherence and identified awkwardness and believability as key issues. The proposed four steps are: deciding whether to ask about adherence or not, pre-questioning preparations, phrasing the question, and responding to the patient's answer.

Systems that electronically monitor patient adherence will never replace health care providers interviewing patients about their experience with taking medications. The provider has a pivotal role – as a facilitator or as the barrier – in the process of engagement and retention of patients in HIV medical care. Especially socially marginalized people living with HIV/AIDS expressed a preference for providers they could trust; they wanted providers who demonstrated respect, caring, communication skills, and expertise (35). Achieving optimal adherence requires the commitment of

both patient and provider. Physicians can best serve their patients by providing through information and open discussion about antiretroviral adherence beginning prior to the initiation of therapy and extending throughout the patient's life time.

According to Bangsberg (35): just as physical exam skills have declined with advances in imaging systems (36), our interest in talking to patients about their treatment strategies should not diminish with more accurate technologies to monitor adherence.

References

1. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 1998;338:853-860.
2. Podlasin RB, Wiercinska-Drapalo A, Olczak A, et al. Opportunistic infections and other AIDS-defining illnesses in Poland in 2000-2002. Infection 2006;34:196-200.
3. Walsh JC. Adherence in clinical trials and in clinical practice. Antivir Ther 1999;4 (Suppl 3):49-54.
4. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med 2000;133:21-30.
5. Bangsberg DR, Moss AR, Deeks SG. Paradoxes of adherence and drug resistance to HIV antiretroviral therapy. J Antimicrob Chemother 2004;53:696-699.
6. Maggiolo F, Ravasio L, Ripamonti D, et al. Similar adherence rates favor different virologic outcomes for patients treated with non-nucleoside analogues or protease inhibitors. Clin Infect Dis 2004;40:158-163.
7. Bangsberg DR, Acosta E, Gupta R, Guzman D, Riley ED, Harrigan PR. Differences in protease and non-nucleoside reverse transcriptase inhibitor adherence-resistance relationships are explained by virologic fitness. AIDS 2005; 20:223-231.
8. Shuter J, Sarlo JA, Kanmatz TJ, Rode RA, Zingman BS. HIV-infected patients receiving lopinavir/ritonavir-based antiretroviral therapy achieve high rates of virologic suppression despite adherence rate less than 95%. J Acquir Immune Defic Syndr 2007;45:4-8.
9. Bangsberg DR, Acosta EP, Gupta R, et al. Adherence-resistance relationships for protease and non-nucleoside reverse transcriptase inhibitors explained by virological fitness. AIDS 2006;20:223-231.
10. Parienti JJ, Massari V, Descamps D, et al. Predictors of virologic failure and resistance in HIV-infected patients treated with nevirapine- or efavirenz-based antiretroviral therapy. Clin Infect Dis. 2004;38:1311-1316.
11. Braithwaite RS, Shechter S, Roberts MS et al. Explaining variability in the relationship between antiretroviral adherence and HIV mutation accumulation. J Antimicrob Chemother 2006;58:1036-43.
12. Carrieri MP, Raffi F, Lewden C, et al, and the APROCO study group. Impact of early versus late adherence to highly active antiretroviral therapy on immuno-virological response: a 3 year follow-up study. Antivir Ther 2003;8:585-594.
13. Miller LG, Liu H, Hays RD et al. Knowledge of antiretroviral regimen dosing and adherence: a longitudinal study. Clin Infect Dis 2003;36:514-518.
14. Goujard C, Bernard N, Sohier N, et al. Impact of a patient education program on adherence to HIV medication. J Acquir Immune Defic Syndr 2003;34:191-194.
15. Gilbert JR, Evans CE, Haynes RB, et al. Predicting compliance with a regimen of digoxin therapy in family practice. CMAJ 1980;123:119-122.
16. Haubrich RH, Little SJ, Currier JS, et al. The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. California Collaborative Treatment Group. AIDS 1999;13:1099-1107.
17. Hugen PWH, Langebeek N, Burger DM, et al. Assessment of adherence to HIV protease inhibitors: comparison and combination of various methods, including MEMS (Electronic Monitoring), patient and nurse report, and therapeutic drug monitoring. J Acquir Immune Defic Syndr 2002;30:324-34.
18. Bangsberg DR, Hecht FM, Heather C, et al. Provider assessment of adherence to HIV antiretroviral therapy. J Acquir Immune Defic Syndr 2001;26:435-442.
19. Ritemeijer CA, Davidson AJ, Foster CT, et al. Cost of care for patients with human immunodeficiency virus infection patterns of utilization and charges in a public health care system. Arch Intern Med 1993;153:219-25.
20. Bozette SA, Joyce G, McCaffrey DF, et al. Expenditures for the care of HIV-infected patients in the era of highly active antiretroviral therapy. N Engl J Med 2001;344:817-23.
21. Tramarin A, Campostrini S, Postma MJ, et al. A multicentre study of patient survival, disability, quality of life and cost of care among patients with AIDS in northern Italy. Pharmacoeconomics 2004;22:43-53.
22. Freedberg KA, Losina E, Weinstein MC, et al. The cost of effectiveness of combination antiretroviral therapy for HIV disease. N Engl J Med 2001;344:824-831.
23. Badri M, Maartens G, Mandalia S, et al. Cost-effectiveness of highly-active antiretroviral therapy in South Africa. PLoS Medicine 2006;3(1):e4.
24. Gardner EM. Maravi ME, Rietmeijer C, Davidson AJ, Burman WJ. The association of adherence to antiretroviral therapy with healthcare utilization and cost for medical care. Appl Health Econ Health Policy 2008;6:145-155.
25. Stone VE, Clarke J, Lovell J, et al. HIV/AIDS patients' perspectives on adhering to regimens containing protease inhibitors. J Gen Intern Med 1998;13:586-593.
26. Stone VE. Strategies for optimizing adherence to highly active antiretroviral therapy: lessons from research and clinical practice. Clin Infect Dis 2001;33:865-872.
27. Delgado J, Heath KV, Yip B, et al. Highly active antiretroviral therapy: physician experience and enhanced adherence to prescription refill. Antivir Ther 2003;8:471-478.
28. Murri R, Antinori A, Ammassari A et al., for the AdICoNA Study Group. Physician estimates of adherence and the patient-physician relationship as a setting to improve adherence to antiretroviral therapy. J Acquir Immune Defic Syndr 2002;31:S158-S162.
29. Casebeer LL, Klapow JC, Centor RM, et al. An intervention to increase physicians' use of adherence-enhancing strategies in managing hypercholesterolemic patients. Acad Med 1999;74:1334-1339.
30. Reiter GS, Stewart KE, Wojtusik L, et al. Elements of success in HIV clinical care: multiple interventions that promote adherence. Top HIV Med 2000;8:21-30.
31. Rogowska-Szadkowska D. Adherence to antiretroviral drugs in HIV infection. HIV AIDS Rev 2005;4:47-51.
32. Bangsberg DR. Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression. Clin Infect Dis 2006;43:939-941.
33. Mannheimer S, Friedland G, Matts J, Child C, Chesney M. The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. Clin Infect Dis 2002;34:1115-1121.
34. Barfod TS, Hecht FM, Rubow C, Gerstoft J. Physicians' communication with patients about adherence to HIV medication in San Francisco and Copenhagen: a qualitative study using Grounded Theory. BMC Health Serv Res 2006;6:154.
35. Bangsberg DR. Monitoring adherence to HIV antiretroviral therapy in routine clinical practice: the past, the present, and the future. AIDS Behav 2006;10:249-251/
36. Jahuar S. The demise of the physical exam. N Engl J Med 2006;354:548-551.

title

Mental impairment and neurocognitive symptoms associated with HIV infection

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summary

Mental health issues are often overlooked in the setting of HIV-infected patient care. However, neurological and psychiatric disorders, such as dementia or depression, may impair a patient's ability to understanding and follow treatment regimens, leading directly to poor HAART adherence. Mental conditions can be successfully improved in HIV/AIDS patients with antidepressant therapy, psychotherapy or antiretroviral drug selection regimens. New treatment strategies for HIV have resulted in marked health improvements. Psychoneurological problems are increasingly recognized as crucial to the overall health of all people with HIV/AIDS disease. For individuals treated with antiretrovirals, there is the added issue of drug-related neuropsychiatric complications, which may arise as a result of drug-related adverse events and which may affect mental well-being. Virus also directly affect mental functioning as a result of advancing HIV inflammatory process in Central Nervous System. The management of mental health concerning the neuropsychitric symptoms, become an integral part of comprehensive HIV/AIDS care. The present article focuses on the review of cognitive disorders in HIV, as well as the management of neuropsychiatric symptoms associated with HIV/AIDS and antiretroviral therapy.

key words

HIV-neuropsychitric symptoms, mental health, cognitive disorders, AIDS-dementia

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Introduction

The Central Nervous System (CNS) symptoms are commonly found in patients with HIV infection. They may be due to preexisting diagnoses or substance abuse before HIV infection, or as a result of neurotropic viral persist infection, and as a result of antiretroviral treatment. Neuropsychiatric symptoms have been reported with several of the medications taken by patients with HIV/AIDS, such as efavirenz, lamivudine, zidovudine, antibiotics, interferon, benzodiazepins, etc. Identification of neurological and psychiatric diseases is an important aspect of mental health care for HIV-infected people. Mild symptoms, such as insomnia, anxiety and depression may be managed by the medical practitioners within regular visit control. However, more advanced mental problems, as well as cognitive deficits or depression, should be referred to specialist for diagnosis, monitoring and treatment. CNS side effects of the antiretroviral agents have consistently been noted in many studies. They include mainly sleep disturbances, vivid dreams, vestibular symptoms, drowsiness. In some cases, change to an alternative therapy regimen should be considered.

HIV-associated neurocognitive disorders (HAND) as a progressing disability, from asymptomatic neurocognitive impairment (ANI) to HIV-associated mild neurocognitive disorder (MIND), and to HIV-associated dementia (HAD), have been recognized as common among HIV-infected people. Early in the HIV epidemic, more than 50% of all HIV-positive patients were diagnosed with HAD. Fortunately, the combination highly active antiretroviral therapy have changed the face of that disease.

An important component of successful HIV treatment is medication management capacity, which has been defined as the cognitive and functional ability to self-administer a medication regimen. This ability includes functional skills such as correctly identifying medications, selecting the proper dose and timing. Recent research has linked poorer adherence with poor understanding of medication instruction, especially among older HIV-infected adults. Everyday functional impairment has been associated with progressive HIV infection. Cognitive dysfunction has been found to be associated with impairments in various activities of daily living, especially regularly drug taking, and with reducing ability to work.

Epidemiology

Epidemiologically, the highly active antiretroviral therapy (HAART) era, has seen significant decline in the incidence of HAD (HIV-Associated Dementia), from approximately 7% per year in pre-HAART era, to 2-3% per year currently (1,2). The prevalence of mild cognitive deficits is poorly documented in studies and it may remain as high as 22% in symptomatic HIV infection, despite of antiretroviral therapy. The prevalence of HAD has greatly diminished while less severe ANI and MND have risen as individuals live longer with the HIV chronic disease (3). Consequently, this chronic mental insufficiency requires long-term medical and psychological management. However, numerous studies have documented the benefits of certain HAART regimens for the full range of HIV-associated neurocognitive symptoms.

