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THE JUSTIFICATION FOR THE EARLY INTRODUCTION OF ANTIRETROVIRAL THERAPY IN PATIENTS LIVING WITH HIV

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ABSTRACT

In the last years the retroviral disease, caused by the human immunodeficiency virus (HIV), turned from an incurable to a chronic disease. This fundamental change happened due to a huge progress in the understanding of the pathogenesis and treatment of this infection. However, one question still remains open: what is the best time to introduce therapy. The CD4 count is the point of reference to start of the treatment in HIV infected patients. Tendency to introduce highly active antiretroviral therapy (HAART) as early as possible has been observed recently. According to the most recent guidelines of the World Health Organization HAART should be started when CD4 reaches ≤ 500 cells/μl. The aim of this paper is justification for the early introduction of antiretroviral therapy in patients living with HIV

Key words: *AIDS, HIV, antiretroviral drugs, introduction of ART, guidelines*

INTRODUCTION

In the last years the retroviral disease, caused by the human immunodeficiency virus (HIV), turned from an incurable to a chronic disease. This fundamental change happened due to a huge progress in the understanding of the pathogenesis and treatment of this infection. However, one question still remains open: what is the best time to introduce therapy. The CD4 count is the point of reference to start of the treatment in HIV infected patients. Tendency to introduce highly active antiretroviral therapy (HAART) as early as possible has been observed recently. According to the most recent guidelines of the World Health Organization of 30 June 2013 HAART should be started when CD4 count reaches ≤ 500 cells/μl. However the question of when to begin the antiretroviral therapy remains still open. The pivotal result of the antiretroviral treatment is reduction of HIV viral load, and protection or eventually reconstruction of the immune system. This leads to a reduction of HIV transmission and decrease of HIV related mortality. On the other hand early introduction of HAART increases cost of the therapy and number of undesirable side effects. Since 1986, when the antiviral effect of zidovudine (AZT) was discovered, there have been diverse opinions on the best moment of antiretroviral therapy introduction. They have ranged from an attitude „hit hard, hit now" to awaiting for decrease of CD4 count below 200 cells/μl.

LYMPHOCYTES T CD4 COUNT AS AN INDICATOR FOR THE INTRODUCTION OF HAART

Lymphocytes T CD4 count has always been an important information for the introduction of the treatment. According to the guidelines of the American Department of Health and Human Services (DHHS) established in 1998, patients with a CD4 count below 200 cells/μl required immediate introduction of antiretroviral therapy (ART). World Health Organization launched such a guidelines only in 2002. Clinical trials in the developing countries, including Haiti, provided crucial evidence that an earlier introduction of treatment in patients with a CD4 count higher than 200 cells/μl but below 350 cells/μl lowers significantly the mortality and incidence of diseases related to HIV infection (1). Results of clinical trials triggered another change in guidelines and the raise of the threshold at which the ART therapy shall be introduced. The first were again the DHHS guidelines (2007), then EU guidelines

Table I. Initiation of ART. Recommendations Polish AIDS Research Society 2013

Initiation of ART			
Recommended as quickly as possible	**Recommended**	**Propose**	**Consider**
○ Symptomatic infection (category B or C according to the CDC classification), regardless of CD4 count ○ Patients with lymphocyte counts less than 350 cells / ml ○ Pregnant women after 14 weeks of pregnancy	○ Age> 50 years ○ The increased risk of cardiovascular disease ○ Diabetes ○ HIV RNA> 100 000 copies/ml ○ Decrease in CD4 cell count of 100 cells / year ○ HIV associated nephropathy ○ HBV co-infection ○ HCV co-infection (at the level of CD4 cell count below 500 cells / uL) ○ Cancer ○ Regardless of the level of CD4 in order to prevent infection sexual partner ○ HIV-associated neurocognitive impairment	○ Patients without symptoms and without additional burden to the number of cells between 350 and 500 cells/ml ○ Patients with HCV coinfection (depending on the plans for the treatment of chronic hepatitis type C)	○ In other cases ○ Postponement of the treatment of the patient's unwillingness to take care

(2008) and the latest one – WHO (2009). Since 2009 it has been recommended that all patients with CD4 < 350 cells/µl should undergo the ART therapy. In 2012 DHHS issued some controversial guidelines which recommended antiretroviral therapy irrespectively of CD4 count (2). It has also been stated that the ART therapy should be recommended to every HIV patient. This strategy has been adopted based on a rule: „test and treat". DHHS has issued the most radical guidelines so far, which became adopted worldwide a few years later. This guidelines were followed during the recent congress of the International AIDS Society in 2013, and finally WHO recommended introduction of ART at 500 cells/µl (3). Polish AIDS Research Society recommends that antiretroviral treatment should be started (as early as possible) in all symptomatic (category B or C according to the CDC classification) patients and those with total CD4 count of <350 cells/ml (4). In patients with CD4 count of 350-500 cells/ml and more, it is recommended to start the treatment in the wide range of patients (see Table I).

