Original Article

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The Pattern of the Initial Anti-retroviral Drug Regimens in HIV Patients at a Tertiary Care Hospital

Infectious diseases Section

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ABSTRACT

Background and objective: The choice of the anti-retroviral drug therapy has been evolving over the last decade. The objective of this study was to evaluate the current prescribing pattern of the anti-retroviral drugs in treatment-naïve patients before initiating the anti-retroviral therapy.

Materials and Methods: A retrospective review of the antiretroviral drugs which had been prescribed to the HIV-infected patients was conducted at a tertiary care hospital in South India. Only adults patients who were of more than 18 years of age, with a positive serology, who had started or had already been receiving the anti-retroviral therapy were included. Their main demographics, the details of the AIDS diagnoses, the laboratory data (CD4 cell counts) and the history of the antiretroviral therapy were collected.

Result: The total number of patients was 108. Among them, 76 (70.4%) were males and 32 (29.6%) were females. The mean age of the patients was 38.67 ±10.02years, the mean weight was 52.47± 11.2kg and the mean CD4 count was 256.57 ± 204.6cells/cumm. Among these patients, 34(31.5%) were on the lamivudine+ zidovudine+ nevirapine regimen, 70(64.8%) were on the lamnivudine + nevirapine+ stavudine regimen (3TC + NVP+ d4T) and 4(3.7%) were on the tenofovir+ emtricitabine +efavirenz regimen. In the first regimen, the mean age of the patients was 39.09 ±9.1years, the mean weight was 51.87±10.7kg and the mean CD4 count was 253.21±177.8cells/cumm. In the second regimen, the mean age of the patients was 38.73 ±10.59 years, the mean weight was 52.37±12.24kg and the mean CD4 count was 262.02± 221.4 cells /cumm. The comparison of the mean age and the mean CD4 count among the patients in the different regimens did not show any statistical significance.

Conclusion: The most frequently used antiretroviral drug regimen was the 3TC + NVP+ d4T combination. The prescription pattern was quite in contrast to that which was followed in the developed countries. Newer NRTIs were less frequently used.

Key Words: ART regimens, HIV, CD4 count

INTRODUCTION

The achievement of an effective treatment for the HIV infection has been one of the most remarkable milestones in the recent history of medicine. This is true, not only for the number of lives that have been saved, but also for the amount of scientific information that has been generated alongside the daily treatment of HIV-infected individuals. The analysis of the changes in the prescription of anti-retroviral drugs is a good exercise of how clinical practice and research may meet continuously to improve the management of HIV-infected patients [1].

Despite the availability of successive national and international guidelines on antiretroviral prescribing, anecdotal evidence suggests a considerable variation in the use of different antiretroviral drugs across and within different the HIV centres. Previous studies have examined the compliance with the guidelines on the timing of the initiation of the therapy, and other aspects of the HIV care, but the interpretation of these findings has been confounded by late presentations [2]. More than 20 approved ARV drugs in 6 mechanistic classes are available to design combination regimens. These 6 classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), the non-nucleoside reverse transcriptase inhibitors (NNRTIs), the protease inhibitors (PIs), the fusion inhibitors (FIs), the CCR5 antagonists, and the integrase strand transfer inhibitors (INSTIs) [3]. The choice of antiretroviral drugs has evolved over the last decade. The recognition of the trends and the determinants of the changes may help in making predictions on the prescription patterns. A variety of factors may influence the physician prescribing practices, which include the patient demographic characteristics, physician training, physician perceptions about the relative importance of various drug characteristics, such as the ease of the use and the side-effect profile and the availability of treatment guidelines, local practice patterns and the pharmaceutical industry. Studies in other areas have demonstrated the effectiveness of various educational strategies which are employed by the pharmaceutical industry in influencing the physician prescribing [4,5]. Hence, this study was planned to evaluate the prescribing pattern of the antiretroviral drugs in treatment-naïve patients for initiating the antiretroviral therapy (ART) over a 5 year period (2007-2011).