Neuropathogenesis

The cellular and molecular changes that have occurred in the brain of HIV-infected individuals, are similar to other chronic infections in CNS. HIV-1 virions may enter the CNS very shortly after primary infection. Even in the presence of appropriate HAART and strong antiviral immune response, virions can escape viral clearance and establish latent viral reservoirs in resting memory CD4+ T cells and the CNS cells (4).

HIV-1 infection in the CNS can persist within macrophages and macrophage-related mocroglial cells despite of effective highly active antiretroviral therapy. Proviral DNA can also integrate into the genome of subpopulations of CD4+ lymphocytes in patients receiving HAART. These latently infected CD4+ T cells represent a permanent potential source of HIV-1 reactivation within the brain and may cause a rebound of HIV-1 viral production throughout the body after interruption of antiretroviral therapy. Studies identified macrophages as a source of virus in HIV-1 infected brain tissue (5,6). The HIV-1 infected macrophages may traffic to the brain bringing virus *via* a "Trojan horse" mechanism. The studies published recently, examining the HIV-1virus in the brain of people with severe HIV-associated dementi a at the time of death. A pattern of viral diversity suggesting increased trafficking of macrophages to the brain (7). In advanced infection, macrophages as a source of HIV-1 in the central nervous system, may play a greater role, and this may be related to the development of HIV-associated dementia. The dysregulation of cytokines and chemokines in the CNS may be a factor in increased trafficking of macrophages.

In early HIV infection, cerebrospinal fluid (CSF) viral loads are thought to stem from plasma lymphocytes, with HIV reproduction augmented by continual and rapid renewal from the bloodstream. Correlations between plasma and CSF HIV-1 viral loads suggest a high level of concurrent virus production in both – the plasma and CSF compartments. Latently infected, resting CD+4 T calls carrying replication-competent HIV-1 in brain areas and they have been established the latent viral reservoirs in patients with primary HIV infection. Antiretroviral treatment in recent infected individuals, as early as 10 days after HIV-1 infection does not prevent the generation of latently infected, resting CD+4 T cells carrying integrated HIV-1 DNA, despite the successful control of plasma viremia shortly after antiviral treatment is instituted (8).

However, HIV infection results in a predominantly frontal lobes pattern of neurocognitive disorders, as determined in the neurocognitive testing and brain imaging (9). The recent studies using of imaging exam (MRI) have shown reductions in glucose uptake in the frontal lobes of people with AIDS dementia. Furthermore, reduced glial cell density and diminution in neuronal volume have been noted in the frontal cortex in those with advanced mental disorders (10). Glial cells, especially astrocytes, tightly control neuronal function, and therefore glial and neuronal abnormalities nay be linked within psychoneuropathology. Virus HIV-1 induce neurodegeneration of dendritic cells and synaptic activities at the genetic level, through cell-cycling genes and neurotransmitters decrease (8,11).

Neurocognitive symptoms associated with HIV infection

Individuals with HIV/AIDS have been experienced a wide range of neuropsychiatric symptoms, including subjective cognitive complaints: depression, mood changes, anxiety, irritability and suicidal ideas, as well as sleep disturbances and fatigue. HIV-associated dementia and minor cognitive motor disorder are reported in the recent studies. Comorbid mental illness and history of substance abuse are also found at higher level among HIV-infected individuals in comparison with the general population. HIV produce a range of cognitive and behavioral symptoms that becomes more frequent and severe as the immune system declines and symptomatic AIDS-related illness have occured.

Neuropsychological deficits in HIV-infection are resemble those have seen in other subcortical-frontal disorders, such as Alzheimer disease; include decreased attention and concentration, psychomotor slowing, reduction of information processing speed, executive dysfunction, eg abstraction, divided attention, shifting cognitive sets etc, and verbal memory impairment (12). Behavioral symptoms associated with cognitive disturbances range from apathy and depression to psychosis. Disorders of language, visual-spatial abilities and praxis have occurred in late-stage AIDS dementia (12,13).

There are two defined clinical CNS pathologies: HIV-Associated Minor Cognitive Disorders (asymptomatic), and HIV-Associated Dementia (HAD), known historically as AIDS-dementia complex (Table 1). The subclinical deficits in neuropsychological tests are frequent and can also seen even in the asymptomatic stages of HIV infection.

Table 1. Neurocognitive symptoms associated with HIV infection

HIV-Associated Mild Cognitive Motor Disorders	HIV-Associated Dementia
Diagnostic criteria: at list 2 symptoms: • impaired attention • concentration • memory • mental and psychomotor slowing • personality change *causing mild functional impairment*	*Diagnostic criteria:* Acquired cognitive abnormality in 2 or more domains: • impaired attention • concentration • memory • mental and motor slowing *causing marked functional impairment* Acquired abnormality in motor performance or behavior change No evidence of other etiology (eg. O.Is, psychopathology, drug/alcohol abuse etc)

Neurocognitive screening tools in HIV/AIDS

The assessment for HIV-associated neurocognitive disorders is difficult. Patient self-reports of cognitive dysfunction may be more reflective of depression or other distress. Cognitive impairment has been assessed by neuropsychological tests. Neuropsychological tests, licensed and validated by a neuropsychological clinics, are the gold standard for HIV-associated cognitive disorders in different stages of HIV infection. Specific neuropsychological test can be time intensive and expensive, and must be performed by experienced clinical psychologist. Commonly have used the *Mini-Mental Scale*, but it assesses the mental status at the moment when exam is performing. This test is insensitive to HIV-associated deficits. The *HIV-Dementia Scale* developed as a rapid screening test to assess for AIDS dementia (12). This test assesses psychomotor processing speed, verbal memory, constructional ability, and executive function (Table 2).

Table 2. HIV-Dementia Scale (J Aquir Immune Defic Syndr 1995; 6:237-278)

Test	Maximum score
Memory-registration	4
Attention	4
Psychomotor speed	6
Memory – recall	4
Construction	2

While this scale may be a useful for AIDS dementia screen, its utility to assessing mild HIV-associated cognitive deficits (HAD) may be limited.

Skinner S and al. has compared the performance of several neuropsychological tools for detection of HIV-associated neurocognitive disorders (HAND) in antiretroviral drug-exposed parsons (13). He analyzed the relative performance of the HIV-Dementia Scale (HDS), International HIV Dementia Scale (IHDS) and the Mini-Mental Status Exam (MMSE) together with neuropsychological tests (Symbol-Digit, Grooved Pegboard and Trial Making) in HIV-infected subjects, compare to seronegative people. The findings in this study indicate, that the MMSE is a weak tool for diagnosing HAND in this group of patients, but the HDS and IHDS demonstrate better efficiencies. Other expert – Gibbie T et al., assessed HIV-seropositive individuals with cognitive problems at baseline and at 2-year follow-up (14). He used depression scale – the Back Depression Inventory (BDI) and Structured Clinical Interview (SCID-CV), and completed a battery of neuropsychological tests including the Cambridge Neuropsychological Test Automated Battery (CANTAB) and the Hopkins HIV Dementia Scale (HDS). In this study 34,8% people suggests depressive symptoms. The SCID-CV revealed that 27% of participants met the criteria for current mood disorder and 7% had a score on the HDS indicated HIV-associated cognitive changes. The results suggest a significant decline in depression scores and an improvement in several neurocognitive domains over time, with a relationship between HIV illness, antiretroviral therapy, symptoms of depression and cognitive performance.

Psychologists have used different diagnostic tools to assess brain impairment in HIV infection, eg. the Wisconsin Card Sorting Test – useful to frontal lobe dysfunction, the Verbal Fluency and Figural Fluency Test – useful to measure the concentration and verbal ability, the Stroop Color-Ward Test, the Towers of London Test – useful to memory and coordination assessment, the Trail-Making Test – to psychomotor slowing assessment, and other various, validated neuropsychological tests (17,18,19).

In general, the neuropsychological tests should assess the following domains: verbal (language, attention) working memory, abstraction/executive, memory (learning and recall), speed of information processing, and motor skills (15). Neuropsychological testing are often nonspecific and they are also problematic to use in a variety of circumstances due to appropriate age, sex, education, and cultural norms and have to be obtained for proper comparison.

Neuroimaging

The magnetic resonance imaging (MRI) techniques can play a critical role in differentiating HAND from alternative etiologies. Conventional scan using T1 and T2 – weighted imaging may show cerebral atrophy and corresponding ventricular enlargement. Magnetic resonance spectroscopy can be performed to assess metabolic changes, eg. a reduction in *n-acethyl-aspartate*, a marker of mature neurons and their axonal processes, and is often associated with an increase in *choline*, a marker of cell turnover, and *myoinositol*, a marker of glial inflammation.

Functional MRI (fMRI) can also be used to evaluation HIV-related brain dysfunction. Blood oxygen level dependent (BOLD) fMRI studies have shown that regional brain activity decreases within areas commonly associated with a simple attention task. The novel technique of arterial spin labeling (ASL) has shown that measurements of resting cerebral blood flow are inversely correlated with neurocognitive impairment.

The multimodal neuroimaging will play an increasing role to further understand the neurobiology of HAND.

Cerebrospinal fluid

The presence of HIV-1 in the CSF alone is not reliable for the diagnosis of HAND. Viral load in CSF can often be detected within both neurologically normal and brain-impaired HIV-infected patients. In era pre-HAART, higher CSF viral loads correlated with lower neuropsychological scores in individuals with more advances disease (8). Since the introduction of antiretroviral treatment, CSF viral loads become a less reliable marker because subjects generally attain undetectable HIV-1 viremia values by current clinical assays. More sensitive assays are required to reliably detected levels of viral replication in the CSF (20).

Recent studies have shown, that markers of immune activation – *neopterin* and *beta-2-microglobulin*, and markers of neuronal destruction (*neurofilament light chain*) are elevated in HAD (20). An accumulation of *beta amyloid* in the brain is accompanied by significant decline in the cerebrospinal fluid among patients with HIV-associate dementia, similar to Alzheimer disease.

Mechanisms affecting access of antiretroviral agents to the Central Nervous System

The presence of HIV-1 in CNS resulting relative protection from antiretroviral agents allows these areas to act as reservoirs for latent HIV infection. This is different viral kinetics and also different antiretroviral therapy responses in the CNS versus in plasma. An important risk associated with the HIV-1 reservoirs in brain, is incomplete suppression of virus replication in the cerebrospinal fluid during antiretroviral therapy.

It has known, that the treatment of any infection requires eradication of the pathogen from the site of infection. Unluckily, many of antiretroviral agents currently used to treat HIV infection, demonstrate only limited penetration into the CNS, and so are often present in cerebrospinal fluid and in brain parenchyma at subtherapeutical drug concentration (21,22).

Many mechanisms, especially the anatomical barriers, limited the access of ARV drugs into CNS. These barriers, include the blood-brain barrier (BBB), the blood-CSF barrier (BCSFB), and the CSF-brain barrier (CSFB), slowing of drug transport across the barriers and into the brain tissue. HIV infection is one of the CNS pathological processes that disrupt the blood-brain barrier (23). In response to HIV-1 virus, some inflammatory agents increase, contributing to significant leak across the BBB. Antiretroviral drugs and their interaction with the anatomical barriers of the blood, brain and CSF determine the extent to which the drugs penetrate the brain.

