Available online at www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2015; 7(5): 364-367

ISSN- 0975 1556

Research Article

Effectiveness of Tenofovir (TDF) / Emtricitabine (FTC) Versus Zidovudine (AZT) / Lamivudine (3TC) in Combination with Efavirenz (EFV) IN Antiretroviral-Naive HIV-Infected Patients IN Eritrea

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Available Online: 31st August, 2015

ABSTRACT
Highly active antiretroviral therapy (HAART), currently recommended is the cornerstone of management of patients with HIV infection. Nucleoside reverse transcriptase inhibitor (NRTI) zidovudine (AZT) and nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir (TDF) are the most common medications given in first-line ART. This research to evaluate the effectiveness of Tenofovir DF, Emtricitabine versus Zidovudine, Lamivudine in combination with Efavirenz in Naive HIV-infected patients. A retrospective cross-sectional study on 94 adult Naive HIV-infected patients received TDF+FTC+EFV and AZT+3TC+EFV on adult age greater than 18 came for two years follow-up and had baseline CD4 cell counts. Data was extracted from the patient's medical record. T-test was used to compare the mean increase in CD4 cell counts between the two independent groups (TDF versus AZT) at various time of interval. In two-years follow-up, patients in TDF+FTC+EFV, maintained their drug regimen. This research has shown the beneficial effects and safe of TDF+FTC+EFV over AZT +3TC+EFV as first line treatment for HIV infected patients in two years of follow-up in terms of CD4 cell response and well tolerance. Since this study has been done for short period of time with different mean CD4 cell counts baseline, further studies to evaluate the safety and effectiveness of long term use of TDF+FTC+EFV in Naive HIV infected patients with same mean CD4 cell counts baseline are needed**.**

Keywords: Effectiveness, Tenofovir, Zidovudine, HIV-infection

INTRODUCTION

Human Immunodeficiency Virus (HIV) is genetically related to member of the Lentivirus genus of the Retroviridae family[1]. HIV is the virus that causes HIV infection in which the virus attacks and destroys the infection-fighting CD4 cells of the body's immune system[2,3,4]. The inability of the immune system to mount an effective response to opportunistic infectious agents and tumors leads to the death of the affected individual[5].

An estimated 38 million people worldwide were living with HIV. About 25 million of this population were in sub-Saharan. Africa where in 2003 alone, an estimated 3 million people became newly infected with HIV, while 2.2 million people died of AIDS[6]. Prevention of HIV is a widely used strategy worldwide to prevent transmission of HIV that involves use of antiretroviral treatment (ART). ART reduces the HIV viral load in the blood, semen, vaginal fluid and rectal fluid to very low levels[7].

In the early 1990s, highly active antiretroviral treatment (HAART) was introduced and revolutionized the treatment of HIV infection, resulting in dramatic reductions in morbidity and mortality[8,9]. Effective ART consistently results in sustained suppression of HIV replication and gradual increases in CD4 T- lymphocyte count[10,11]. First-line therapy should consist of a nucleoside reverse transcriptase inhibitors (NNRTI) + two nucleotide reverse transcriptase inhibitors (NRTIs), one of which should be zidovudine (AZT) or tenofovir[12,13].

Despite these encouraging results, the early optimism generated by HAART was tempered by regimen complexities, adverse effects, toxicities, and cost[14,15]. Durable suppression of replication of the human immunodeficiency virus (HIV) depends on the use of potent, well-tolerated antiretroviral regimens to which patients can easily adhere and improve the quality of

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Table 1: Level of CD4 cell counts at various times of interval between TDF+FTC+EFV and AZT+3TC+EFV

	Regimen	N	Means±SD
CD4 (0 month)	TDF+FTC+EFV	47	128.36±105.24
	AZT+3TC+EFV	47	185.96±85.35
CD4 (6 months)	TDF+FTC+EFV	42	193.33±110.62
	AZT+3TC+EFV	46	257.41±115.51
CD4 (12 months)	TDF+FTC+EFV	45	269.02±136.31
	AZT+3TC+EFV	43	322.53±158.71
CD4 (24 months)	TDF+FTC+EFV	46	351.20±165.68
	AZT+3TC+EFV	46	392.80±186.47

Note: normal range of CD4: 500-1000 cells/mm^3 * p<0.05

Table 2: Level of Hb at various time interval between TDF+FTC+EFV and AZT+3TC+EFV

	Regimen	N	Means±SD
Hb (0 month)	TDF+FTC+EFV	47	11.17±2.94
	AZT+3TC+EFV	47	13.32±1.75
Hb (6 months)	TDF+FTC+EFV	42	11.56±1.88*
	AZT+3TC+EFV	46	12.86±1.62
Hb (12 months)	TDF+FTC+EFV	42	11.85±1.37*
	AZT+3TC+EFV	45	12.94±1.39
Hb (24 months)	TDF+FTC+EFV	43	12.92±1.40
	AZT+3TC+EFV	45	13.12±2.31

Note: normal range of Hb: 11.5-16.5 g/dl* p<0.05

life[16].