MATERIALS AND METHODS

A retrospective review of the anti-retroviral drugs which had been prescribed to HIV-infected patients was conducted at a tertiary care hospital of South India. This study was approved by the institutional ethics committee. Only adults who were older than 18 years, with a positive serology, who had started on or were already receiving antiretrovirals were included. Their main demographics, which included the age, gender and the risk group were recorded. The data was collected in a suitably designed proforma, which included the demographic characteristics, the details of the AIDS diagnoses, the laboratory data (CD4 cell counts) and the ART history.

STATISTICAL ANALYSIS

All the descriptive results were given as total numbers and percentages. The continuous variables were analyzed by the Student's 't' test and the categorical variables were analyzed by the Chi square test. A p value of less than 0.05 was considered as significant.

RESULTS

The total number of patients was 108. Among them, 76 (70.4%) were males and 32 (29.6%) were females. The mean age of the patients was 38.67 ±10.02years, the mean weight 52.47± 11.2kg and the mean CD4 cell count was 256.57±204.6cells/cumm. There was a significant difference between the mean age and the weight among the males and the females respectively (p=0.042and 0.008 respectively). Also, there was significant difference in the mean CD4 count among the males and females [Table/Fig-1].

Around 34(31.5%) patients were on the 3TC +NVP+ZDV (lamivudine + nevirapine+ zidovudine) regimen, 70(64.8%) were on the 3TC +NVP+d4T (lamnivudine + nevirapine+ stavudine) regimen and 4(3.7%) were on the TDF+FTC+EFV (tenofovir+ emtricitabine + efavirenz) regimen. In the 3TC +NVP+ZDV regimen, the mean age of the patients was 39.09 ±9.1years, the mean weight 51.87±10.7kg and the mean CD4 count was 253.21±177.8cells/cumm. In the 3TC +NVP+d4T regimen, the mean age of the patients was 38.73 ±10.59 years, the mean weight was 52.37±12.24kg and the mean CD4 count was 262.02± 221.4 cells/cumm. The comparison of the mean age and the mean CD4 count among the patients in the different regimens did not show any statistical significance [Table/Fig-2].

DISCUSSION

A combination ART regimen generally consists of two NRTIs + one active drug from one of the following classes: NNRTI, PI (generally boosted with ritonavir), INSTI, or a CCR5 antagonist. The selection of a regimen should be individualized, based on the virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, and the patient's comorbid conditions. The "preferred regimens" are those regimens which have been studied in randomized controlled trials and have been shown to have optimal and a durable virologic efficacies, favourable tolerability and toxicity profiles, and ease of use. The "alternative regimens" are those regimens that are effective but have potential disadvantages as compared to the preferred regimens. In certain situations and based on the individual patient's characteristics and needs, a regimen which has been listed as an alternative may actually be the preferred regimen for a specific patient. Some regimens are classified as "acceptable regimens" because of their reduced virologic activity, lack of efficacy data from large clinical trials, or other factors (such as greater toxicities, the need for additional testing, pill burden, or the drug interaction potential) compared. The preferred regimens include efavirenz (EFV)/TDF/FTC, ATV/r + TDF/FTC, DRV/r (once daily) + TDF/FTC, raltegravir (RAL) + TDF/FTC [3].

Characteristics	Males (n=76)**	Females (n=32)	Total (n=108)
Age (years)	39.93±9.942	35.66±9.691*	38.67±10.017
Weight(kg)	54.69±11.687	46.06±9.673*	52.47±11.763
CD4 count (cells/cumm)	262.21±209.473	243.72±196.076	256.57± 204.614

[Table/Fig-1]: Demographics of the patients

Patient characteristics	ART Regimens		
	3TC+NVP+ZDV	3TC +NVP+d4T	TDF+FTC+EFV
Total n(%)*	34 (64.82)	70 (31.5)	4(3.7)
Males n(%)	21(61.8)	52(74.3)*	3(75)
Females n(%)	13(38.2)	18(25.7)	1(25)
Age in years (mean ±SD)	39.09±9.18	38.73±10.60	34.00±6.16
Weight in kg (mean±SD)	51.87±10.72	52.37±12.25	71.00±2.46
CD4 count (cells/cumm) (mean±SD)	253.21±177.89	262.00±227.47	194.50±86.45