Blood-brain penetration of antiretroviral agents and their concentration in cerebrospinal fluid

Antiretroviral classes of drugs, and individual drugs within classes have different CNS penetration potentials, that are dependent upon a variety of biological and virological factors. Unfortunately, only limited data about CNS penetration of the most widely used antiretroviral agents are available from studies in humans and animals.

NRTIs (Nucleoside Reverse Transcriptase Inhibitors) class has better CNS penetration than do NNRTIs and PIs. Among the NRTIs, zidovudine (20%) and stavudine (30%) reach brain tissue at concentrations considerably higher than those of didanosine (<4%) (24). Zidovudine penetrated slowly into the CSF, reaching maximal concentration 2 hours after the start of the drug administration and it was cleared from cerebrospinal fluid with a mean half-life (t½) of approximately 3 hours. Lamivudine and stavudine may also be useful in preventing AIDS-related dementia, as they have proven effective in inhibiting HIV-1 replication within the Central Nervous System. Abacavir may also prove promising; studies suggest a plasma to CSF ratio is 18-36% (21,22,24). All NRTIs have another advantage in HIV-1 reservoirs, such as the CNS: NRTIs are able to prevent infection of resting CD4+ lymphocytes and macrophages. Tenofovir may also have activity in resting CD4+ cells.

NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors) such as nevirapine and efavirenz, play an important role in initiation regimen among treatment-naïve patients. NNRTIs are generally, as a class, more strongly protein-bound than NRTIs (99,5% vs 60%), which may limit their CNS access. A unique issue with efavirenz is the very common neurological complaints that has occured when treatment is initiated. More than 50% of treated patients experienced sleep changes (vivid dreams, insomnia, hypersomnia etc). Nevirapine is an attractive antiretroviral drug, because of high CNS penetration, which has been good documented in trials. Despite of having a great molecular weight (266 Da), it exhibits approximately 10 times the blood-brain barrier penetration than other NNRTIs (25). Nevirapine may have greater usefulness than other NNRTIs in the treatment of HIV-1 encephalopathy.

Efavirenz has been associated with a wide range of neuropsychiatric symptoms; the most common are sleep disturbances, ranging from insomnia to vivid dreams and night terrors. In large trials, more than 50% of patents who took efavirenz reported central nervous system effects (26). Dizziness and difficulty concentrating are reported frequently and tend to resolve within 2-4 weeks after therapy initiation. Only 4% of patients discontinued therapy for the CNS symptoms, according to data of ACTG 5097 study – a blind, randomized trial, comparing efavirenz and non-efavirenz regimens in HIV-infected treatment-naïve individuals (26). Serious adverse experiences including severe depression, suicidal attempts, aggressive behavior, and maniac reactions have been reported in this study. Some studies have proved that individuals with a history of mental health problems may be at an increased risk of developing complications related to efavirenz treatment (24,26). However, at this time, no data indicate that this drug should not be used in patients with cognitive or psychiatric symptoms.

Protease inhibitors (PIs) agents generally exhibit poor Central Nervous System penetration, due to large molecular weight, high lipophilicity, and relatively high degree of protein binding within plasma. In addition, PIs are actively removed from the cerebrospinal fluid, because they act as substrate of *P-glycoprotein*, a polarized membrane transporter protein, that actively pumps PIs across the blood-brain barrier. Therefore, many studies have reported undetectable in CSF concentrations of nelfinavir, and ritonavir (27). Although, some investigator reported that PIs can reach the brain parenchyma, despite being present at undetectably levels in cerebrospinal fluid.

Lopinavir, which is >90% protein-bound in the cerebrospinal fluid, reaches a high concentration (17,0 ug/L), and data suggest that lopinavir may have a significant antiviral activity in the CSF (27,28). Within the CHARTER study, Letendre at al. determined validation of the ***C**entral nervous system **P**enetration – **E**ffectiveness rank* for quantifying antiretroviral penetration into the brain (CPE) (28). Studies have proved good correlation between CPE and antiretroviral agents effectiveness. CPE rate >1,5 has shown good penetration to CNS. On the base of CPE rate, Letendre et al. formulate the antiretroviral regimen score (Table 3).

Table 3. Central nervous system Penetration-Effectiveness score(CPE) for ARV regimens

	CPE
LOPINAVIR/r	
LPV/r + ABC + 3TC	2,5
LPV/r + ZDV + 3TC	2,5
LPV/r + FTC + TDF	2,0
EFAVIRENZ	
EFV + ABC + 3TC	2,0
EFV + ZDV + TDF	2,0
EFV + FTC + TDF	1,5
ATAZANAVIR/r	
ATV/r + ABC + 3TC	2,0
ATV/r + ZDV + 3TC	2,0
ATV/r + FTC + TDF	1,5
SAQUINAVIR/r	
SQV/r + ABC + 3TC	1,5
SQV/r + ZDV + 3TC	1,5
SQV/r + FTC + TDF	1,0

Neurocognitive interventions in HIV-infected subjects

Psychological interventions for HIV-infected persons requires the cognitive-behavioral techniques in purpose of reducing negative affect and stress as well as improves emotion and adaptive behaviors. Stress management is one of the more common of these interventions. For some patients it is a few-week, group-based intervention, including the training in cognitive therapy, coping skills, interpersonal skills, and relaxation technique. Relaxation training and meditation-based interventions may improve psychological status among HIV-positive persons (29).

Initiation of antiretroviral therapy can improve neurocognitive function in HAND-affected patients (30). However, no consensus guidelines have been formulated as to when to start ART for HAND prophylactic. Current recommendations for initiating or changing antiretroviral treatment, depend on peripheral markers of infection, such as plasma viremia and CD4 lymphocyte count, and not the status of in CNS infection. The appropriate antiretroviral regimens are specifically targeted to the Central Nervous System and may be beneficial in treatment efficacy.

Drugs that well penetrate into the Central Nervous System, play an important role in improving CNS function in HIV-dementia. A study from Letendre et al. in cognitively-impaired, HIV-infected people, starting a new ARV regimen, showed a significantly greater reduction in CSF viral load in individuals who received a greater number of CSF-penetrating drugs (28). The group of patients have achieved virological suppression in the cerebrospinal fluid, demonstrated signifincantly greater neuropsychological improvements than those, who did not receive high CSF-penetrating drugs. Furthermore, patients have achieved in their CSF a viral suppression (VL <50 c/mL), had better neurocognitive outcomes. BOLD fMRI has also provided additional validation, with HIV-infected patients on higher CNS penetrating antiretroviral regimens. These findings suggest that cognitive outcomes of ARV treatment may be enhanced by selecting antiretroviral regimen that optimize penetration across the blood-brain barriere.

Conclusions

Mental and neurocognitive impairment associated with HIV infection, has changed with the advent of antiretroviral treatment. Fatal disease with severe subcortical dementia is now a chronic inflammatory disease requiring long-term medical management. The main therapeutic goal is optimizing the drugs effectiveness in the Central Nervous System, as well as developing neuroprotective therapies, that can both repair and protect vulnerable neurons. Establishing etiology of mental symptoms, eg. neuropathy, changes in cognition, dementia, and depression, neurocognitive symptoms, anxiety, substance abuse, drug toxicity, and other complications, have been a significant challenge in management of HIV-infected subjects. In the past several years, much has been learned about the neuropathogenesis and treatment of HIV-associated neurocognitive disorders. Thus, effective and well-tolerated therapies, neuroprotective, and adjustable treatment need to be develop.

References

1. Reinvang I, Froland SS, Skripeland V. Prevalence of neuropsychological deficit in HIV infection. Incipient signs of AIDS dementia complex in patients with AIDS. Acta Neurol Scand. 1991; 83:289-293.
2. Neuenburg JK, Brodt HR et al. HIV-related neuropathology, 1985-1999: rising prevalence of HIV encephalopathy in the era of highly active antiretroviral therapy. J Acquir Immune Defic Syndr. 2002; 31:171-177.
3. Eggers C, Herton K, Sturenburg HJ, van Lunzen J, Stellbrink HJ. Delayed central nervous system virus suppression during HAART is associated with encephalopathy, but not with viral drug resistance or poor central nervous system drug penetration. AIDS. 2003; 17(13):1897-1906.
4. Lambotte O, Deiva K, Tardieu m. HIV-1 persistance, viral reservoir, and the central nervous system in the HAART era. Brain Pathol. 2003; 13:95-103.
5. Finizi D, Hermankova M, Pierson T, et al. Identification of a resorvoir for HIV-1 in patients on highly active antiretroviral therapy. Science. 1997; 278: 1295-1300.
6. Achim CL, Wiley CA. Inflammation in AIDS and the role of the macrophages in brain pathology. Curr Opin Neurol. 1996; 9:221-225.
7. Ricardo-Dukelow M, kadiu I, Rozek W, et al. HIV-1 infected monocyte-derived macrophages affect the human brain microvascular endothelial cell proteome: new insights into blood-brain berrier dysfunction for HIV-1 associated dementia. J Neuroimmunol. 2007; 185:37-46.
8. Strain MC, Letendre S, Pillai SK, et al. Genetic composition of human immunodeficiency virus type 1 in carebrospinal fluid and blood without treatnment and during failing antiretroviral therapy. J Virol. 2005; 79:1772-1788.
9. Langfod D, Marquie-Beck J, de Almeida S et al. Relationship of antiretroviral treatment to postmortem brain tissue viral load in human immunodeficiency virus-infected patients. J Neurovirol. 2006; 12:100-107.
10. Ernst T, Chang L, Arnold S. Increased glial metabolotes predict increased working memory network activation in HIV brain injury. Neuroimage. 2003; 19:1686-1693.
11. Price RW, Epstein LG, Becker JT, et al. Biomarkers of HIV-1 CNS infection and injury. Neurology. 2007; 69:1781-1788.
12. Ances BM, Ellis RJ. Dementia and neurocognitive disorders due to HIV-1 infection. Semin Neurol. 2007; 27:86-92.
13. Gonzalez-Scarano F, Martin-Garcia J. The neuropathogenesis of AIDS. Nat Rev Immunol. 2005; 5:69-81.
14. Skinner S, Adewale AJ, DeBlock L, Gill MJ, Power C. Neurocognitive screening tools in HIV/AIDS: comparative performance among patients exposed to antiretroviral therapy. HIV Medicine. 2009; 10(4):246-52.
15. Gibbie T, Mijch A, Ellen S, Hoy J, Hutchison C, et al. Depression and neurocgnitive performance inindividuals with HIV/AIDS: 2-year follow-up. HIV Medicine. 2006; 7(2): 112-121.
16. Petrsen RC, Smith GE, Waring SC et al. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999; 56(3):303-8.
17. Beatty W, Manson N. Comparison performance on the Wisconsin and California Card Sorting Tests. Journal of Geriatric Psychiatry and Neurology. 1990; 3:163-171.
18. Anderson S, Damasio H, Jones RD, Tranel D. Wisconsin Card Sorting performance as a measure of frontal lobe damage. Journal of Clinical and Experimental Neuropsychology. 1991; 13:909-922.
19. Baldo JV, Shimamura AP. Letter and category fluency in patients with frontal lobe lesion. Neuropsychology. 1998; 12: 259-267.
20. Ellis RJ, Hsia K, Spector SA, et al. Cerebrospinal fluid human immunodeficiency virus type 1 RNA levels are elevated in neurocognitively impairmed individuals with acquired immunodeficiency syndrome. HIV Neurobehavioral Research Center Group. Ann Neurol. 1997; 42:679-688.
21. Kearney BP, Aweeka FT. The penetration of anti-infectives into the central nervous system. Neurol Clin. 1999; 17: 883-900.
22. Wynn HE, Brundage RC, Fletcher CV. Clinical implications of CNS penetration of antiretroviral drugs. CNS Dugs. 2002; 16:595-609.
23. Berger JR, Avison M. The blood brain barrier in HIV infection. Front Biosci.2004; 9:2680-2685.
24. Letendre S, Marquie-Beck J, Capparelli E, et al. Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. Arch Neurol. 2008; 65:65-70.
25. vonGiesen HJ, Koller H, Thelsen A, arendt G. Therapeutic effects of nonnucleoside reverse transcriptase inhibitors on the central nervous system in HIV-infected patients. J Acquir Immune Deic syndr. 2002; 29:363-367.
26. Cliford DB, Evans S, Yang Y, et al. Impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals. Ann Intern Med. 2005; 143:714-721.
27. Letendre SL, Ellis RJ, Grant I, McCutchan JA et al. The CSF concentration/IC50 ratio: a potential predictor of antiretroviral efficacy in the CNS. The 8th Conference on Retroviruses and Opportunistic Infections, 2001; Chicago Abs 614
28. Letendre SL, McCutchan JA, Childers ME, et al. Enhancing antiretroviral therapy for human immunodeficiency virus cognitive disorders. Ann Neurol. 2004; 56:416-423.
29. Hinkin CH, Castellon SA, Durvasula RS, et al. Medication adherence among HIV+ adults: effect of cognitive dysfunction and regimen complexity. Neurology. 2002; 59:1944-1950.
30. Safren SA, O'Cleirigh C, Tan JY, Raminani SR, Reilly LC, Otto MW, et al. A randomized controlled trial of cognitive behavioral therapy for adherence and depression in HIV-infected individuals. Health Psychology 2009; 28(1):1-10.