The WHO 2013 ARV guidelines promotes simplification of ART delivery by reducing the number of preferred first-line regimens (TDF + 3TC or FTC + EFV), which is available as a once-daily fixed-dose combination and can be used for most people[17]. The USA Panel of the International AIDS Society recommends combination therapies that comprise a NNRTI or a protease inhibitor boosted with low-dose ritonavir, each combined with two NRTIs or NRTIs, for the treatment of HIV infection in adults[18].

The present study assessed the effectiveness of two regimen containing TDF/FTC versus AZT/3TC in HIV-infected Naive patients in terms of immunological response and well-tolerance at Halibet National Referral Hospital, Asmara, Eritrea.

MATERIALS AND METHODS

Patients and Naive HIV-infected samples

A retrospective observational cohort study was conducted on adult Naive HIV-infected and visits for follow-up at Halibet National Referral Hospital, Zoba Maekel, Asmara, Eritrea. This study begun in March and finish in April 2015 at Halibet National Referral Hospital Asmara, Eritrea.

Technique for data Collection

Data was extracted from Patient's medical record using data collection form. Patient demography such as age, gender, marital status, medication prescribed including the name of the Drug, baseline CD4 cell counts, serum Cr and Hb was recorded throughout the 24 months. Any adverse events occurring with the ART was also recorded

Statistical Analysis

Mean with standard deviation (SD) and frequency (%) were used to describe patient's characteristics. Continuous data was also expressed as mean with SD. T-test was used to compare means between two independent groups (TDF versus AZT). Confidence interval (Cl) with 95%, P-value of less than 0.05 were considered as significant for all statistical tests.

RESULTS

The major Laboratory tests used to assess the effectiveness of ARV treatment on the study subjects were CD4 cell counts, hemoglobin and creatinine.

CD4 cell counts

The study Data are reported on 94 participants of whom 55 were females (58.5%) and 39 were males (41.5%). The level of CD4 cell at baseline in TDF and AZT are 128.36±105.24 cells/mm^3 and 185.96±85.35 cells/mm^3, respectively. The complete data is showed in Table 1.

Mean CD4 cell counts at each visit starting at HAART initiation were compared between TDF +FTC +EFV and AZT +3TC +EFV regimen using Independent Samples T-Test with 95% confidence interval (Cl), P-value of less than 0.05 were considered as significant for all statistical tests.

Hemoglobin

As the Table 2 indicated, level of Hb at various time of interval for the study subjects was recorded. Patients in TDF regimen had low baseline Hb level compare to patients in AZT. Patients in AZT regimen had more frequency of Hemoglobin test. Complete Hb data for the study subjects is given in Table 2.

Creatinine

The Table 3 represented the level of Cr level and P-value at various time of interval. The independent sample T-test

Table 3: Level of Cr in various times of interval between TDF+FTC+EFV and AZT+3TC+EFV

	Regimen	N	Means±SD
Cr (0 month)	TDF+FTC+EFV	47	0.74±0.38
	AZT+3TC+EFV	42	0.76±0.18
Cr (6 months)	TDF+FTC+EFV	33	0.83±0.27
	AZT+3TC+EFV	17	0.82±0.10
Cr (12 months)	TDF+FTC+EFV	29	0.92±0.25
	AZT+3TC+EFV	14	0.81±0.16
Cr (24 months)	TDF+FTC+EFV	37	0.93±0.21
	AZT+3TC+EFV	11	0.96±0.22

Note: normal range of creatinine: 0.7-1.5 mg/dl* $p<0.05$

was done to compare the Cr level between the two drugs (TDF and AZT), at various time of interval and showed no significant difference between the two regimens though out the study period.

Concomitant diseases

Concomitant diseases (OIs) were observed during ART initiation as a result of HIV disease progression and were treated symptomatically. Cotrimoxazole was the most concomitant drug used by the study subjects for both (treatment and prophylaxis of OIs) and 6 (6.38%) cases were hypersensitive to cotrimoxazole. None of the study subjects show concomitant diseases and drugs during the two-year follow-up.