The experts call for an intensification of multicenter randomized clinical trials in order to find the advantages of an early ART introduction. There are already several randomized prospective population trials which reveal the advantages of an early introduction of the therapy, irrespectively of the number of CD4 count. Such trials as: NA-ACCORD, NA-ACCORD, When to Start Consortium, HIV-CAUSAL, CASCADE, COHERE, ATHENA (Table II) reveal that the introduction of ART goes in line with a lowered mortality and progression of the disease towards the AIDS (5-8).

We are still awaiting final results of probably the most important international multicenter trial START, which is supposed to decide whether the treatment of patients with CD4 exceeding 500/µl is really unambiguously beneficial. The START trial, is also addresses to the non-AIDS related diseases. The protocol of this clinical trial is constructed in a way which enables to gain data related to potential advantages for a patients, as well as eventual adverse reactions resulting from the early introduction of ART. Patients in this trial are characterized up to now by an unusually high adherence. The first phase of START included over 1000 patients from 100 centers in 23 countries, including Poland. The trial shall be extended to 237 centers in 36 countries and reach the number of 4000 participants (9). Unfortunately, WHO guidelines are not based on strong evidence data and did not take into consideration potential adverse effects resulting from an early ART

Table II. Studies on the time of ART introduction depending on CD4 count

Name of the studies	Number of participants	Outcome (study end-point)	CD4 cells/µl
NA-ACCORD	8362	Death	CD4 <350 vs 350-500
NA-ACCORD	9155	Death	CD4 <500 vs > 500
When to Start Consortium	24444	AIDS or death	CD4 251-350 vs 351-400
HIV-CAUSAL	20971	AIDS or death	CD4 <350 vs <500
CASCADE	9455	Death	CD4 350-499 vs delayed treatment
COHERE	75336	AIDS death	CD4 350-<500 on ART CD4 ≥ 500 on ART
ATHENA	3068	AIDS or death, not-AIDS	CD4<200 vs <500
START	4000	AIDS or death, not-AIDS, Advantages and damage of an early ART introduction	CD4<350 vs CD4>500

introduction. The majority of participants included in previous clinical trials were young people without accompanying chronic diseases which could potentially worsen course of ART.

Many researchers observe that HIV infection, irrespectively of CD4 count, is related to the risk of non-AIDS-related complications. It is also known that HIV replication triggers the activation of the immune system causing inflammation or incorrect immunological response. These processes in turn lead to a faster progression of atherosclerosis development, higher risk of neoplasmatic diseases, and it may be involved in HIV-associated neurocognitive impairment (10-13). The SMART trial, even though it has not been finished yet, has already shown that patients with a delayed antiretroviral treatment develop 7 times more often heavy cardio-vascular, kidney, liver and bones diseases than those on early ART treatment (14, 15). It has also been proven that the risk of death due to these diseases is much higher among untreated patients. The introduction of HAART in patients with CD4 count above 350/μl lowers the risk of not-AIDS-related complications, such as diseases of the cardio-vascular system (data from the trials of HOPS Cohort, FIRST, SMART), neoplasmatic diseases (French Hospital, Chiao), or diseases of the central nervous system (CHARTER) (16).

Polish researchers also note that HIV infection is associated with an increased risk of developing cancers. In Polish HIV-infected patient population, there is an increasing number of non-AIDS-defending malignancies (NADCs) (17). Polish AIDS Research Society recommends to begin ART unconditionally (regardless the CD4 cell count) in the case of a patient affected with NADCs.

CO-INFECTION OF HIV AND HBV OR HCV

Numerous patients living with HIV are also co-infected with hepatitis B (HBV) or hepatitis C (HCV) viruses. An early introduction of the treatment may decrease the risk of chronic viral hepatitis B or C progression to liver cirrhosis and hepatocellular carcinoma. It is important particularly for HBV/HIV coinfection because of availability of medication suppressing replication of both viruses (18).

Progression of chronic viral hepatitis to liver cirrhosis is significantly accelerated in HIV coinfection. The most important source of collagen in the liver are hepatic stellate cells (HSC). HSC express the chemokine receptors such as CCR5 and CXCR4 , which play the role of co-receptors for HIV . Even same protein of HIV gp 120 could directly stimulate hepatic stellate cells by chemokine receptors CCR5 and CXCR4, which results in increased chemotaxis and secretion tissue inhibitors of metalloproteinases (TIMP) and IL-6. Inglot et al. points out that advanced fibrosis closely correlates with immune deficiency associated with HIV infection, which is manifested clinically by a decrease in CD4 cell counts (19). The introduction of ART may slow down the progression of liver fibrosis by restoring immune function and decrease associated with HIV infection, immune activation (20) .