title

Adherence Improvement Factors Among Patients Addicted to Psychoactive Substances Treated with Antiretrovirals

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summary

Drug-addiction should not be an obstacle in starting ARV therapy, but a cause to give more emphasis to complementary work with the patient in order to strengthen his/her adherence (1) . The objective of the comparative study was to evaluate factors improving cooperation in accomplishing ARV therapy regimes with drug addicts compared to non-addicts.

The study was performed on the basis of a questionnaire among 30 drug addicts. The control group comprised 30 non-addicted patients.

Respondents from both groups pointed to the importance of the leading physician's commitment to the treatment process. Perceptible effects of therapy, support of family and friends and the notion of continual medical care constitute elements that help improve adherence in the opinion of both drug-addicted and non-addicted patients.

key words

drug addicted, antiretroviral treatment, adherence

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Bacground

An important moment, in view of not only the length but also the quality of life of sero-positive patients, was year 1996 when HAART(Highly Active Antiretroviral Therapy) was first used in treatment(2).The effectiveness of ARV (Antiretroviral) therapy is closely connected with adherence to therapeutic regimes, which requires preciseness in administering medications. At the same time, the therapy is burdened with adverse effects, drug toxicity, risk of drug resistance and above all treatment failure – among others because of lack of cooperation on the patient's part. For this reason, physicians often evaluate the extent to which a particular patient is capable of adhering to recommendations regarding antiretroviral medicines (3). Attention ought to be drawn to the fact that when starting ARV therapy the physician must eliminate prejudice, intolerance and discrimination.

This is particularly important in case of drug-addicted patients (4).The fact that an individual is a drug addict should not lead to delaying the start of *antiretroviral* therapy, especially as patients encounter problems in adhering to therapy regimes regardless of whether or not they are or were drug-addicted (3). It is crucial to build awareness among drug-addicted patients that addiction considerably impedes the success of the therapy (4). Therefore, it is necessary to undertake intensive and multi-discipline works with drug-addicted patients oriented on changing the quality of their life and refraining from the addiction. The expected result of such actions is to achieve a high level of adherence and constituent elements:

- Compliance – behaviour in line with therapeutic recommendations (5),
- Persistence in long-term treatment, irrespective of the occurring difficulties (6).

The objective of the comparative study was to assess factors improving cooperation in adhering to ARV therapy regimes among drug-addicted patients, compared to a control group comprising non-addicted patients.

Material/Methods

The study included drug-addicted patients treated with substitutes (Methadone Maintenance Therapy), mainly from Warsaw methadone programmes, especially the methadone programme of Hospital for Infectious Diseases. The control group consisted of non-addicted patients from the whole territory of Poland, beneficiaries of programmes undertaken by societies providing aid to sero-positive individuals_– *associations like: Stowarzyszenie Wolontariuszy Wobec AIDS „Bądź z Nami", Stowarzyszenie Ogólnopolska Sieć Osób Żyjących z HIV/AIDS „Sieć Plus"* .

The selection criterion was ARV therapy. Respondents represented a broad range of experience relating to such treatment since all were administered ARV medications, it means aboute 3 years. Both groups differed in terms of age and sex. The study was based on a customized questionnaire filled in anonymously and discretionarily within the period from July to September 2008. Each group comprised 30 respondents.

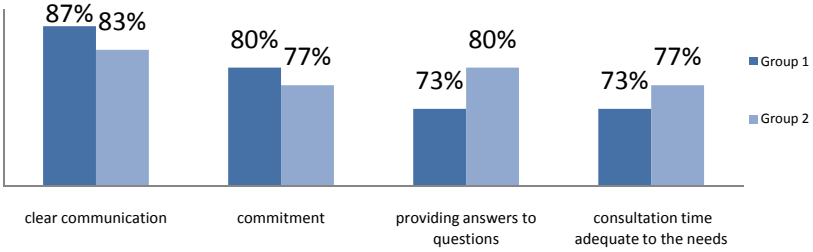
*In the study***,** drug addicts treated with substitutes and ARV are referred to as "1st Group" and non-addicts treated with ARV are referred to as "2nd Group".

Results

Physician – patient cooperation throughout the treatment process

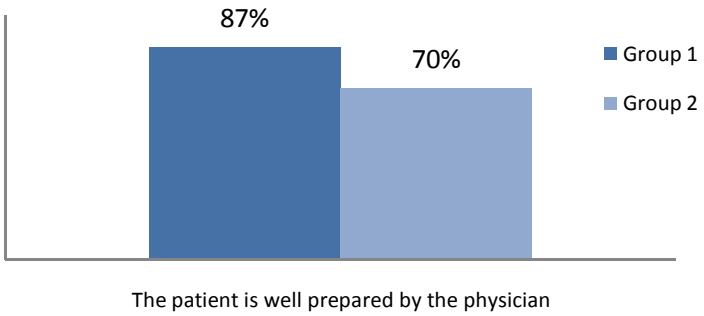
With a long-term, burdensome and restrictive therapy, it is necessary to prepare the patient for the treatment in a way as to allow him/her to decide knowingly about the start of the therapy and to become familiarized with its afflictions. To prepare a patient to begin antiretroviral therapy requires from the physician time, patience and ability to communicate openly (3). Respondents were asked about their opinion on how they were prepared by the physician to ARV therapy.

Figure1. Preparing for ARV therapy by the physician appraised positively in the opinion of patients



In both groups, there were no significant differences in the answers. Most respondents stressed that information about treatment was provided in a comprehensible manner, the patients felt that the physician listened to them carefully, demonstrated commitment and answered all their questions. In respondent's opinion, the fact that the length of consultation was adjusted to their needs was important. They did not notice any hurriedness on the physician's part. The ability to obtain information important for the patients as regards the therapy proved essential in particular for non-addicted patients (80% vs. 73%). At the same time, joint planning of the treatment process helps build a positive patient – physician relation in a natural way.

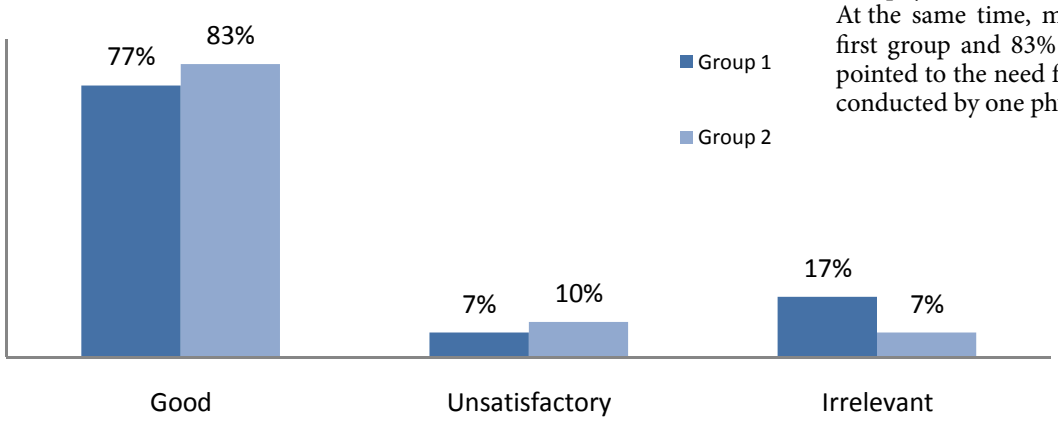
Figure 2. Evaluation of the physician's performance in treatment planning in the opinion of patients



Among 30 drug-addicted patients 87% responded they were invited by the physician to cooperate in planning ARV therapy, which was confirmed by 21 (70%) of respondents from the control group.

The study also aimed to explore the confidence in the leading physician, an issue important from the point of view of adherence. Respondents were asked whether they could speak openly with the physician about experience relating to treatment and express their concerns and doubts.

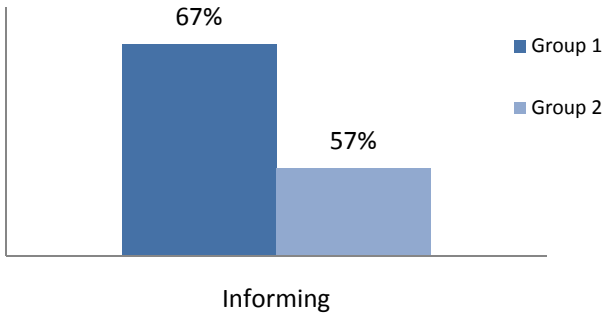
Figure 3. Opinion about patient – physician communication



23 respondents (77%) among 30 drug-addicted patients admitted they could speak explicitly with the physician on every treatment-related subject, whereas 5 patients (17%) said they did not need to go into every detail and analyse their experience in this respect. A similar result was achieved in the second groups, i.e. 25 persons (83%) pointed to the possibility of open communication in patient – physician relation and just 7% respondents said they had no such expectations. Respondents referring to the possibility of addressing every important issue as regards ARV therapy in their meetings with the physician explained it in the following manner: "the leading physician knows my disease record and private life. I can disclose to him/her […] even my private life".

The extent to which respondents trust their leading physician is proved also by their readiness to talk about failure to observe medical recommendations, i.e. insufficient adherence.