[Table/Fig-2]: Comparison of patient characteristics among different regimens

The most frequently used regimen in our patients was 3TC + NVP+ d4T, which was used in 64.8% of the patients. The 3TC + NVP+ ZDV regimen was taken by 30.5% of the patients. Because of the higher prevalence of anaemia in our patients, zidovudine was less commonly used. The regimens which were followed in our patients were at par with the standard guidelines which were laid down by National Aids Control Organization (NACO) [6]. The current NACO treatment guidelines for first-line ART recommends two classes of drugs for the initial treatment i.e. 2 NRTI + 1 NNRTI. The preferred first line regimen is 3TC + NVP+ ZDV if the haemoglobin level is above 8gm/dl. Stavudine is used in place of zidovudine if the haemoglobin level is less than 8 gm/dl. The current NACO treatment guidelines recommend that the protease inhibitor (PI) class is reserved for, and therefore characterizes the second-line ART. Ritonavir boosted protease inhibitors (bPIs) are recommended, supported by two agents from the NRTI class. There was no significant difference between the patients who were on different regimens with regards to the mean CD4 count, the mean weight or the mean age. Very few patients were on the newer NRTIs like tenofovir and emtricitabine, which may have been due to the fact that these are drugs were comparatively more expensive. Abacavir was almost not used in our patients, as it required the HLA testing facility to predict the risk of acute hypersensitivity reactions. Hence, it could be used in specialized centres which have the facility for these tests. Stavudine, though it is more toxic in terms of the lactic acidosis and the peripheral neuropathy, is very commonly used in the first line regimens (as an alternative to zidovudine) because of its easy availability at all the ART centres and its affordability.

The trend of the prescription in our patients was quite different from the trends which were observed in the western literature. In contrast to our reports, Jiménez-Nácher, et al., [1]. reported that the relative use of nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) had risen in the recent years, while the prescription of non-nucleoside reverse transcriptase inhibitors had declined, as compared to that in the period from 1999-2001, when it had peaked. Among the NRTIs, the use of zalcitabine, stavudine and didanosine had dramatically declined or vanished, while the use of zidovudine, lamivudine, abacavir and tenofovir had gained relevance. Among the PIs, indinavir and nelfinavir had almost disappeared, being replaced by ritonavir-boosted PIs, mainly atazanavir and lopinavir. After its first introduction in the year 1999, efavirenz has been generally preferred over nevirapine. EFV has been compared with a number of other antiretroviral drugs in the combination regimens which contained two NRTIs [7]. To date, no regimen has been proven superior to the EFV-based regimens with respect to the virologic responses.

The RTV-boosted PI-based regimens have shown good virologic and immunologic responses but they are often associated with more gastrointestinal symptoms, whereas the EFV-based regimens are associated with more rash and central nervous system adverse effects. Both the types of regimens may be associated with hepatic transaminase elevations [8].

The EFV-based regimens had a comparable virologic activity when they were compared with NVP. Studies that compared the EFV-based regimens with other regimens demonstrated that the combination of EFV with two NRTIs was superior virologically to some PI-based regimens [9]. Tenofovir (TDF) and emtricitabine (FTC) were the latest NRTIs to enter the market, but they have rapidly gained positions, which is most likely, due to a combination of good tolerance, convenience and potency. TDF is a nucleotide analogue with a potent activity against both HIV and the hepatitis B virus and with a long intracellular half-life that allows for once-daily dosing. TDF, when it was used with either 3TC or FTC as a part of an EFV-based regimen in ART-naive patients, demonstrated a potent virologic suppression and it was superior to ZDV/3TC in the virologic efficacy (up to 144 weeks) [10].

The dual-NRTI combination of zidovudine (ZDV)/3TC has extensive durability, safety, and tolerability experience. Bone marrow suppression, which was manifested by macrocytic anaemia and/or neutropaenia, was seen with ZDV. ZDV was also associated with gastrointestinal toxicity, fatigue, and possibly, mitochondrial toxicity, which included lactic acidosis/hepatic steatosis and lipoatrophy. Because of its greater toxicity as compared to TDF/FTC or abacavir (ABC)/3TC and the need for a twice daily dosing, the panel recommends ZDV/3TC as an acceptable, rather than a preferred or alternative, dual-NRTI option [11].

