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Treatment outcomes of first-line antiretroviral therapy in HIV-1-positive patients in Serbia

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Abstract

Introduction: Access to combination antiretroviral treatment (cART) and toxicity profiles of antiretroviral medications have significantly improved during the last three decades. In order to optimise treatment outcomes, achieve favourable virological suppression and immunological status, balanced with potential adverse effects of cART, it is considered beneficial to maintain first-line antiretroviral treatment for as long as possible. However, the Republic of Serbia, as a resource-limited setting, often experiences interruptions to drug supplies. Data are very limited in Serbia concerning the initial antiretroviral regimens prescribed and the reasons for treatment changes.

Aims: The aim of this study was to determine the most frequently prescribed antiretroviral drugs within first-line cART regimens in drug-naïve patients in Serbia and the reasons for switching drugs.

Methods: All HIV-infected individuals who started cART at the HIV/AIDS Center of Infectious and Tropical Diseases, Clinical Centre of Serbia, from 1 January 2004 until 1 July 2014 were included. A cohort of 339 patients were retrospectively analysed to review their initial treatment regimens. All analyses were performed using the SPSS statistical package version 11.0. Descriptive measurements and Kaplan–Meier survival curves were used.

Results: The most frequently prescribed nucleoside reverse transcriptase inhibitor (NRTI) backbones in the cART regiment were fixed combinations of abacavir and lamivudine (*n*=181, 53.3%) and of zidovudine and lamivudine (*n*=103, 30.5%). Efavirenz was the most commonly prescribed 'third' drug (*n*=254, 75%). Where given, reasons for switching initial cART were shortage of antiretroviral drugs (e.g. out of stock, *n*=53, 37.6%), toxicity (*n*=49, 34.3%), physician choice (*n*=21, 14.6%), resistance (*n*=15, 10.6%), and patient choice (*n*=4, 2.9%). Mean duration of first-line cART was 20±17 months.

Conclusion: The most frequently prescribed initial cART regimen in Serbia is not the preferred first choice, but an alternative option according to the international antiretroviral treatment guidelines. Duration of first-line cART is short and a switch to second-line cART is often made due to a shortage of antiretroviral medications and the more severe side effects resulting from the use of older drugs.

Keywords: HIV/AIDS, first-line cART, switch, drug shortages

Introduction

Since 1996, when combination antiretroviral therapy (cART) was introduced worldwide, HIV-1-related morbidity and mortality have been significantly reduced [1–5]. Antiretroviral treatment strategies includes a combination different classes of antiretroviral drugs in order to limit replication at several stages of the viral life cycle [6,7]. A first-line cART regimen generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) [1–3,6,7]. Access to antiretroviral treatment and toxicity profiles of cART medications have significantly improved during the last three decades, thus enhancing quality of life for patients [3,5]. Progress in recent years has been exemplified by the proven superior efficacy of integrase inhibitors in comparison to other drug regimens as first line therapy and the recommendation for its use in treatment naïve patients [8,9].

Despite its many benefits, antiretroviral treatment is still associated with many problems [1–3]. cART can cause side-effects, some of them potentially serious, or even life-threatening, such as lactic acidosis, acute pancreatitis and peripheral neuropathy. Furthermore, poor adherence to therapy, mainly due to complicated drug schedules, remains a problem *per se* and may result in treatment failure, suboptimal immunological and virological outcomes, and/or the development of resistance to one or several classes of antiretroviral medications with limited further treatment options [5,10,11]. In order to optimise treatment outcomes, achieve favourable virological suppression and immunological status, balanced with the potential adverse effects of cART, data show that it is beneficial to maintain first-line antiretroviral therapy for as long as possible [11,12]. This is particularly important for resource-constrained settings, compared with developed countries, as they have fewer medications to choose from for the optimal antiretroviral therapy. Furthermore, the switch to second-line cART is associated with other limitations, such as increased toxicity and costs, especially in resource-limited settings where the number of treatment options is limited [13].

The Republic of Serbia, as a resource-limited setting, experiences drug shortages and a lack of access to new medications and clinical trials [10]. In addition, there are limited data on the first-line antiretroviral regimens prescribed and the reasons for switching. Therefore, the goal of this study was to determine the most frequently prescribed antiretroviral drugs for first-line cART in drug-naïve HIV-1-positive patients in Serbia and the reasons for a change in drug regimen.