Figure 4. Informing the physician about drug discontinuation

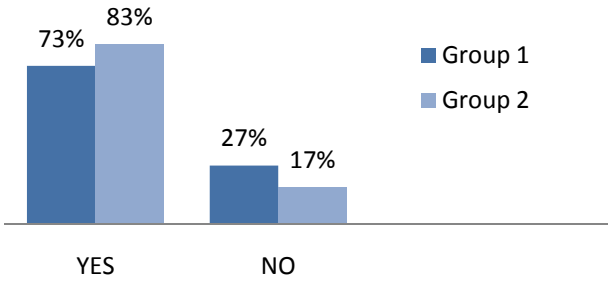


Among drug-addicted patients, 20 respondents (67%) have admitted that they reveal to the physician situations when the therapeutic regime is not observed. The same was admitted by more than half of respondents from the control group (57%). Reasons for which respondents do not talk with the physician about adherence failures with regard to ARV therapy include failure to recognize the importance of such exchange, concern about the physician's reaction, considering such events purely as a private matter.

The possibility of regular visits with a leading, i.e. chosen physician undoubtedly motivated the patient's readiness to cooperate throughout the treatment process. Information was collected about whether ARV treatment was performed by a leading physician and whether the respondents recognize such need.

From the 1st group 20 respondents (67%) and 63%, i.e. 19 respondents from the control group have admitted they do not have one physician managing ARV treatment. At the same time, majority – 73% in the first group and 83% in the second group pointed to the need for ARV therapy to be conducted by one physician.

Figure 5. Patient need for ARV therapy to be monitored by a one physician



The importance of pursuing treatment with one physician was explained by respondents in the following manner: "the leading physician […] knows us and knows what we expect […] we know […] whether we can trust him/her, whether he/she will give us good advice", "[…] you don't have to starting telling everything about yourself from the beginning as happens when the doctors change", "knows the patient's life situation". Among advantages of such situation for the patient – physician relation the following is listed: trust, sense of security, understanding also in point of view of adherence, feeling the medical care is a continual process. In both groups few respondents have admitted that consulting different physicians is valuable because "I like to make appointments at a time convenient for me", a different physician "has a different approach" and "is unbiased" and "physicians have the same knowledge" on ARV treatment.

The study also addressed reasons for making appointments.

Among drug-addicted patients 53%, it means 16 respondents have admitted that they consult a physician in the HIV Outpatient Clinic for various reasons, including medical reasons, not only related to ARV treatment. Similar results were accomplished in the control group – 18 (60%) respondents said that they needed to contact the physician – as cited – "just to talk to somebody …".

Table 1. Reasons for making appointments with the physician

Reasons	GROUP 1		GROUP 2	
	n	%	n	%
Related to ARV	14	47	12	40
Other	16	53	18	60
In total	30	100	30	100

Compliance

Compliance, besides persistence, is the most important indicator of success in ARV therapy. Respondents were asked whether they applied ARV medicines according to the physician's recommendations.

Among drug-addicted patients 23 respondents (77%) and among non-addicted patients 20 (67%) respondents admitted they adhered to physician's recommendations, whereas just 23%, i.e.7 drug-addicted respondents did not follow the recommendations compared to 10 respondents (33%) from the control group. The lack of adherence in applying medications is caused to a great extent by "lack of remembrance", "sometimes when I feel bad I give myself a one-day break" and also "I think that with time I have started to forget about treatment […], I do not attach as much importance to it as once", and "I adjust the taking of medicines […] to my curriculum and not the other way round".

Maintaining the continuity of the therapy is essential for avoiding drug resistance syndrome. Among drug-addicted patients 14 respondents (47%) and 16 (53%) of respondents from the control group emphasized that they had no such intervals. Respondents, who suspended treatment independently, were asked for reasons of such behaviour.The main reason for suspending treatment in case of 69% of respondents in the 1st group and 50% of respondents in the non-addicted group was the difficulty in coping with side effects of medications. Other reasons included long-term treatment according to 5 patients (36%) of the control group and large number of medications according to 3 respondents (19%) in case of drug-addicted patients.

Persistence in continuing ARV therapy

When analyzing the experience of respondents in the accomplishment of ARV assumptions, patients have been asked to indicate factors which in their opinion make continuing the therapy difficult and which encourage persistence in long-term ARV treatment.

The occurrence of adverse effects such as diarrhoea or lipodystrophy are considered a considerable obstacle in the continuation of treatment according to more than half, it means 18 drug-addicted patients (60%), while only 2 respondents (7%) consider that the lack of progress in treatment and also lack of motivation are an obstacle – as cited "lack of motivation, confidence in the general sense of treatment" and the fact that treatment "overthrows the action of methadone". Among non-addicted patients more persons, i.e. 22 (73%) pointed to adverse effects as considerable burden in continuing treatment, while 14 respondents (47%) pointed to drug intolerance. Only one person in that group admitted that the hours during which the medication could be received were troublesome.

Table 2. Factors obstructing the continuation of ARV therapy

Factors	GROUP 1		GROUP 2	
	n	%*	n	%*
Adverse effects	18	60	22	73
Change of medications	10	33	14	47
Long distance to the health care centre	3	10	7	23
Other possibilities	2	7	1	3

* Do not add up to 100% because respondents could choose more than one answer

Despite difficulties relating to the therapeutic regime, respondents pointed also to factors strengthening their motivation to continue treatment.

Table 3. Motivating factors to ARV therapy

Factors	GROUP 1		GROUP 2	
	n	%*	n	%*
↑ CD4 , ↓ HIV-RNA	25	83	23	77
The physician approach	18	60	19	63
Support of friends and/or family	18	60	19	63
Accessibility of medical care	14	47	22	73
Improvement of physical condition	16	53	18	60
A Aid of a psychologist/therapy specialist	9	30	14	47
Other possibilities	–	–	4	13

* Do not add up to 100% because respondents could choose more than one answer

For 25 (83%) among 30 drug-addicted patients the increase of CD4 levels and reduction of HIV-RNA to untraceable levels provide a strong incentive to continue treatment. Similar answers were given by 23 (77%) of patients of the control group. Another element important for continuing the therapy for 22 (73%) of non-addicted patients is the accessibility of medical care, pointed out by 14 (47%) of drug-addicted patients. Almost an equal number of respondents in both groups of 30 patients, i.e. 18 (60%) vs. 19 (63%) pointed to further two elements important for persistence in continuing ARV treatment, i.e. friendly, responsive attitude of the physician and emotional support provided by family and friends. In addition, 4 (13%) non-addicted patients admitted that their motivation to continue taking ARV medications stemmed from "eagerness to live", "positive approach" and "acceptance" of the treatment and also "what must be, must be". Respondents were asked about persons who most often provide help and show interest in the aspect of ARV therapy.

In case of 20 drug-addicted patients (67%) the main source of support are members of the family and for half of the non-addicted patients, i.e. 15 (50%) apart from the family – also the leading physician.

Respondents were asked also whether the duration of treatment increased their motivation to continue treatment. In most cases, i.e. 23 drug-addicted patients (77%) and 18 non-addicted patients (60%) – respondents noticed a relation between the duration of treatment and increase of their readiness to continue such treatment, which was

explained in the following manner "with time you get the habit", "awareness increases about better results of the therapy", "to see the results, you have to take medications". On the other hand, 4 (13%) patients of the 1st group compared to 33%, i.e. 10 patients of the 2nd group believe that the duration of treatment is not correlated with an increase of motivation to continue it – "after some time the results get better and I forget about the medications more and more often", "in the beginning everything is new – then it becomes a routine", "in the beginning there is fear, then it vanishes", "after several years […] you become indifferent and tired".

Table 4 . Source of emotional support in ARV treatment process

Source	GROUP 1		GROUP 2	
	n	%*	n	%*
Family	20	67	15	50
Physician	12	40	15	50
Friends	8	27	14	47
Psychologist/Therapy specialist	3	10	2	7

* Do not add up to 100% because respondents could choose more than one answer

Conclusion

From the point of view of patient-physician cooperation, it is essential to prepare the patient adequately before the start of the ARV treatment. It is important for the patient's confidence in the physician, understanding of the physician's expectations and the patient's awareness of his/her role and responsibility for the results of treatment. In both groups, respondents emphasized the commitment of the physician accompanying them in deciding about ARV treatment. Non-addicted patients demonstrated a greater need for information regarding all aspects of treatment. At the same time agreeing on successive appointments and examinations, possibility of contact, e.g. in case of an urgency and furthermore – discussing and planning the treatment process facilitate communication with the patient. The physician's commitment to the treatment process, demonstration of concern and consideration combined with a complex approach to the patient's problems are of especially important for drug-addicted patients. For those patients the experience in social contacts, including health care, is often trivial conduct rather than offering professional and expected aid. The drug-addicted respondents alike non-addicted patients gave emphasis to the fact that they were invited by the physician to cooperate and assume responsibility for the treatment process and its results. The relation patient – physician founded on confidence in the leading physician is also important and influences the readiness of patients to adhere to ARV therapy recommendations. Both drug-addicted patients (77%) as well as non-addicted patients (83%) admitted that they had confidence in their physician whom they could talk to about every matter of their concern, not only about their health. Such confidence is also manifested by the patients' readiness – more stressed by drug-addicted respondents (67%) compared to the control group (57%) – to report and discuss with the physician reasons for adherence failures. Respondents also pointed to the importance of ARV treatment monitored by one physician, which in their opinion helped build a positive relation founded on a sense of security and continuance of medical care. This emphasizes the role of the physician in establishing a patient – physician relation based on cooperation, providing grounds for sustaining regularity and persistence in the therapy. In most cases, both drug-addicted and non-addicted patients adhere to treatment regimes. The main cause for suspending the therapy on their own initiative and hindering its continuation are the adverse effects of medications. Then again recognizing the effects of treatment based on an improvement of CD4 and HIV-RNA parameters, apart from the support of family and friends and the physician as well as accessibility of medical care – are the main factors motivating patients from both groups to continue the therapy. At the same time, the initial incentive to begin to have therapy is connected with concerns about own health and life, hence the perception of treatment results may be replaced with time by routine and lesser importance attached to strict observance of the regime. This indicates an important direction for the future, in particular when working with patients administered ARV medications on a long-term basis – their commitment and readiness to apply therapeutic recommendations routinely must be monitored on a constant basis. Motivational therapy is perceived as important, especially in patients applying the treatment for many years, in order to encourage them to cooperate throughout the process. Then again commitment in the ARV therapy for drug-addicted patients and non-addicted patients proves it is necessary to support their partnership role throughout the treatment process.

Acknowledgments

The autors would like to thank all participants, therapy specialists and Association like: Stowarzyszenie Wolontariuszy Wobec AIDS „Bądź z Nami" ,Stowarzyszenie Ogólnopolska Sieć Osób Żyjących z HIV/AIDS „ Sieć Plus" who contributet data collection for this study.