AGING OF PEOPLE LIVING WITH HIV

People living with HIV get older and older – their life expectation gets closer to the age of the general population. Older individuals are exposed to numerous new infections. Therefore, age-related diseases affect also HIV infected population. Furthermore, age-related diseases develop much faster in people living with HIV. The older age is associated with a higher risk of development of AIDS, as well as of not AIDS-related death (21, 22). These facts were reflected in the DHHS guidelines, which recommend the introduction of the ART therapy should be independent of CD4 count in patients over 50 years of age, whereas the IAS-USA guidelines increased this border line to 60 years of age. Polish AIDS Research Society in 2012 recommended the introduction of antiretroviral treatment in patients over 50 years of age when CD4 count is ≤ 500 cells/μl. Polish AIDS Research Society (2013) currently recommends the implementation of antiretroviral therapy in all patients over 50 years of age, regardless of the number of CD4 T-cells.

ART AS A PROPHYLAXIS OF SEXUAL TRANSMISSION

The main goal of HAART is the suppression of viral load leading to the reduction of infectiveness. ART should be considered as an efficient element of the prevention of infection among "serodiscordant couples" i.e. those in which one of the partners is HIV seropositive and the other - is not infected with HIV. The trial HPTN-052 revealed a significantly lower transmission risk (up to 96%) in couples, in which the seropositive partner started the ART therapy without delay (23, 24). Therefore WHO guidelines recommend the HAART introduction to all HIV infected patients remaining in serologically discordant relationships. The effectiveness of such a strategy is confirmed by among others to the retrospective observational trial conducted in China: which revealed that the strategy „treat-as-prevention" significantly lowered the risk of transmission of the HIV infection among 40 000 couples (25). In this and other trials, which involved the MSM men who have

sex with men) population of San Francisco, it was unambiguously proven that lower viral load is associated with decreased risk of partner's infection.

THE REDUCTION OF THE COST OF THE TREATMENT RELATED TO EARLY ART INTRODUCTION

An early introduction of the ART treatment is one of the most effective methods preventing spread of HIV infection in a population. The economic aspect of early ART introduction is also important. It was proven that early HAART introduction is cost-effective due to reduction of "the population HIV viremia". The lowering of the costs related to an early introduction of the therapy was observed not only in the industrialized countries, but also in the developing countries of Africa, such as Uganda (26). Relaying on the mathematical models and socioeconomic observations it has been proven that an immediate introduction of ART irrespectively of CD4 count is financially beneficial (26, 27).

CONCLUSIONS

The current worldwide guidelines are inconsistent. DHHS (2012), IAS-USA (2012) recommend starting treatment in all patients, regardless of the number of CD4 T-cells. WHO (2013) recommends to start ART in the patients with CD4 count of ≤ 500 cells/μl. EACS (2013) recommends ART for patients with CD4 count of < 350 cells/μl, in patients with CD4 count above 350 cells/μl the treatment is only recommended for patients with a symptomatic HIV infection (group B, C, according to the CDC), and in the diseases supposedly related to HIV, but only such as: HIV- associated nephropathy, impaired cognitive function associated with HIV, cancers associated with HPV infection, Hodgkin's lymphoma. In other cases of EACS the treatment should be only considered (28).

It seems that efforts should be made to standardize those guidelines in the world. Every patient should have the right to choice of the treatment and should be informed about the advantages as well as potential risk and side effects of ART. There are more and more examples showing that we lose a lot while waiting for decrease of CD4 count to the value below 350 cells/μl. Moreover, this period of time, seems to be relatively short in comparison of life-lasting treatment.

We often have a tendency to look at the patient as an independent being. Usually we are focused on one particular case only, and forgot so-called population benefits. Numerous research provided crucial evidence that an immediate introduction of the therapy basing on a rule „test and cure" minimalizes the risk of HIV transmission, so as a result it lowers the natural reservoir of the virus in the population and plays the key role for the public health.

It should be noted that most of the studies on which the recommendations are based are cohort studies. Little data is available about the potential damage to the body being the result of the earlier introduction of ART. It is also underlined that most of the patients in the clinical trials are young and not suffering from chronic diseases. However, the data from clinical trials are still coming in and speak for the earlier introduction of ART in patients with HIV. At the present time there is a rapid progress in the area of simplification of the treatment, which is an important issue in life-long therapy.

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