Methods

Study design

This retrospective study enrolled treatment-naïve HIV-1-infected patients who had initiated cART between 1 January 2004 and 1 July 2014 at the HIV/AIDS Center at the University Hospital for

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Infectious and Tropical Diseases in Belgrade (HCB). This is the largest HIV/AIDS centre in the Republic of Serbia, with around 1500 patients receiving treatment. The inclusion criteria were: confirmed HIV infection, age older than 18, the initiation of cART during the study period, and regular laboratory and clinical follow-up during the study period. We collected data about patient demographic characteristics, clinical status including AIDS-defining illnesses at the time of cART initiation and the type of drugs started as a first-line regimen. During the routine check-ups, duration of the first-line regimen, reasons for treatment interruptions, and type of toxicity considered as a reason for the drug switch were recorded.

Antiretroviral drugs available in Serbia during the study period included (a) nucleoside reverse transcriptase inhibitors (NRTIs): zidovudine and lamivudine (as single drugs or in combination as a single pill), didanosine, stavudine, abacavir, and a fixed-dose combination of abacavir and lamivudine; (b) non-nucleoside reverse transcriptase inhibitors (NNRTIs): nevirapine and efavirenz; (c) protease inhibitors (PIs): saquinavir, nelfinavir, indinavir, fosamprenavir, lopinavir/ritonavir and ritonavir as a booster. For toxicity reasons nelfinavir and indinavir use was stopped in 2008. Enfuvirtide was registered in 2007 exclusively for use in highly experienced patients. Similarly, newer drugs, for example raltegravir, darunavir, tenofovir and maraviroc were available only as a salvage therapy during the study period and not in routine clinical practice. These drugs were donated to patients by pharmaceutical companies on compassionate release.

All patients provided written informed consent to participate in the study and the study was approved by the Ethics Committee of the School of Medicine University of Belgrade.

Immunological and virological parameters

The immunological and virological outcomes were measured every 6 months during the study period with assessment of CD4+ T cell count and HIV-1 RNA plasma viral load (pVL). Peripheral CD4+ T cell counts were measured by flow cytometry and HIV-1 RNA pVL by quantitative reverse transcriptase polymerase chain reaction (Ultrasensitive Assay Version 1.5, Roche Molecular Systems, Branchburg, NJ, USA), with a lower limit of detection of 50 HIV-1 copies/mL (1.7 $\log_{10}$).

Statistical analyses

All statistical analyses were performed using the SPSS statistical package version 11.0. Categorical variables were presented as frequencies with percentages. Non-parametric variables were analysed using chi-squared or Fisher's exact test, as appropriate. The Kaplan–Meier method was used to estimate the time to the initiation of a second antiretroviral regimen, as well as the probability of survival in the patients with sustained virological suppression according to the level of the baseline CD4+ T cell count. The level of statistical significance was $P<0.05$.

Results

A total of 339 treatment-naïve HIV-1-infected patients were included in the final analysis. There were 301 (88.8%) males and 38 (11.2%) females. The mean age at treatment initiation was 36±11 years . At the time of treatment initiation, 162 (47.8%) patients had been diagnosed with AIDS. Hepatitis C virus (HCV) co-infection was diagnosed in 38 (11.2%) patients, whereas hepatitis B virus co-infection (HBV) was diagnosed in 20 (5.9%) patients. Tuberculosis was diagnosed in 11 (3.2%) patients. Demographic data are presented in Table 1.

Table 1. Patient characteristics at commencement of antiretroviral therapy

Gender	301 (88.8%) male
	38 (11.2%) female
Age (mean±SD)	36±11 years
Risk factor	
Homosexual contact	190 (56.1%)
Intravenous drug users	20 (5.9%)
Heterosexual contact	118 (34.8%)
Blood/blood products	11 (3.2%)
AIDS	162 (47.8%)
HCV co-infection	38 (11.2%)
HBV co-infection	20 (5.9%)
Tuberculosis co-infection	11 (3.2%)

Mean CD4+ T cell count at treatment initiation was 254±176 cells/mm^3, and after 6 and 12 months of cART, 418±236 cells/mm^3 and 450±213 cells/mm^3, respectively. Constantly undetectable HIV-1 RNA pVL (e.g. less than 50 copies/mL) was achieved in 263 (77.5%) patients. Mean duration of first-line cART was 20±17 months.