References

1. Shannon K, Kerr T, Lai C, Ishida T, Wood I, Montaner JS, Hoog RS, Tyndall MW. Nonadherence to Antiretroviral Therapy Among a Community With Endemic Rates of Injection Drug Use. J Int Assoc Physicians Aids Care , 2005;4; 66-72
2. Rogowska-Szatkowska D. Jakość życia osób zakażonych HIV. Aspekty Nr. 1 (35)/2008, dodatek do Biuletynu Krajowego Centrum ds. AIDS „ Kontra". Krajowe Centrum ds. AIDS.
3. Rogowska-Szatkowska D: Zakażenie HIV, uzależnienia i metadon. In: Chrostek – Maj J, Wodowski G, editors. Szczypta naszej nadziei Leczenie substytucyjne uzależnionych od opiatów w Krakowie, 2000-2007. Stowarzyszenie życzliwa Dłoń, Kraków 2008.
4. Cholewińska G:Standardy opieki i rzeczywiste możliwości terapii antyretrowirusowej dla osób uzależnionych od środków psychoaktywnych w Polsce. In: Zapewnienie opieki i leczenia zakażenia HIV osobom przyjmującym narkotyki: wnioski płynące z badań. Społeczny Komitet ds. AIDS , 2007.
5. Gaciong Z, Kuna P. Adherence, compliance, persistence – współpraca, zgodność i wytrwałość – podstawowy warunek sukcesu terapii. In : Medycyna po Dyplomie, spec. edition 03/2008.
6. Sewerynek E. Czynniki wpływające na przestrzeganie zasad terapii i efektywność leczenia osteoporozy – rola współpracy lekarz–pacjent. Medycyna po Dyplomie, spec. edition 03/2008, 39-41.

title

HIV infections in deceased organ donors in Poland in years 1998-2008

authors

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summary

First incidences of HIV or AIDS disease in Poland were reported in 1985. Up to the end of 2008 0,03% of polish population had been infected of HIV virus.

The aim of this document was determination of HIV occurrence in Polish organ donor population in 1998-2008, determination of percentage of withdrawal in case of HIV infection, determination of HIV positive organ donor profile and comparison of frequency of HIV infection in deceased organ donors and general population in Poland.

In 1998-2008 5954 possible deceased organ donors had been reported to Polish Transplant Coordinating Center Poltransplant, organ recovery took place in 4875 (82%) cases In 1079 cases (18 %) organs were not recovered because of medical reasons (46%) and family or prosecutor objections (54%).

HIV antibodies had been tested in 90% possible organ donors. Positive HIV antibodies were reported in 0,3% cases.

The occurrence of HIV infection in deceased organ donors in Poland in the years 1998-2008 was 10 times higher than in general Polish population. In general population HIV infections occur mainly in young people, in possible organ donor population infections occurred mostly between older one.

HIV infection in donor is rare but significant reason of withdrawal.

key words

HIV infections, AIDS disease, deceased donors

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Background

First documented occurrence of HIV infection was recorded in 1981 in USA. First incidences of HIV or AIDS disease in Poland were reported in 1985.

Than is more than 65 million infections recorded and more than 25 million HIV/AIDS related death reported all over the world. More than 40% of all HIV infections concern people between 14 and 24 years old (1).

According to World Health Organization incidences of HIV/AIDS infections might be three times more. It has been estimated that every third infected person in Europe is not aware of this fact (2).

There have been 12014 recorded HIV infections in Poland between 1985 – November 2008 which is 0,03% of all country population. 46% of the infections are connected with drug addiction (3). AIDS occurred in 2177 cases, there are 961 AIDS/HIV related deaths recorded.

Blood tests for HIV antibodies subtype 1 and 2 (anti-HIV 1/2) are mandatory for every possible organ or tissue donor (4).

Organs, cell and tissues from donors infected HIV virus can not be used (4). However, there is an exception in few countries, where HIV positive organs are transplanted to HIV positive recipients.

Aim

1. Determination of HIV occurrence in Polish organ donor population in 1998-2008.
2. Determination of percentage of withdrawal in case of HIV infection.
3. Determination of HIV positive organ donor profile (HBV/HCV infections, risk factors, age, reason of death, region)
4. Comparison of frequency of HIV infection in deceased organ donors and general population in Poland.

Materials and methods

In 1998-2008 5954 possible deceased organ donors had been reported to Polish Transplant Coordinating Center Poltransplant, organ recovery took place in 4875 (82%) cases (fig. 1). In 1079 cases (18 %) organs were not recovered because of medical reasons (46%) and family or prosecutor objections (54%). The most often medical reason of withdrawal from the procedure were: cardiac arrest before organ collection, neoplasia, organ pathology, renal failure, hepatitis B and C infections (positive HbsAg and anti-Hbcore and anti-HCV), HIV infection (5,6).

All data came from coordinating cards.

Results

HIV antibodies had been tested in 5358 organ donors (90%). Positive HIV antibodies were reported in 17 cases (0,3%) (fig. 2 and 3). Detection of blood HIV antibodies in blood and confirmatory tests were made with ELISA method in regional transplant centers. None of these possible deceased donors were qualified for organ recovery.

Cause of death of HIV positive possible deceased organ donors, was CVA (65%) and head trauma (35%) (fig. 4).

HIV positive possible organ donor age ranged from 26 to 62 years (mean 49,5) (table 1).

82% of deceased organ donors anti-HIV positive were male and 18% - female (fig. 5). 5 (33,3%) of anti-HIV positive deceased donors were abusing alcohol, 1 donor was in prison, another one had a tattoo. There were no risk factors marked in coordinating cards in the rest of HIV positive donors. Among 5 (25%) of anti-HIV positive donors, hepatitis B and C had been also reported (table 2).

Table 1. Deceased organ donors (anti-HIV +) age

deceased organ donors age	26 y.o.	28 y.o.	32 y.o.	43 y.o.	47 y.o.	49 y.o.	52 y.o.	53 y.o.	56 y.o.	59 y.o.	62 y.o.
number of deceased donors anti-HIV +	1	1	1	1	1	1	2	3	2	2	2

Table 2. HIV virus in provinces

province	anti-HIV +	HbsAg +	anti-Hbc +	anti-HCV +
dolnośląskie	2	-	1	-
kujawskopomorskie	2	-	-	-
łódzkie	3	1	-	-
pomorskie	2	-	-	1
śląskie	2	-	-	-
warmińskomazurskie	1	-	-	-
wielkopolskie	4	-	1	-
zachodniopomorskie	1	-	-	-
total	**17**	**1**	**2**	**1**

Figure 1. Deceased organ donors in Poland in 1998-2008

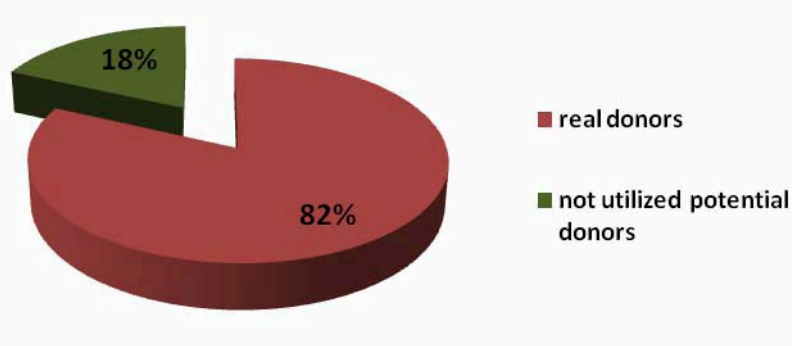


Figure 2. HIV antibodies in deceased organ donors in Poland in 1998-2008

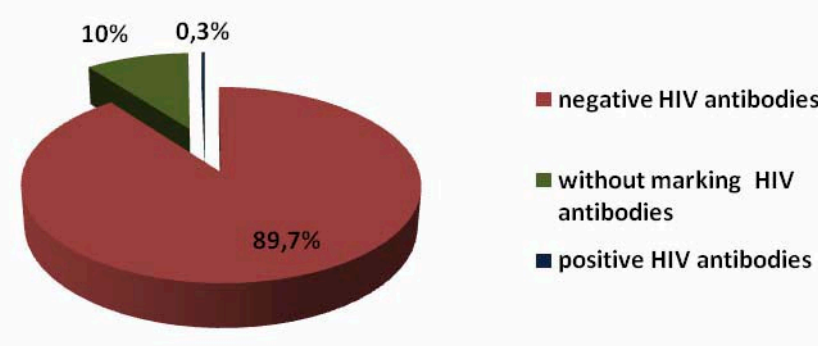


Figure 3. HIV positive possible organ donors in years 1998-2008 in Poland

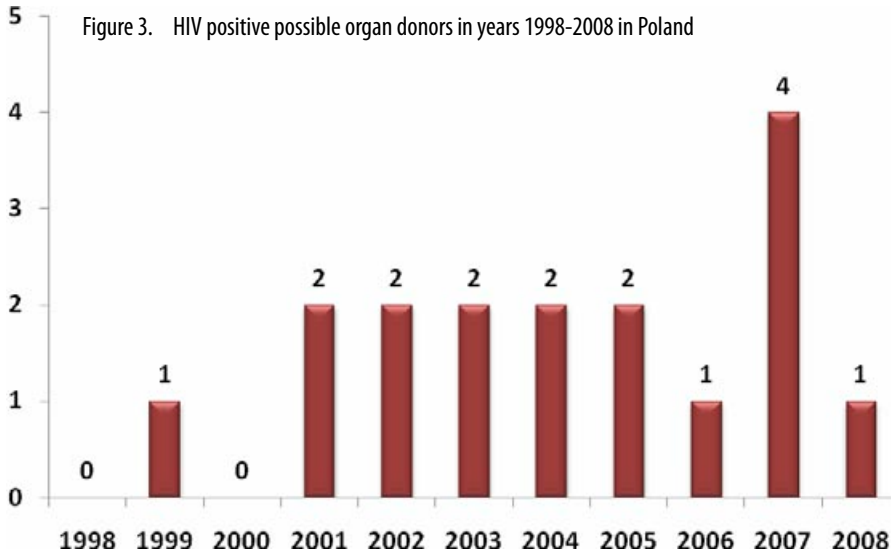


Figure 4. Cause of deceased HIV positive organ donors death in Poland in 1998-2008

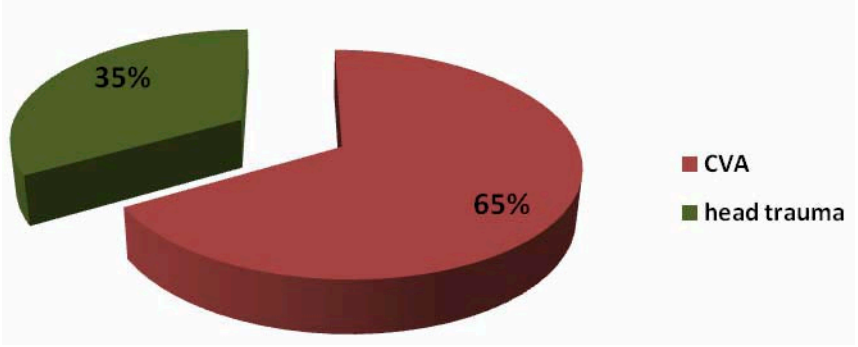
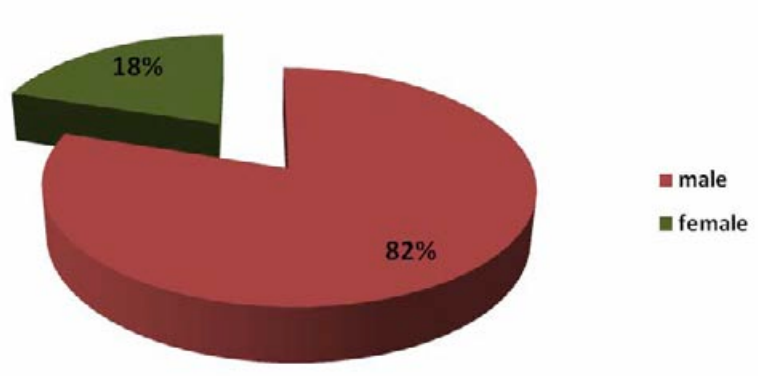


Figure 5. Gender of deceased organ donors anti-HIV positive



Conclusions

1. The occurrence of HIV infection in deceased organ donors in Poland in the years 1998-2008 was 10 times higher than in general Polish population.
2. HIV infection in donor is rare but significant reason of withdrawal .
3. In general population HIV infections occur mainly in young people, in possible organ donor population infections occurred mostly between older one.

