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Assessment of Antioxidants Enzymes, Cd4+ and Uric Acid Profile in HIV Sepropositive Subjects Attending Federal Medical Centre Owo

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Abstract **Original Research Article**

The purpose of this study was to determine the level of selected antioxidant enzymes, CD4+ cell count and Uric in HIV seropositive individual attending Federal Medical Centre Owo, Ondo State. Glutathione peroxidase, catalase and superoxide dismutase levels were determined in one hundred and fifty subjects comprising, fifty [50] seropositive subject on anti-retroviral therapy, fifty [50] seropositive subject not on anti-retroviral therapy and fifty [50] seronegative subject, the control group using spectrophotometry method. The result shows that the mean catalase activities of the subjects when compared with that of HIV patients without ART was statistically significant ($p<0000$), mean catalase activities between HIV patient on ART and those without art were also highly significant. Catalase activity in the sampled showed no significant correlation with CD4-cell count ($p>0.05$). SOD activities in HIV patient on ART and those without ART were higher than the control subjects, but not statistically significant ($p>0.05$). Uric acid level showed a highly significant increase in both sero positive patients when compared with control. ($p>000$). Glutathione peroxidase activity in HIV patient without ART and those on ART was found to be significantly higher (p-value) when activity in the control subject, ($p<0.000$) significant CD4 depletion was observed in HIV patient without the ART treated patients, SOD positively correlates with CD4+ cell count ($p<0.05$) showing protective role of SOD against oxidative CD4+ cells destruction. In conclusion, the oxidant capacity of HIV patients without HAART confirmed the involvement of oxidative stress in lymphocyte destruction of HIV in these subjects. Oxidative stress will amplify the impact of the adverse effects of HIV infection in premature death of immune cells. The level of antioxidant enzymes in our study population is now known. The study created an avenue for the establishment of the relationship between HIV and antioxidant enzymes (CAT, SOD, GPX) Uric acid and CD4+ cell counts.

Keywords: HIV, Antioxidant Enzymes, CD4+ Cell Count, Uric Acid, Glutathione Peroxidase (GPX), Catalase (CAT), Superoxide Dismutase (SOD), Oxidative Stress, Antiretroviral Therapy (ART), Seropositive, Seronegative, Lymphocyte Destruction, Immune Cells, Spectrophotometry, Federal Medical Centre Owo, Ondo State, HAART, Premature Cell Death.

INTRODUCTION

Generation of reactive oxygen species (ROS) is a normal process in the life of aerobic organisms. Under physiological conditions, these deleterious species are mostly removed by the cellular antioxidant systems, which include antioxidant vitamins, protein and non-protein thiols, and antioxidant enzymes (Banerjee et al., 2003). Many process occurring in the body at all-time require oxygen, but this life giving oxygen can create harmful side effects these processes induce the production of reactive oxygen species such as free radicals in the cells which can lead to cellular degeneration and DNA damage. (Hazra et al., 2008). These oxygen radicals are capable of reversibly or irreversibly damaging compound of all biochemical classes including nucleic acid, protein free amino acid, lipids, lipoprotein, carbohydrate and connecting tissue micro-molecules. All most all tissue components, i.e. lipid, nucleic acid, protein n and carbohydrate are thus susceptible to free radical injury. The most important mechanism of cellular injury is a chain reaction known as lipid per-

oxidation. These species (ROS) may have impact on such cell activities as membrane function, metabolism and gene expression. The degree of damage can be assessed by measuring the levels of antioxidants, since they also serve as footprint of oxidant damage. The free oxygen radicals (superoxide anion, hydrogen peroxide and hydroxyl radicals) are produced by sequential incomplete reduction of oxygen molecule and are promptly scavenged by antioxidant enzymes present in vivo. Oxidative stress can then be defined as an imbalance between the oxidant and antioxidant system, with an advantage towards the oxidant system: A variety of enzymatic (Superoxide dismutase (SOD), Catalase (CAT), Glutathione Peroxidase (GSH-Px) etc.) and non-enzymatic (Carotenoids, Tocopherols, Ascorbate, bioflavonoids, Uric acid etc.) antioxidants are present in human serum (Suresh et al, 2009).