The most frequently prescribed NRTI backbones within first-line cART were a fixed combination of abacavir and lamivudine in 181 (53.3%) patients and a fixed combination of zidovudine and lamivudine in 103 (30.5%) patients (Figure 1a). Didanosine was used as an NRTI backbone in 48 (14%) patients and a combination of abacavir and zidovudine in only three (0.9%) patients. Tenofovir as a backbone was used in two (0.6%) patients, whereas abacavir and didanosine were used in one (0.3%) patient. The most commonly prescribed third drug was an NNRTI, with the most frequently prescribed being efavirenz in 254 (75%) patients, followed by lopinavir and ritonavir in fixed combination in 42 (12.5%) patients and nevirapine in 26 (7.5%) patients. Protease inhibitors as the third drug were prescribed in 17 (5%) patients (Figure 1b).

During follow-up, first-line cART was maintained in 160 (47.2%) patients, while 152 (44.8%) patients made a switch to another regimen. Eight patients (2.4%) died during the study, while 19 (5.6%) patients were lost to follow-up. Where given, the most common reasons for switching to different regimens were drug shortages in 53 (37.6%) patients, side effects in 49 (34.3%) patients, physician choice in order to avoid side effects in 21 (14.6%) patients, treatment failure in 15 (10.6%) patients, and patient choice in four (2.9%) patients. The number of patients who switched to the second-line regimen due to drug shortages increased over time (Figure 2). By the end of the third year of receiving the initial cART, 39% of patients who had made a switch to the second-line regimen did so owing to shortage of the drug supply (Figure 2). Treatment changes due to serious adverse events were for peripheral neuropathy, acute pancreatitis and lactic acidosis in 41 (12.2%), 13 (3.8%) and nine (2.8%) patients, respectively.

Out of 152 patients who switched to second-line cART, 105 (69.1%) switched to drugs within the same drug class, while in 34 (22.3%) patients the entire regimen was changed, both NRTI backbone and the third drug. Switch of only one drug to a different drug class was found in 13 (8.6%) patients, usually from an NNRTI to a PI or vice versa.

The overall estimated probability of 14-year survival using the Kaplan–Meier method was significantly better in patients with baseline CD4+ T cell counts >350 cells/mm^3 (Figure 3). The

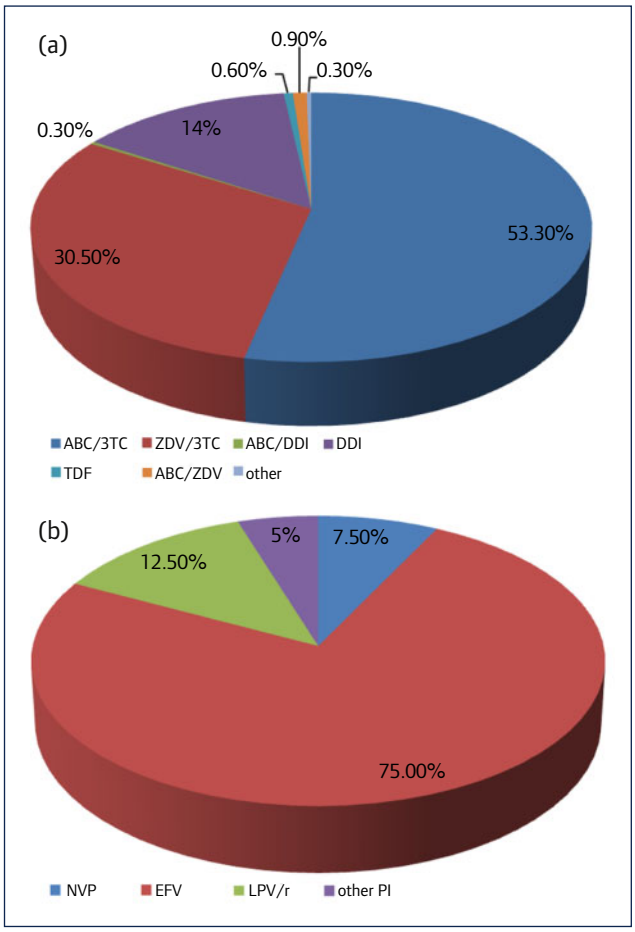

Figure 1. (a) NRTI backbones prescribed for first-line cART. (b) The third drug prescribed for first-line cART. ABC: abacavir; ZDV: zidovudine; 3TC: lamivudine; DDi: didanosine; TDF: tenofovir; NVP nevirapine; EFV: efavirenz; LPV/r: ritonavir-boosted lopinavir