Discussion

The occurrence of HIV infection in deceased organ donors in Poland in the years 1998-2008 was reported in 0,3% cases. It is impossible to compare it to European data because majority of patients with HIV infections are disqualified as possible organ donors and are not reported to transplant centers.

The occurrence of HIV infections in blood donors in Poland through 20 years was reported in 0,005-0,007% cases (7). It is less than in organ donors population. Blood donors, compared to the organ donors, come from the whole population and possible organ donors might come from the higher infection risk groups (drug addict, alcoholic, prisoners).

Summary

Population of deceased organ donors in Poland is not comparable to general population in geographical (different donation index in provinces) and demographical (different layout of sex and age) way. It is important in epidemiological way because it is not chosen particularly and it indirectly gives an overview of HIV/AIDS occurrence and demanded ways of treatment in future.

References

1. Report on the global AIDS epidemic, Geneva: UNAIDS, 2006.
2. Derkacz M., Mosiewicz J., Myśliński W.: Ocena poziomu wiedzy na temat zakażeń HIV wśród młodzieży wybranych szkół średnich województwa lubelskiego, Annales Universitati Mariae Curie-Skłodowska Lublin-Polonia, Vol. LXII, Suppl. XVIII, N. 2, 110, Sectio D, 2007, p:27.
3. www.pzh.gov.pl.
4. Fischer_Frohlich C.L., Lauchart W.: Viral screening in organ donation: practical considerations, Organs and Tissues, (2), The Journal of European Transplant Coordinators Organization, Italy 2004, p:121-127.
5. Antoszkiewicz K., Czerwiński J., Malanowski P.: Pobieranie i przeszczepianie narządów w Polsce w 2007r., POLTRANSPLANT-biuletyn informacyjny, 2008, 1(16):11-12.
6. Pszenny A., Czerwiński J., Malanowski P. i wsp.: Organ donation and transplantation in Poland in 2007, Annals of Transplantation, 2008, 13(4):17.
7. Mikulska M., Sulkowska E., Grabarczyk P. i wsp.: Częstośc zakażeń wirusem HIV w populacji krwiodawców w Polsce w latach 1988-2007, Journal of Transfusion Medicine, rok 2008, tom 1, nr 1.

title

Mediastinal tumour as a symptom of immune reconstitution inflammatory syndrome in the course of AIDS with pulmonary tuberculosis

authors

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summary

A case report of immune reconstitution inflammatory syndrome in an AIDS patient with pulmonary tuberculosis, manifested as a mediastinal lump. The location of the lesion and the uncharacteristic CT scan image precluded the exclusion of mediastinal malignancy for a considerable time.

key words

HIV infection, antiviral therapy, tuberculosis, immune reconstitution inflammatory syndrome (IRIS)

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Introduction

After the initiation of antiretroviral therapy (ART) in patients with low CD4+ T cell counts, immune reconstitution inflammatory syndrome is observed, in which the improvement of immune response occurs concomitantly with a deterioration in the clinical status. This is accompanied by the development of symptoms of opportunistic infections, not diagnosed previously and/or intensification of manifestations of already diagnosed infections (1,2). In the case of increased symptom severity during the first weeks/months of ART, it is necessary to perform laborious differential diagnostics that would enable effective treatment.

Case report

Patient, aged 24, was admitted to the hospital in March 2008 due to fever and enlarged lymph nodes. On histopathological examination of the lymph nodes, extensive coagulative necrosis was diagnosed, with macrophage accumulation and generation of poorly separated nodules with single giant cells. In view of a positive anti-HIV test result, the patient was transferred to the on-site clinic, where HIV infection was confirmed with the use of Western blot.

On physical examination, fever was found, as well as generalised lymph node enlargement, disseminated lesions symptomatic for molluscum contagiosum on the facial and trunk skin, and oral and oropharyngeal candidiasis. In view of behavioural disturbances, the patient underwent psychological consultation, which revealed a complex of adaptation symptoms. Tuberculostatics were ordered, along with antifungal and symptomatic drugs, achieving body temperature normalisation. In laboratory tests, transient increase in the activity of liver enzymes was found, not necessitating the drug dose modification. The CD4+ T cell count was 135/mm^3. Three weeks later, ART was initiated (Trizivir), after three days of which an elevation of body temperature was seen again, in the presence of negative blood culture and patient's good general state. In order to exclude adverse drug reaction (Abacavir), the ART regimen was modified (Truvada+Stocrin), after which no febrile states were observed in the patient. Chest CT scan performed at that time did no reveal any abnormalities (Figure 1).

In June 2008, one month after patients discharge from the hospital, a significant enlargement of right supraclavical lymph nodes and right axillary lymph nodes, accompanied by subfebrile states were found. In blood laboratory tests, elevated inflammation markers, such as high ESR, and low level of iron were seen. Chest CT scan revealed a large mass in posterior mediastinum (no changes on CT two months earlier). The above lesion did not affect the passage of food, despite the pressure it exerted on the oesophagus (Figure 2). No atypical cells were found on bronchoscopy. In immunophenotyping of peripheral blood lymphocytes, features of haematopoietic system malignancy were excluded. In histopathological examination of the lymph node specimen taken from axillary fossa, tuberculosis-like changes were found, without neoplastic changes. It was decided to continue the ART and anti-TB treatment.

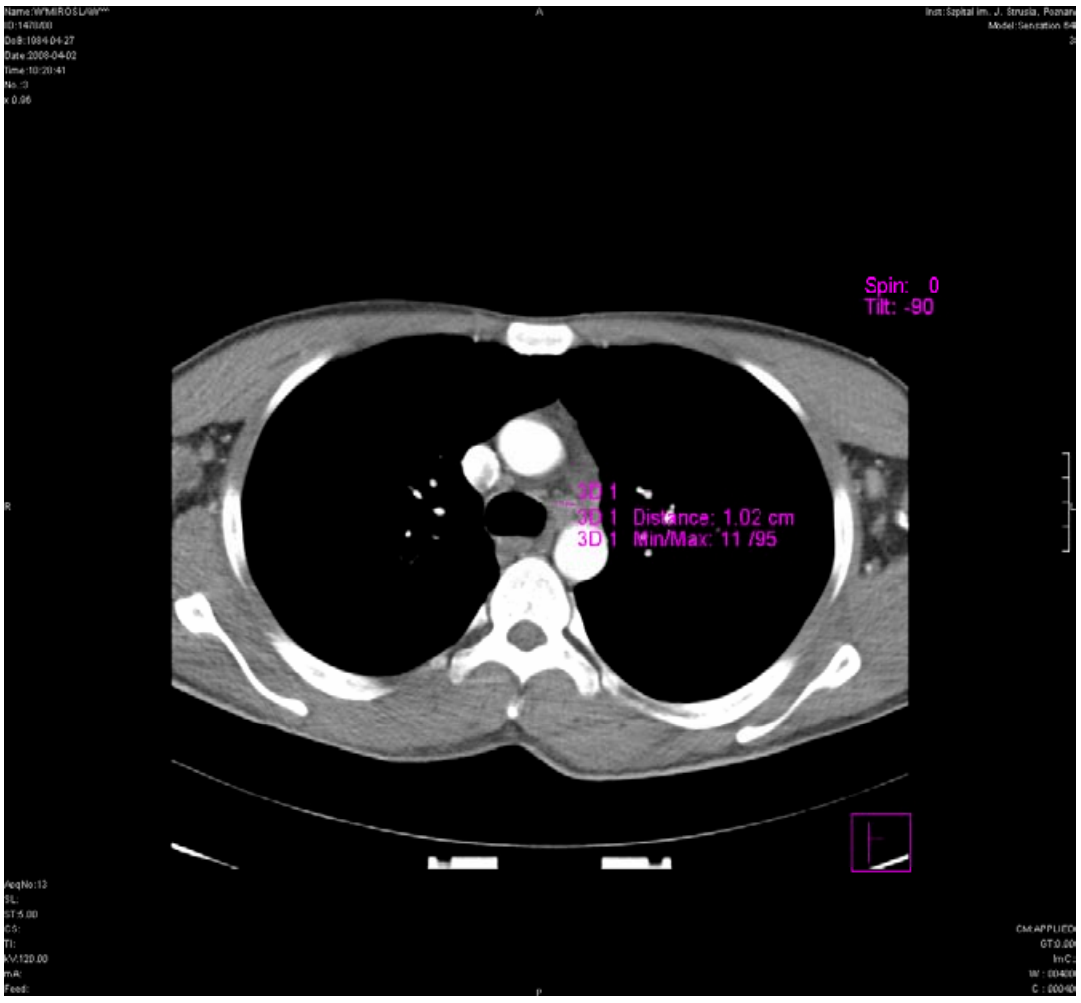
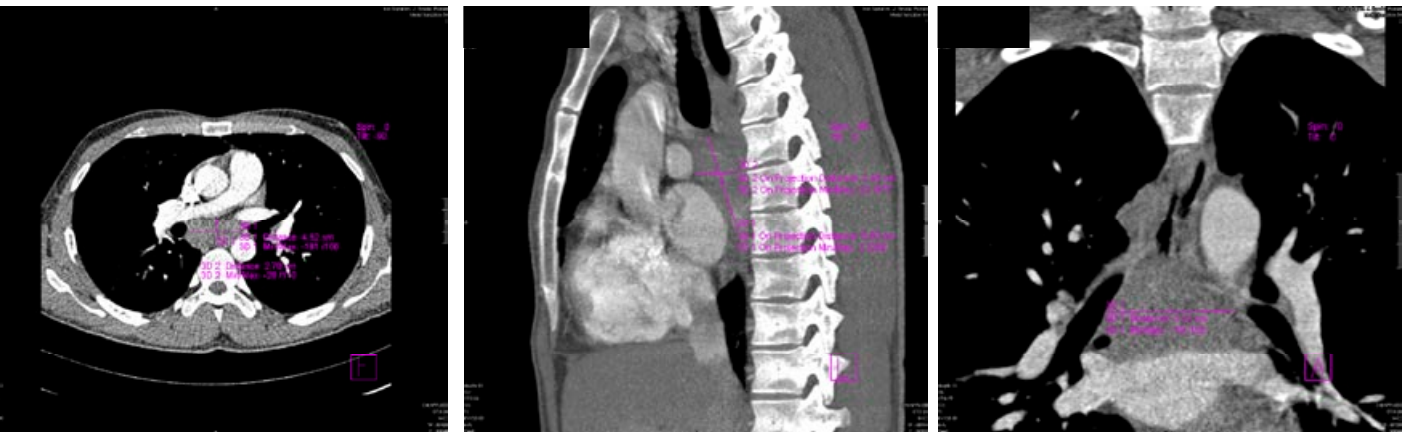


Figure 1. Mediastinal lymph nodes – April 2008

Figure 2. Mediastinal tumor – June 2008



In September 2008, body weight gain was observed (+ 10 kg), with no abnormalities in the physical examination and patient history. A chest CT scan performed again, revealed persisting lesion in the mediastinum, of the size similar to that seen in June 2008. Peripheral blood lymphocyte phenotype remained free of neoplastic proliferation features.