Free radicals are reactive chemical species that have an unpaired electron in their outer orbit (Rahman, 2007). The attain stability by stealing electron from surrounding molecules which in turn form new radicals and start chain reactions. Free radicals stabilize by pairing electron with biological macromolecules like protein, lipid or DNA in healthy cells thereby causing lipid peroxidation, protein and DNA damage and this contributes to cancer, aging, atherosclerosis, cardiovascular disease and inflammatory disease (Maxwell, 1995; Braca et al, 2002). However, all human cells protect themselves from free radical damage with enzymes like SOD, CAT and GSH Px (Niki et al, 1994). Decreases SOD and GSH-Px activities may contribute to pathophysiological mechanisms. Conversely, increased uric acid (UA) may serve a protective role responding to superoxide radical arising from increased Xanthine Oxidase (OX) activity or other sources (Yildirim et al., 2004). The natural antioxidant systems which consist of a series of antioxidant enzymes such as superoxide dismutase (SOD), Catalase, Glutathione peroxidise as well as numerous endogenous and dietary antioxidant compounds that are capable of reacting with and inactivating ROS; thereby protects the functional ad structural molecules against ROS-mediated tissue damage (Aquaro et al., 2008).

This study seeks to determine the effect of HIV infection prior and during antiretroviral drug on selected antioxidant enzymes, uric acid biophysical parameters.

OBJECTIVES OF THE STUDY

The specific objectives of this study include;

i. To estimate and know the definitive pictures of selected antioxidant enzymes uric acid measures with CD4 in newly seropositive patient and those on anti-retroviral drug.

ii. To compare these Biochemicals between various group (seronegative, newly seropositive and antiretroviral patients).

HUMAN IMMUNODEFICIENCY VIRUS

Human immunodeficiency virus HIV is a lentivirus virus (a number of retrovirus family) that causes immunodeficiency syndrome (AIDS), a condition in human in which progressive failure of the immune system allows life threatening opportunistic infections and cancer to thrive. HIV infects vital cells in the human immune system such as helper T cells (specifically CD4+ T cells), macrophages, and bad dendritic cells. HIV infection leads to low levels of $CD4^+$ T cells through three main mechanisms: First, direct viral killing of infected cells; second, increased rate of apoptosis in infected cells; and third viral killing of infected CD4+ T cells by CD8 cytotoxic lymphocytes that recognize infected cells. When CD4+ T cells number decline below a critical level, cells- mediated immunity is lost, and the body becomes progressively more susceptible to opportunities infections.

Human immunodeficiency virus HIV is the ethiologic agent of the disease known as acquired immunodeficiency syndrome (AIDS). It causes a progressive impairment of the body's cellular immune system by destroying CD4+ T cells leading to increased susceptibility to various infections. HIV/AIDS is a major public health problem with socio-economic burden and a serious threat to development. Nine out of 10 people living with HIV are in the developing world. 60 to 70% of these are in sub- Saharan Africa, but the disease is spreading

in every region, with fierce epidemics threatening to tear through countries such as India, China, Russia and the island of the Caribbean. As HIV spreads, it interact with other infectious diseases, facilitated by the clinical course of both diseases. (Olajide et al., 2010) acquired immunodeficiency syndrome is a fatal illness caused by the retrovirus known as the HIV that breaks down the body's immune system, infects CD4+ cells initially, and progressively lead to AIDS (Gouripur et al., 2012).

MECHANISM OF HIV INFECTION

HIV is a member of the gene ***Lentivirus*** (ICTV, 2002), part of the family retriviridae lentivirus have many morphologies and properties in common. Many species are infected by lentiviruses, which are characteristically responsible for long duration illness with a long incubation period (Levy. 1993). Lentiviruses are transmitted as single-stranded, positive-sense, envelope RNA viruses. Upon entry into the target cells, the viral RNA genome is converted (reverse transcribed) into double-stranded DNA by virally encoded reverse transcriptase that is transported along with the viral genome in the virus particle. The resulting viral encoded integrase and host co-factors (Smith and Daniel. 2006). Once integrated, the virus may become latent, allowing the host and virus to avoid detection by the immune system. Alternatively, the virus may be transcribed, producing new RNA genome and viral proteins that are packaged released from the cells as new virus particle that begin the replication cycle anew.