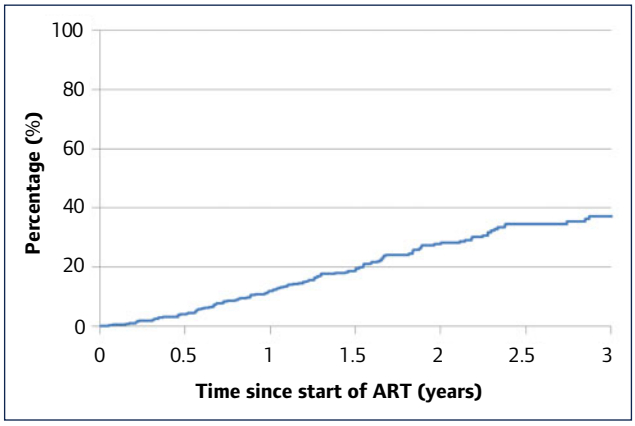

Figure 2. Percentage of patients who switched first-line cART due to drug shortages

14-year survival was 90% and 89% in patients with CD4+ T cell count between 350 and 500 cells/mm^3 and higher than 500 cells/mm^3, respectively, while the 14-year survival was 75% in patients with a CD4+ T cell count between 200 and 350 cells/mm^3 and 70% in patients with baseline CD4+ T cell counts less than 200 cells/mm^3 (P=0.0126, log rank).

Discussion

Recognising the need to initiate cART early, while the CD4+ T cell count remains high and AIDS-defining diseases have not yet been diagnosed, has shown very substantial improvements in clinical outcomes by achieving virological and immunological success, lower levels of resistance, and a prolonged life expectancy for HIV-1 positive people [3,5,11,14–16]. These positive outcomes have

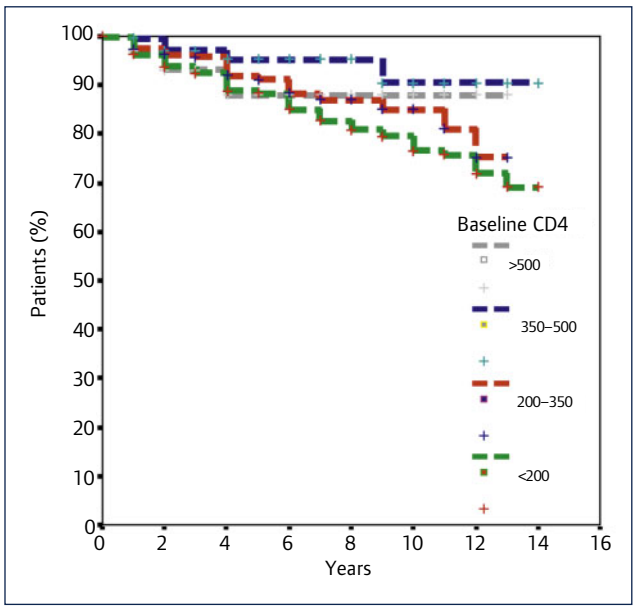

Figure 3. Survival of cART-treated patients related to baseline CD4 cell counts

already been reported in high-income countries, but results from resource-limited settings are still limited. Our study has shown that almost half of the patients in Serbia still initiate cART in the late stages of the disease, with a low baseline CD4+ T cell count and often, clinical AIDS. This study, however, reports better results than our previous publication in which we showed significantly higher numbers of patients who developed clinical AIDS and with lower peripheral CD4+ T cell count at the time of cART initiation [10]. These differences reflect a rising trend in Serbia for receiving a diagnosis earlier in the course of the infection and therefore the possibility for earlier initiation of antiretroviral therapy. However, initial CD4+ T cell counts are still significantly lower than in developed countries, where people are more aware of HIV testing, with higher testing rates and therefore earlier treatment initiation and better survival outcomes [5,10,17,18].