Jiménez-Nácher et al., [1] showed that three major forces have driven the prescription of different antiretrovirals in the last decade, namely their efficacy, safety profile and simpler administration. It is vital to make these assessments in both clinical trials (reflecting the efficacy of the therapy which is given under experimental conditions) and community-based settings (reflecting the effectiveness of the therapy as it is prescribed and used in practice). To conclude, the most frequently used antiretroviral regimen was the 3TC + NVP+ d4T combination. Its prescription pattern was quite in contrast to that which was followed in the developed countries. The newer NRTIs were less frequently used and this may be because of the affordability of the patients and their availability.

REFERENCES

[1] Jiménez-Nácher I, García B, Barreiro P, Rodriguez-Novoa S, Morello J, González-Lahoz J, et al. The trends in the prescription of anti-retroviral drugs and their impact on the plasma HIV-RNA measurements. *J. Antimicrob. Chemother*. 2008; 62 : 816-22.

[2] Easterbrook P, Phillips A, Hill T, Matthias R, Fisher M, Gazzard B, et al. The UK Collaborative HIV Cohort (CHIC) Study Steering Committee. The patterns and the predictors of the use of different antiretroviral drug regimens at the treatment initiation in the UK. *HIV Medicine*, 2008;9: 47–56.

[3] The Panel on Anti-retroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. October 14, 2011; 48–63. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed [accessed on 16 march 2012].

[4] Bogart LM, Kelly JA, Catz SL, Sosman JM. The impact of medical and nonmedical factors on the physician decision making for the HIV/AIDS anti-retroviral treatment. *J AIDS* 2000; 23: 396–404.

[5] Golub ET, Benning L, Sharma A, Gandhi M, Cohen MH, Young M ,et al. The patterns, predictors, and the consequences of the initial regimen type among HIV-infected women who received a highly active antiretroviral therapy. *Clin Infect Dis*. 2008 Jan 15;46:305-12.

[6] The National Aids Control Organisation. The national guidelines on the second- line ART for adults and adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Ministry of Health and FW, Govt. of India. April, 2011; 9–26. Available at http://www.nacoonline.org.pdf. Accessed [accessed on 19 march 2012].

[7] Riddler SA, Haubrich R, DiRienzo AG, Peeples L, Powderly WG, Klingman KL et al. The AIDS Clinical Trials Group Study A5142 Team. Class-sparing regimens for the initial treatment of the HIV-1 infection. *N Engl J Med*. 2008;358:2095-106.

[8] Haubrich RH, Riddler SA, DiRienzo AG, Komarow L, Powderly WG, Klingman K, et al. The AIDS Clinical Trials Group (ACTG) A5142 Study Team. The metabolic outcomes in a randomized trial of nucleoside, non-nucleoside and protease inhibitor-sparing regimens for the initial *HIV treatment. AIDS*. 2009;23:1109-18.

[9] van Leth F, Phanuphak P, Ruxrungtham K, Baraldi E, Miller S, Gazzard B, et al. Comparison of the first-line anti-retroviral therapy with regimens which included nevirapine, efavirenz, or both the drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet*. 2004;363:1253-63.

[10] Arribas JR, Pozniak AL, Gallant JE, Dejesus E, Gazzard B, Campo RE, et al. The combination of tenofovir disoproxil fumarate, emtricitabine, and efavirenz as compared to that of zidovudine/lamivudine and efavirenz in treatment-naive patients: a 144-week analysis. *J Acquir Immune Defic Syndr*. 2008;47:74-8.

[11] Vibhagool A, Cahn P, Schechter M, Smaill F, Soto-Ramirez L, Carosi G, et al. Triple nucleoside treatment with abacavir plus the lamivudine/zidovudine combination tablet (COM) as compared to indinavir/COM in the anti-retroviral therapy in naive adults: the results of a 48-week open-label, equivalence trial (CNA3014). *Curr Med Res Opin*. 2004;20:1103-14.

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