CLASSIFICATION OF HIV

Two types of HIV have been characterised: HIV-1 and HIUV-2. HIV-1 is the virus that was initially discovered and termed both LAV and HTLV-III. It is more virulent, more infective (Gilbert et al., 2003), compared to HIV-1 implies that fewer of those exposed to HIV-2 will be infected per exposure. Because of its relatively poor capability for transmission, HIV-2 is largely confined to West Africa (Reeves and Doms, 2002).

Table 2.1: Comparism of HIV Species

Species	Virulence	Infectivity	Prevalence	Inferred origin
HIV-1	High	High	Global	Common Chimpanzee
HIV-2	Lower	Low	West Afica	Sooty Mangaby

(Reeves and Doms. 2022)

Structure and molecular features of HIV

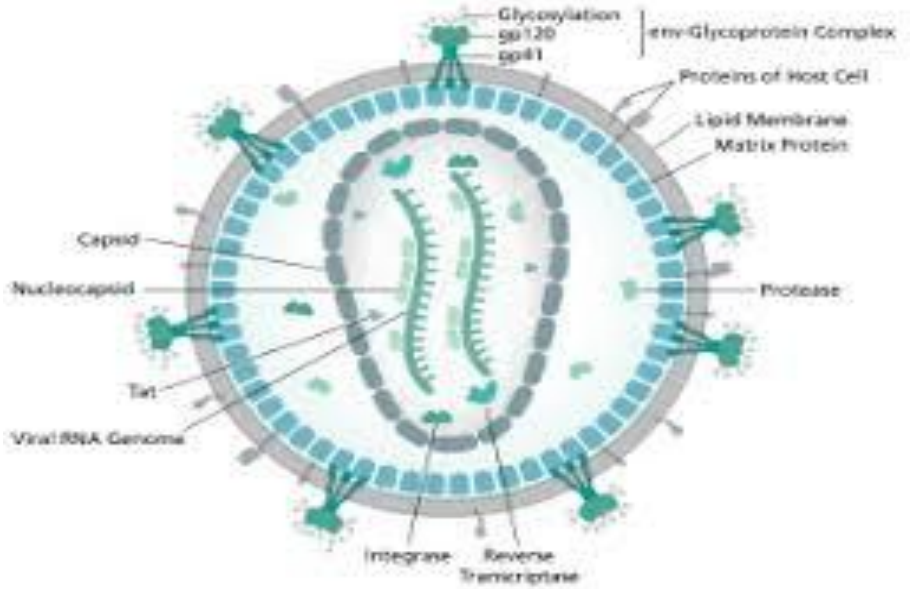

Fig. 2.1: Schematic Diagram of HIV virion (Chatterjea and Shinde 2012).

HIV-1 virion, according to electron microscopic observation, has shaped core or capsid which consists of

- The major capsid protein p24
- The nucleocapsid protein p7/p9
- The diploid single stranded RNA genome and
- The three viral enzymes, protease, reverse transcriptase and integrase

Reverse transcriptase is the hallmark of a retrovirus and is capable of transcribing its genomic RNA into double stranded DNA. This DNA copy of the retroviral genome is called a provirus. After integration into the host genome, the provirus serves as a template for cellular DNA-dependent RNA polymerases to genome new viral RNA genome as well as shorter sub genomic messenger RNAs. The unsliced and singly spliced viral RNAs are translated into the protein component of the viral core and the envelope proteins and the multiplied viral RNAs into the small accessory/regulatory proteins. Surrounding the capsid lies the matrix constituted by myrisylated p17 gag protein, which is located underneath the virion envelope. The matrix protein is involved in the early stage of the viral replication cycle and plays a part in the formation and transport of the pre-integration DNA complex into the nucleus cells. The virion envelope consist of a lipid bilayer membrane, derived from the host cell. Like all retroviruses, an envelope consisting of viral glycoproteins embedded in a host cell derived lipid bilayer surrounds HIV-1. The virus surface is constituted by 72 knob containing trimers and tetramers. The envelope glycoproteins are synthesised as gp160 precursor in the rough endoplasmic reticulum. Asparagine linked, high mannose sugar chain is added to gp160, which is then assembled into oligomers. These are then transported to the Golgi apparatus where cellular proteases cleave gp160 into the external surface (SU) envelope protein or gp120 and transmembrane (TM) protein or gp41.