In December 2008, enlarged lymph nodes and liver were found on physical examination revealed. Elevated ALT activity was found in laboratory tests. In response to ART, the CD4+ T cell count increased to 420/mm^3. Abdominal CT scan revealed infiltration in spleen, undetectable in ultrasound examination, while the mediastinal lesion was described as a cluster of lymph nodes. Based on peripheral blood leukocyte phenotyping, no markers of lymphatic system malignancy were found. Immunoelectrophoresis revealed elevated IgA as well as lambda light chain levels. Haematological consultation still did not provide basis for diagnosing haematopoietic malignancy.

In March 2009, another chest CT scan showed a decrease in the previously observed mediastinal lesion which was described as a sequela after a past lymph node inflammation (Figure 3). In a check-up immunoelectrophoresis of serum proteins, a tendency to immunoglobulin normalisation occurred. At that time, the patient has completed the anti-TB treatment, and currently continues the ART. The CD4+ T cell count in March 2009 was 661/mm^3. The chest CT scan findings are presented in Table 1.

Discussion

Immune reconstitution inflammatory syndrome is observed often in patients with HIV infections and tuberculosis (3). Its diagnosis is associated with the necessity to exclude additional conditions, e.g. previously undiagnosed concomitant infections. The most common clinical symptoms include fever, abdominal pain and cough. Another clinical manifestation may be lymph node enlargement with necrosis. These changes usually involve abdominal, axillary and mediastinal lymph node clusters (36%). Sometimes, fine nodules tending to effuse are formed (4). Rare forms of IRIS have also been described, for example with accompanying pericardial effusion (5). In the case presented here, none of the above clinical symptoms were observed, except for a transient asymmetric subclavical lymph node enlargement. No characteristic lesions in lungs were observed either – it was only after 6 months that the described mediastinal lesion acquired lymph node features.

The factors predictive of IRIS development include low CD4+ T cell count, anaemia, a number of opportunistic infections and young age (2,6). Although the patient described in this report did not meet all the IRIS criteria, the low CD4+ T cell subpopulation count, patients young age, as well as the presence of inflammatory lesions in the lymph nodes mentioned earlier, enabled the diagnosis of this syndrome. It was not possible to measure serum Interleukin 6 (IL-6), believed to be an IRIS marker in patients with HIV infection and coexisting tuberculosis (7). The diagnostic difficulties stemmed from the location of observed lesions in the mediastinum, which precluded the collection of material for patomorphological examination. Thus, it was not possible to obtain data allowing to exclude, for certain, lymphatic system malignancies which belong to the diseases indicative of AIDS.

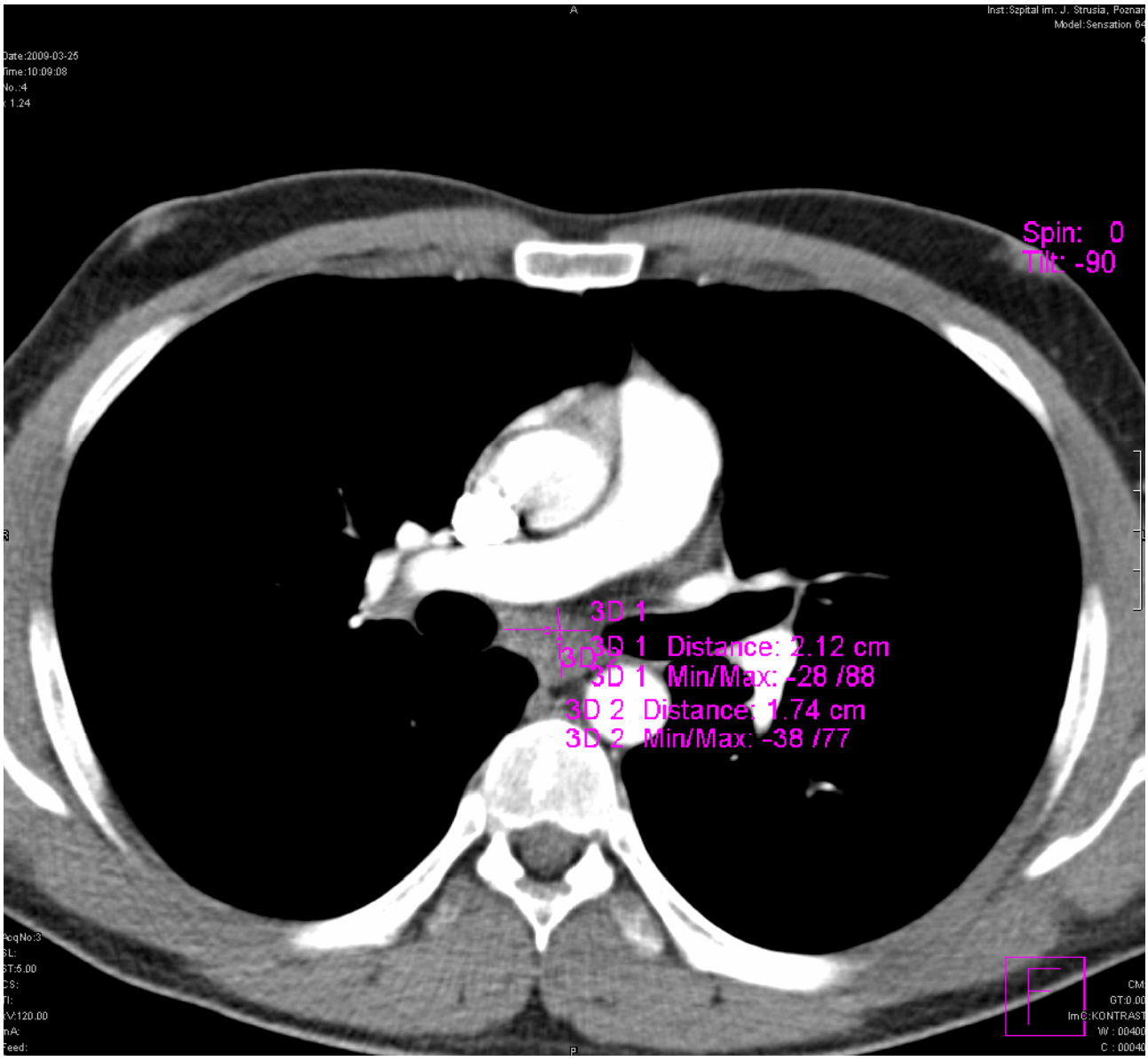
References

1. Ratman I, Chiu C, Kandala NB, Easterbrook PJ: Incidence and risk factors for immune reconstitution inflammatory syndrome in an ethnically diverse HIV type 1-infected cohort. Clin Infect Dis., 2006 Feb1;42(3):418-27.
2. Breen RA, Smith CJ, Bettinson H, Dart S, Bannister B, Johnsos MA, Lipman MC: Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. Thorax 2004,8:704-7.
3. Michailidis C, Pozniak AL, Mandalia S, Basnayake S, Nelson MR, Gazzard BG: Clinical characteristics of IRIS syndrome in patients with HIV and tuberculosis. Antivir Ther, 2005; 10(3):417-22.
4. Rajeswaran G, Becker JL, Michailidis C, Pozniak AL., Padle SP: The radiology of IRIS (immune reconstitution inflammatory syndrome) in patients with mycobacterial tuberculosis and HIV co-infection: Appearances in 11 patients. Clin Radiol, 2006; Oct; 61(10):833-43.
5. Rapose A, Sarmat B, Sarria JC: Immune reconstitution inflammatory syndrome presenting as pericarditis and pericardial effusion. Cardiology, 2008;110(2):142-4.
6. Robertson J, Meier J, Ying J, Fichtenbaum CJ: Immune reconstitution syndrome In HIV: validating a case definition and identifying clinical predictors in persons initiating antiviral therapy. Clin Infect Dis., 2007 Jan, 42(11):1639-46.
7. Morlese JF, Orkin CM, Abbas R *et al.*: Plasma IL-6 as a marker of mycobacterial immune restoration disease in HIV infection. AIDS 2003,17,1411-1413.

Table 1. Results of chest CT scan and CD4+ T cell count during the observation

Date	Chest CT scan findings	CD4
Apr 2008	Single, fine lymph nodes in the aortopulmonary window; diameter 8-10 mm, regular shape, oval. No enlargement of anterior or posterior mediastinal lymph nodes, nor axillary, infraclavicular or hilar lymph nodes.	135
Jun 2008	Presence of a mass located in the posterior mediastinum, starting slightly below the level of tracheal forking into main bronchi and descending along the anterior spinal surface, surrounding the oesophagus and aorta from the medial and anterior surface, as well as involving the initial parts of main bronchi branches. Downwards, the lesion ends above the level of left atrium, not pressuring or reshaping it. Lesion dimensions: 43×25× -56-60 mm. No presence of enlarged lymph nodes in the mediastinum. Numerous axillary lymph nodes on both sides, not clustering, with diameters of 10-12 mm. Visible lymph node described in the referral, located below the right clavicle, max. diameter: 18-20 mm. Visible single small lymph nodes of diameter below 1 cm, located in the upper anterior mediastinum. Hilar lymph nodes not enlarged.	
Sep 2008	Examination does not reveal enlarged upper mediastinal or hilar lymph nodes. Presence of an area below carina, density of ca. 36 jH, polycyclic outline – the picture may reflect enlarged lymph nodes located below the tracheal bifurcation. Lesion dimensions: 45×27× ca. 50 mm.	420
Dec 2008	Visible lymph node cluster below the tracheal bifurcation with dimensions of 43×26 mm. Normal vascular structure of both hili.	
Mar 2009	Small nodes located in the upper mediastinum at the level of arterial departing from the aortic arch, as well as a single, larger node of irregular outline and max. diameter of 17 mm. In the left paraartic region: no enlarged lymph nodes but visible heterogeneous connective tissue hypertophy. Fine pretracheal lymph nodes, diameter: 5-7 mm, of no clinical significance. Below the carina, presence of a soft-tissue region of 17-20 mm, well separated. The picture may reflect cicatrical lesions in the location of the nodular mass preciously described. No typical for the CT picture of lymph nodes polycyclic, round structures. The examination does not reveal enlarged hilar lymph nodes. Present only very fine axillary lymph nodes on both sides; diameter of a few millimetres – of no clinical significance. Conclusions: Marked remission of lesions noticeable, as compared to the previous examination. No active process within lymph nodes found. Doubts are raised only by a single area, located in the upper anterior mediastinum, behind the sternum and anterior to the vessels originating from the aortic arch, which may be a single enlarged lymph node or, alternatively, a connective tissue mass in the course of post-treatment changes.	661

Figure 3. Remains in mediastinum – March 2009



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Acknowledgements. List all contributors who do not meet the criteria for authorship, such as technical assistants, writing assistants or head of department who provided only general support. Financial and other material support should be disclosed and acknowledged.

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