Adverse events of the regimen

Mild ART drug toxicities (Gastrointestinal disturbance) during the initiation of ARV therapy was observed in three cases (two in AZT and one in TDF) only. Five study subjects in AZT regimen changed to TDF containing regiment and none of the study subjects in TDF changed to other ART regiment.

DISCUSSION

This study intended to evaluate the effectiveness of regimen containing TDF Versus AZT based on Immunological responses (increase CD4 cell counts), safety (well tolerance) and occurrence of treatment failure among 94 Naive HIV-infected patients visited at Halibet National Referral Hospital, Eritrea for two years follow up. The study was conducted among adult HIV patients age greater than 18 years who started ART treatment and had two years follow up. Pregnant women, lactating and children were excluded from the study subjects.

Once treatment begins, the clinical progress of the patient needs to be reviewed regularly[12]. A rise in CD4 lymphocyte count of 90-150 cells to be following successful initiation of HAART would be expected[19]. Increasing CD4 cell level among the two regimen of study subjects was compared for two-year follow-up.

Following 6 months, mean CD4 cell counts was 193.33±110.62 cells/mm^3 and 257.41±115.51 cell/mm^3 for patients in TDF and AZT, respectively (p=0.10). The significant different at 6 months was due to the mean differences between the two regimen at baseline. However, patients in TDF had greater mean increasing from baseline CD4 cell counts compared to patients in AZT (140.00 TDF and 136.57 AZT) during the first year. For the consecutive level of CD4 cell (at 12 and 24 months) there was no significant differences between the two regimens (269.02±136.31 cell/mm^3 in TDF, 322.53±158.71 cell/mm^3 in AZT, p=0.93) at 12 months and (351.20±165.68 cell/mm^3 in TDF, 392.80±186.47 IN AZT, p =0.261) at 24 months. However, patients in TDF had greater increase (75.69 cell/mm^3 in TDF and 65.12 cell/mm^3 in AZT).

During the first three consecutive Hb level tests, there was a significant difference in Hb level being higher in patients in AZT regimen. However, at 24 months both patients in TDF and in AZT had similar Hb level with no significant differences. This revealed a decrease Hb level in patients in AZT regimen. When Cr level was assessed though out the follow up, there was no significant different between the two study subjects indicated that no TDF toxicity was developed.

As a general principle, mild toxicities do not require the discontinuation of ART or drug substitution[19,20,21]. Mild ART drug toxicities (gastrointestinal disturbance) during the initiation of ARV therapy was observed in three cases (two in AZT and one in TDF) and was treated symptomatically.

Moderate or severe toxicities may require substitution of the drug with another, of the same ARV class, but with a different toxicity profile**.** Severe life-threatening toxicity requires discontinuation of all ARV drugs until the patient is stabilized and the toxicity is resolved [19]. Four study subjects in AZT regimen showed severe ART drug toxicities (anemia, which is the most common AZT side effect) and changed to TDF containing regiment However none of the study subjects in TDF showed ART toxicities (didn't change the regiment). No life-threating ART toxicities were observed among all the study subjects. Treatment failure (reduction in CD4 cell counting after increased from the baseline) didn't occurred among all study subjects.

CONCLUSION

The study was conducted to evaluate the effectiveness of TDF versus AZT in adult HIV-infected at Halibet National Referral Hospital and has shown the beneficial effects and safe of TDF+FTC+EFV over AZT +3TC+EFV as first line treatment for HIV patients in two years of follow-up in terms of CD4 cell counts and well tolerance. Since this study has been done for short period of time with different mean CD4 cell counts baseline, further studies to evaluate the safe and effects of long

term use of TDF+FTC+EFV in Naive HIV-infected patients with same mean CD4 cell counts baseline are needed**.**