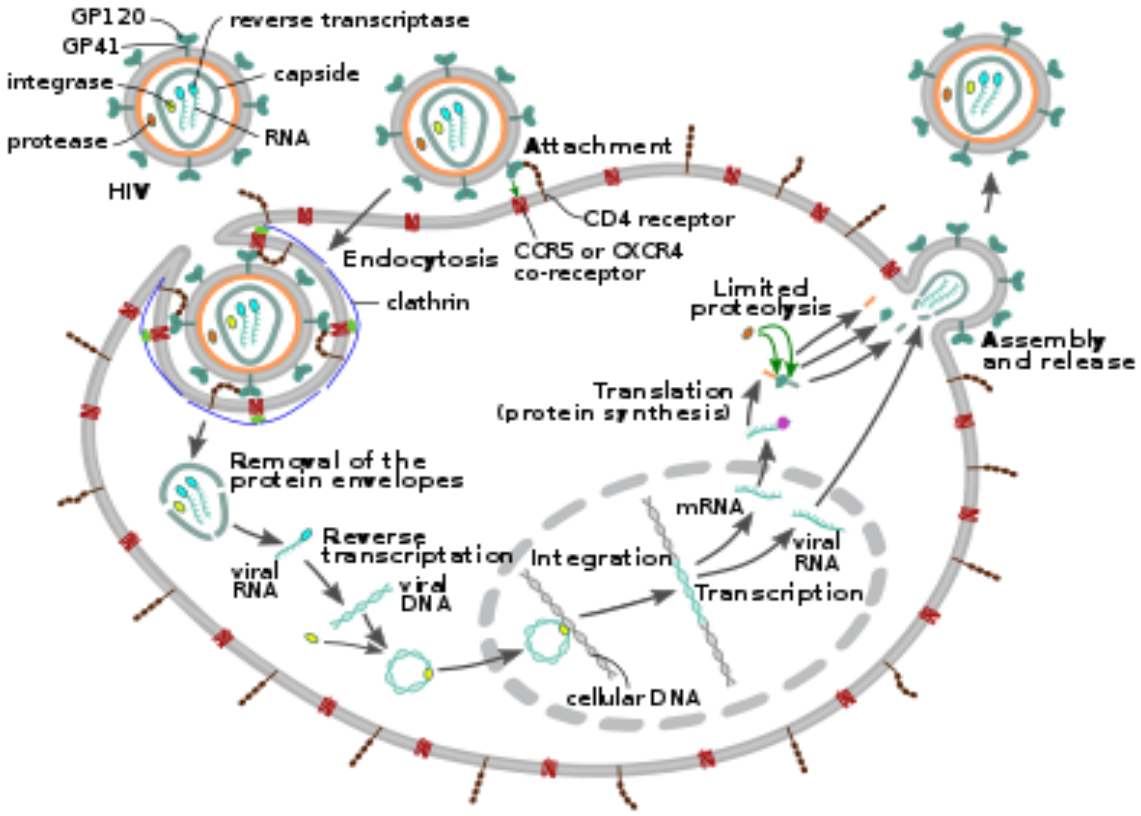

Fig 2.3: Replication Cycle of HIV (Chan and Kim, 1998).

ENTRY OF HIV INTO SUSCEPTIBLE CELL

HIV enters macrophages and CD4+ T cells by the adoption of glycoprotein on its surface to receptor on the target cell followed by fusion of the viral envelope with the cell membrane and the release of the HIV capsid into the cell. Entry to the cell edging through interaction of the trimeric envelope complex (gp160 spike) and a chemokine receptor (generally either CCR5 or CXCR4, but other are known to interact) on the cell surface. Gp120 bind to integrin $\alpha_4\beta_7$ activating LFA-1 the central intergrin involved in the establishment of virological synapses, which facilitate efficient cell-to-cell spreading of HIV-1. The gp160 spike contains binding domains for both CD4 and chemokine receptors (Chan and Kim, 1998; Wyatt, 1998).