The maintenance of successful first-line cART for a prolonged period of time is predictive of an enhanced life expectancy and quality of life [19,20]. However, data from our study show a short duration of first-line cART of approximately 2 years. These poor results are mainly due to drug shortages in Serbia, as a low-income country, which, even though patients were virologically suppressed, led to switches to other antiretroviral medications.

The most frequently prescribed NRTI backbone in our study was a fixed combination of abacavir and lamivudine, which is proven to be effective and safe. Other NRTI drugs prescribed as a backbone, such as didanosine and stavudine, are no longer recommended by international treatment guidelines [17,21]. The most frequently prescribed third drug in our study was efavirenz, which is in accordance with international treatment guidelines. Current European AIDS Clinical Society Guidelines recommend a fixed combination of tenofovir and emtricitabine as the cART backbone, or alternatively abacavir and lamivudine (when preferred regimens are not feasible or available), in combination with rilpivirine out of the NNRTIs, darunavir out of the PIs, or dolutegravir or raltegravir out of the integrase inhibitors [22]. The same recommendations are made by the International AIDS Society (IAS)–USA, with additionally recommended use of boosted elvitegravir, efavirenz and atazanavir as the third drug in the initial cART regimen [21]. In 2015, BHIVA guidelines also suggested use of tenofovir and emtricitabine with atazanavir, darunavir, dolutegravir, raltegravir, boosted elvitegravir and rilpivirine as first-line cART. The same guidelines suggest an alternative first-line

regimen, if the preferred regimens are not feasible or available, of abacavir and lamivudine with efavirenz [23]. Many of these drugs are still unavailable in Serbia, and therefore guidelines may not be followed thoroughly. For instance, during the study period the National Health Insurance Fund in Serbia provided tenofovir for only a few cART-naïve patients, despite the guideline recommendations, due to drug shortages. However, the most frequently prescribed regimen in Serbia is the combination of abacavir and lamivudine with efavirenz, which most guidelines still regard as an alternative and satisfactory first-line cART.

Reasons for switching from first- to second-line cART, in both high- and low-income settings, are drug toxicity and/or treatment failure [14,15]. The main reasons for a switch from first-line cART in Serbia are shortages of antiretroviral drugs and side effects of old drugs. The lack of HIV-1 drug supply is not recognised in the world literature as a reason for treatment interruption [11–15,24–26]. In our study, the switching rate increased during the first 3 years of cART. In a comparative study of South African and Swiss patients, treatment changes were mostly reported in the first 3 months of initial cART, due to side effects and drug toxicity [14]. Comparing these two settings, more severe toxic events (e.g. lactic acidosis) appeared in South Africa, a resource-limited setting, than in Switzerland, due to widespread use of older drugs such as stavudine [14]. In another study, Cicconi *et al*. showed the main reasons for switching cART in Italy between 1997 and 2007 were drug toxicity (58.5%), poor adherence (24%) and treatment failure [24]. By contrast, in Serbia, lack of drug availability and toxicity of prescribed drugs appear to be the main reasons for switch. Our study revealed a higher number of patients undergoing switch due to toxicity than in other studies [27]. This difference is directly influenced by 'older' antiretroviral drugs used in Serbia, with serious toxicity-related side effects such as HIV-associated neurological complications, lactic acidosis and acute pancreatitis. Similar findings about toxicity-related switch, mainly due to prolonged stavudine use, were reported by Keiser *et al*. in a South African cohort [14]. Prescription of 'older' cART regimens as a main determinant for treatment switch were recognised previously, and consequently, these regimens are no longer recommended [25,28].

In our study, better survival rates were associated with the higher baseline CD4+ T cell count, which has also been demonstrated by other authors [18,29,30]. These data confirm clinical benefits for patients who start cART early, based on achieving virological suppression, immunological recovery and overall health improvement, and support current recommendations to initiate antiretroviral treatment in all HIV-infected patients, regardless of CD4+ T cell count [21].

Conclusion

The most frequently prescribed initial cART in Serbia is not the preferred first choice, but an alternative option according to international antiretroviral treatment guidelines. Duration of first-line cART is short and switch to second-line cART is often made due to shortages of specific antiretroviral medications and severe side effects of older but still-prescribed drugs.

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