REFERENCES

1. Bryntesson, F., *The Life Cycle of the Human Immuno-Deficiency Virus: A Useful Tool for Teaching Scientific and New Chruch Principles in the Biology Classrom.* The new philosophy, 2009. 112(1-2): 761-790.
2. Alimonti, J.B., T.B. Ball, and K.R. Fowke, *Mechanisms of CD4+ T lymphocyte cell death in human immunodeficiency virus infection and AIDS.* Journal of General Virology, 2003. 84(7): 1649-1661.
3. Duggal, S., T.D. Chugh, and A.K. Duggal, *HIV and Malnutrition: Effects on Immune System.* Clinical and Developmental Immunology, 2012. 2012: 8.
4. Streeck, H. and D.F. Nixon, *T Cell Immunity in Acute HIV-1 Infection.* Journal of Infectious Diseases, 2010. 202(Supplement 2): S302-S308.
5. Mondol, R., S. Paul, S. Ray, and S. Maiti, *Polymeric Nanocarriers: A Promising Research Avenue for the Delivery of Anti-HIV Drugs.* International Journal of Applied Pharmaceutics, 2010. 2(2): 1-5.
6. UNAIDS, *Report on the global HIV/AIDS epidemic.* 2004, UNAIDS: Geneva.
7. WHO, *Antiretroviral treatment as prevention (TASP) of HIV and TB*. 2012.
8. Arts, E.J. and D.J. Hazuda, *HIV-1 Antiretroviral Drug Therapy.* Cold Spring Harbor Perspectives in Medicine, 2012. 2(4): a007161.
9. Lu, X.F. and Z.W. Chen, *The development of anti-HIV-1 drugs.* Yao Xue Xue Bao, 2010. 45(2): 165-176.
10. Mutugi, M.W., L.M. Kaguu, and S.N. Maangi, *Efficacy and Challenges of Adherence to Anti Retroviral Therapy: Experience from Nyeri Provincial Hospital, Kenya.* International Journal of Medicine and Medical Sciences, 2010. 2(2): 24-28.
11. Leone, A., M. Rohankhedkar, A. Okoye, A. Legasse, M.K. Axthelm, F. Villinger, M. Piatak, J.D. Lifson, B. Assouline, M. Morre, L.J. Picker, and D.L. Sodora, *Increased CD4+ T Cell Levels during IL-7 Administration of Antiretroviral Therapy-Treated Simian Immunodeficiency Virus-Positive Macaques Are Not Dependent on Strong Proliferative Responses.* The Journal of Immunology, 2010. 185(3): 1650-1659.
12. WHO, *Antiretroviral Therapy for HIV Infection in Adult and Adolescent: Recommendation for a Public Health Approach 2010 Revision*. 2010.
13. Spaulding, A., G.W. Rutherford, and N. Siegfried, *Tenofovir or zidovudine in three-drug combination therapy with one nucleoside reverse transcriptase inhibitor and one non-nucleoside reverse transcriptase inhibitor for initial treatment of HIV infection in antiretroviral-naive individuals.* Cochrane Database Syst Rev, 2010(10): Cd008740.
14. Montaner, J.S., R. Hogg, E. Wood, T. Kerr, M. Tyndall, A.R. Levy, and P.R. Harrigan, *The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic.* Lancet, 2006. 368(9534): 531-536.
15. Tadesse, W., A. Mekonnen, W. Tesfaye, and Y. Tadesse, *Self-reported adverse drug reactions and their influence on highly active antiretroviral therapy in HIV infected patients: a cross sectional study.* BMC Pharmacology and Toxicology, 2014. 15(1): 32.
16. FDA, *Brief Document Tenofovir Disproxil Fumarate for the Treatment of HIV-1 Infection in Adults in Combination with Other Antiretroviral Agents*. 2001: USA.
17. WHO, *Global Update on HIV Treatment 2013: Result, impact and opportunities.* 2013.
18. Hammer, S.M., M.S. Saag, M. Schechter, J.S. Montaner, R.T. Schooley, D.M. Jacobsen, M.A. Thompson, C.C. Carpenter, M.A. Fischl, B.G. Gazzard, J.M. Gatell, M.S. Hirsch, D.A. Katzenstein, D.D. Richman, S. Vella, P.G. Yeni, and P.A. Volberding, *Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society--USA panel.* Top HIV Med, 2006. 14(3): 827-843.
19. Bucy, R.P., R.D. Hockett, C.A. Derdeyn, M.S. Saag, K. Squires, M. Sillers, R.T. Mitsuyasu, and J.M. Kilby, *Initial increase in blood CD4(+) lymphocytes after HIV antiretroviral therapy reflects redistribution from lymphoid tissues.* Journal of Clinical Investigation, 1999. 103(10): 1391-1398.
20. Murphy, R.A., H. Sunpath, D.R. Kuritzkes, F. Venter, and R.T. Gandhi, *Antiretroviral Therapy—Associated Toxicities in the Resource-Poor World: The Challenge of a Limited Formulary.* Journal of Infectious Diseases, 2007. 196(Supplement 3): S449-S456.
21. Pryce, C., R. Pierre, J. Steel-Duncan, T. Evans-Gilbert, P. Palmer, J. Moore, B. Rodriguez, and C. Christie, *Safety of antiretroviral drug therapy in Jamaican children with HIV/AIDS.* West Indian Medical Journal, 2008. 57: 238-245.