CD4-T CELLS AND HIV

CD4-T helper cells are white blood cells that are an essential part of the human immune system. They are often referred to as CD4 cells, T- helper cells or T4 cells. They are called helper cells because one of their main role is to send signals to other types of immune cells, including CD8 killer cell, which then destroy the infectious particle. If 4 cells become depleted, for example in untreated HIV infection, or following immune suppression prior to a transplant, the body is left vulnerable to a wide range of infections that it would otherwise have been able to fight. CD4 is a co-receptor that assists the T cells receptor (TCR) in communicating with an antigen-presenting cell. Using its intracellular domain, CD4 amplifies the signal generated by the TCR by recruiting an enzyme, the tyrosine knase Lack, which is essential for activating many molecular component of the signalling cascade of an activated T cell. Various types of T helper cells are thereby produced. CD also interacts directly with MHC class II molecules on the surface of the antigen-presenting cell using its extracellular domain adopts an immunoglobulin-like beta-sandwich with seven strands in 2 beta sheets, in a Greek key topology (Brady et al., 1993). HIV-1 uses CD4 to gain entry into host T-cells and achieves this through its viral envelope protein known as gp120 (Kwong et al., 1998).

MATERIALS AND METHOD

Study Area

The study done at Federal Medical Centre (FMC) Owo Local Government area of Ondo state in collaboration with Global HV and AIDS initiative in Nigeria (GHAIN)/ Heart to heart centre, FMC Owo is located on Latitude 7.19^0N and longitude -6.59^0E. It is situated in Western part of Nigeria in Ondo north Senatorial district with population size of 850,000 according to National Population Census.

Study Population

Two study groups were constituted in the course of this work. The case studies were 100 subjects and the control group were 50subjects. The case study group were further subdivided into:

- Study group 1, 50 HIV patient on anti-retroviral therapy
- Study group 2, 50 HIV patients not on antiretroviral therapies who shall satisfy the inclusion criteria while. A control group of 50 apparently healthy 34 males and 16 female subject above 18 years of age and not on any drug therapy were selected according to world health organisation definition (1999).

Based on sample size calculation, the sample size for the study should be 48, but for statistical significance, cost and availability of reagent 50 participants were recruited. The study population were recruited by simple random sampling of average of 100 patients attending the Heart to Heart clinics weekly in ratio 1:5 i.e. every fifth patient was recruited for the study.

Test Procedure Protocol

	Blank	Test
0.34MH2O2	5.0ml	5.0ml
Distilled water	0.5ml	
6MH2SO4	1.0ml	1.0ml
0.01MKMnO4	1.0ml	1.0ml
Sample		0.5ml

Absorbance of the sample were read at 480nm, and at 0sec, 20sec, 40sec, 60sec and 80sec for each sample

Calculation;

The activity of serum Catalase was calculated using the formula:

$$\text{Catalase (unit/serum)} = \frac{\Delta\text{ABS of test} \times V \times 1000}{M \times v \times L \times y}$$

Where; ΔOD = Mean of the difference in the absorbance for each test

V = total volume of the reaction mixture

m = molar extinction coefficient for $H_2O_2 = 40\ M^{-1}\ cm^{-1}$

L = Light path = 1cm

v = Volume of sample used

y = Total protein (g/dl) for the respective sample

The activity; unit/g = mole of H2O2 consumed per minute

Conversion: units/ml (nmol/min/ml) × 1000 = 1µmol/min/ml

RESULTS

Results

Results generated from this work are shown in tables 4.1 to 4.8. Results are expressed in mean ± standard deviation.

Table 4.1: There are equal number in each group with more male among control subject than female. Female are more among the patients considered for this research than male with percentage ratio of 68% female to 32% male.

Table 4.1: Shows the Gender Distribution among the Groups

	Groups			
	Seronegative	Naïve retroviral	Anti -retroviral	Total
Gender				
Male	34(68%)	16(32%)	16(32%)	66(44%)
Female	16(32%)	34(68%)	34(68%)	84(56%)
Total	50(100%)	50(100%)	50(100%)	150(100%)

Table 4.2: There is clear significant difference in age, weight and body mass index (BMI) of the patients compared to control group while no difference was observed with height

Table 4.2: shows the biophysical parameters considered and statistical significant in non- anti-retroviral patients with seronegative group (mean and standard error of mean).

	Groups			
Biophysical	Non-anti-retroviral N=50	seronegative n=50	t- value	P. value
Age (years)	37±2	28±1	5.13	P<0.0000
Weight (kg)	57.6±0.44	41.2±0.75	24.24	P<0.0000
Height (M)	1.5±0.05	1.52±0.01	0.87	P>0.05
BMI	25±0.6	17±0.10	58.59	P<0.0000.

Table 4.3: shows the statistical presentation of biochemical profile of non-anti-retroviral patients with control group (mean and standard error of mean)

Biochemicals	Non anti-retroviral	seronegative	t- value	P. value
	N=50	n=50		
Catalase (u/g)	81.2±20	368±25	0.91	P>0.05
GPx (UI)	2903±93	366±17	20.49	P<0.0000
SOD(IU/ml)	1.71±0.2	1.63±0.02	0.46	P>0.05
Uric Acid(mmol/l)	11.5±0.36	0.47±0.06	19.02	P<0.0000
CD4(cells/ml)	250±15	910±20	23.46	P<0.0000

Table 4.3: No significant difference were observed in age and height while weight and BMI shows slight increase among those on anti-retroviral therapy compare with newly diagnosed.

DISCUSSION

Human immunodeficiency virus (HIV) infection is a pandemic infection with more spread in Africa, southern Asia and mid-East (UNAIDS, 2008). The infection causes various metabolic disorders through induction of various redox reactions in the body (Teto et al, 2013). These study asses the effect of HIV infection and retroviral therapy on selected antioxidant enzymes and uric acid in patients attending antiretroviral clinic. From the results, CD4+ was significantly higher in seronegative controls compared with the HIV groups. T lymphocyte CD4+ is the main target of HIV. Clinical and laboratory manifestations observed in HIV infection are due to a massive destruction of CD4+ lymphocytes. Several mechanisms are implicated in the depletion of this cell population. However, CD4+ was significantly higher in HIV patients on antiretroviral compared with those not on drug. This is consistent with established literature and patients' response to treatment (Pasupathi *et al.*, 2008).

Glutathione peroxidase (GPx), catalase (cat), superoxide dismutase (SOD) and uric acid (UA) shows discordant pattern in difference group in this study. Previous study has reported increased in oxidative stress in HIV/AIDs patients (Edeas *et al.*, 1999) with corresponding reduction in circulating and intracellular antioxidants. This study demonstrates higher SOD in HIV patients not on anti-retroviral drugs compared to seronegative patients but this was not significant. While HIV patients on anti-retroviral drugs also have higher SOD compared with those not on drugs. Although this was not statistically significant. These results are at variance with that of Edeas *et al.,* (1999) and Pasupathi *et al.,* (2009) which showed a decrease in SOD activity in people living with HIV/AIDS which could be explained by the nature of these protein enzymes which would target free radicals.

The main role of glutathione peroxidase which is a selenoenzyme is to eliminate lipid peroxides resulting from the effect of oxidative stress on the polyunsaturated fatty acids (Morris *et al.,* 2012). This study found a significantly higher GPx in patients not on anti-retroviral compared to seronegative controls and also, GPx was significantly higher in patients on anti-retroviral drugs compared with those who are not on drug. In another research, Pasupathi *et al.,* (2008) noted that even though HIV-infected patients have a consistently lower mean level of glutathione as compared to healthy subjects which is at variance with this study, the distribution of values is wide, suggesting individual variation. In another study, it was observed that long-term selenium deficiency contributes to the fall in activity of glutathione peroxidase in people living with HIV (Kupka *et al.,* 2014).

In this study, catalase is significantly lower in HIV patients not on anti-retroviral drugs compared to seronegative control. However, drug treatment seems to improve catalase activity as seen in a significantly higher catalase activity in HIV patients on antiretroviral compared to those who are not. In another study, it was found that serum catalase

activity increases as AIDS progresses, while serum glutathione peroxidase levels appear to remain similar to those of healthy subjects (Pasupathi *et al.*, 2008).

In addition to these three enzymes, this study showed UA to be significantly increased in HIV patients on antiretroviral compared to those not on drugs which may be due to the positive effect of antiretroviral therapy.

CONCLUSION

The oxidant capacity of HIV patients without HAART confirmed the involvement of oxidative stress in lymphocyte destruction of HIV in these subjects. Oxidative stress will amplify the impact of the adverse effects of HIV infection in premature death of immune cells.

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