

The effect of antiretroviral therapy in newly diagnosed people living with HIV and AIDS, and their correlation with common inflammatory markers and lipid profile

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Abstract

Introduction: Studies have shown that there is a connection between erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lipid profile, and death among individuals with acquired immunodeficiency syndrome (AIDS) not taking human immunodeficiency virus (HIV) medications. Those, who later developed AIDS or died during the analysis had their inflammatory markers measured (tumor necrosis factor – TNF, interleukin (IL)-6, CD27, ESR, and CRP). This study was conducted with the aim to evaluate the role of antiretroviral therapy (ART) in newly diagnosed people living with HIV and AIDS (PLWHA), and their correlation with inflammatory markers and lipid profile.

Material and methods: This prospective study was conducted among 222 newly diagnosed PLWHA arriving at ART center or in-patients for a duration of one year. 181 were started on TLD (tenofovir disoproxil fumarate, lamivudine, and dolutegravir), and 41 on TLE (tenofovir, lamivudine, and efavirenz). Subjects were examined, and a pre-tested questionnaire was used to collect data, including age, sex, comorbidity, history of disease, family history, treatment compliance, clinical profile, and laboratory parameters. Blood sample was taken among subjects using aseptic precautions for blood investigation, inflammatory markers, CD4, and lipid profile. Data was then entered into MS excel spreadsheet for analysis.

Results: Low HDL (high-density lipoprotein) was the commonest lipid profile abnormality in PLWHA before ART and after ART. No significant correlation between WHO stage and CD4 count with alteration of lipids in both the groups was observed.

Conclusions: Significant number of patients showed improvement in inflammatory markers, more among those with recently added TLD regimen, which was evident due to normalization of ESR and CRP. Low HDL was the commonest lipid profile abnormality in PLWHA before ART and after ART.

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Key words: lipid profile, antiretroviral therapy, CRP, ESR, people living with HIV, PLWHA.

Introduction

Human immunodeficiency virus (HIV) latency period is a time when the virus is inactive for years. However, in re-

cent analysis, HIV latency period may not be what it was believed to be since HIV has a greater impact on human body and immune system than thought. Previously, it was believed that the more the CD4 count, the more the pro-

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tection, and when count was high, the risk of opportunistic diseases was believed to be low. Nowadays, there are more serious conditions, such as major cardiovascular events and deranged hepatic and renal functions with higher or normal CD4 counts. Moreover, a significant number of people are dying with CD4 > 200. It seems that HIV is not silent during its “latency period”, and CD4 levels may not indicate what is happening inside the human body, with inflammation affecting different organs [1, 2].

In SMART trial, individuals with CD4 > 350 who stopped HIV medications, had increased rates of opportunistic diseases when compared with those on HIV therapy. They had higher RNA load in blood, and these higher levels were mainly associated with inflammation. Therefore, even though a lab result can show a high CD4 count, the inflammation may be on a cellular level, which may lead to diseases of multiple organs, including heart, kidney, bones, etc. [3].

The increase in inflammation has been connected with HIV virus. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), interleukin (IL)-6, D-dimer, and tumor necrosis factor alpha (TNF- α) were found to be elevated in people living with HIV and AIDS (PLWHA) with thickened arteries. An increased monocyte chemoattractant protein-1 (MCP-1) and RANTES were observed in PLWHA with increased urinary proteins [3]. Studies have shown that there is a connection between ESR, CRP, and death in AIDS individuals not taking HIV medications. Those, who later developed AIDS or died during the analysis, had their inflammatory markers measured (TNE, IL-6, CD27, ESR, CRP, and CD40). Higher levels of all these markers were found in newly diagnosed PLWHA, or in those who died before taking HIV medications. Levels of TNF- α , CD27, and CD40 were greater before treatment was started in individuals, who later developed cancer due to AIDS or who died. Most of them had low viral loads and CD4 > 200 [4-6].

Therefore, inflammation may be causing damage early during HIV disease, despite lower viral loads and higher or normal level of CD4 counts, and that it may play a role in both HIV-related cancers and death [7, 8]. Hence, the present study was conducted with the aim to evaluate the role of antiretroviral therapy (ART) in newly diagnosed individuals living with HIV and AIDS, and their correlation with common inflammatory markers and lipid profiles. Elevated level of inflammatory proteins in PLWHA (whether on ART or not) may suggest that HIV can be the reason for multiple organ dysfunction, especially cardiac events and deranged renal and liver functions, which can be seen at higher CD4 counts (INFLAM-AGING).

Material and methods

The present prospective study was conducted among newly diagnosed PLWHA (with pre-existing dyslipidemias) arriving at ART center, or in-patients of the department of medicine, MGM Medical College and MY Hospital, Indore, India, for a duration of one year (from June 2020 to May 2021) after IEC approval (approval number: EC/MGM/

MAY-20/94). Informed consent was obtained from all patients prior to enrollment into the study. Subjects with diabetes, tuberculosis, hypertensive chronic renal failure, hypothyroid, chronic smoker, nephrotic syndrome, hepatitis B or C, arthritis, and known cardiac disease were excluded from the study. A total of 222 subjects (181 were started on TLD [tenofovir disoproxil fumarate, lamivudine, and dolutegravir], and 41 on TLE [tenofovir, lamivudine, and efavirenz]) were included in the study during the defined period.

The enrolled subjects were clinically examined, and a pre-tested questionnaire was used to collect data, including age, sex comorbid factors, history of disease, family history, treatment compliance, clinical profile, and laboratory parameters. Blood sample was taken from all enrolled subjects with aseptic precautions for routine blood investigation (complete blood count [CBC], liver function tests [LFT], and renal function tests [RFT]), common inflammatory markers (CRP and ESR), CD4, and lipid profile (low-density lipoprotein [LDL], high-density lipoprotein [HDL], triglycerides [TGs], and total cholesterol) during enrollment into the study (1st visit). During follow-up, at 3- (2nd visit) and 6-month visits (3rd visit), blood samples were taken again with aseptic precautions.

Statistical analysis

The collected data was entered into MS Excel spreadsheet, and analyzed. Categorical data were presented as percentage and proportion, and continuous data were shown as mean and standard deviation. χ^2 analysis was applied to analyze the difference in variables (dependent and independent) during the three planned visits, and variables with *p*-value of < 0.05 were considered having significant association.

Results

In the study, out of 181 individuals who were on TLD, 140 (77.4%) were males and 41 (21.9%) females. Out of 41 individuals who were on TLE, 30 (73.2%) were males and 11 (26.8%) females. Around 126 (69.6%) patients were in the age group of 31-45 years who were started on TLD, and 3 (1.6%)

Table 1. Demographic distribution of study subjects

| Variable | TLD, n (%) | TLE, n (%) |
|-------------------|------------|------------|
| Gender | | |
| Male | 140 (77.4) | 30 (73.2) |
| Female | 41 (21.9) | 11 (26.8) |
| Age group (years) | | |
| 15-30 | 30 (16.5) | 6 (14.6) |
| 31-45 | 126 (69.6) | 32 (78.1) |
| 46-60 | 22 (12.3) | 3 (7.3) |
| > 60 | 3 (1.6) | 0 (0.0) |

TLD – tenofovir disoproxil fumarate, lamivudine, and dolutegravir, TLE – tenofovir, lamivudine, and efavirenz

Table 2. Comparison of common inflammatory markers among subjects during 1st, 2nd, and 3rd visits

| Variable | 1 st visit, n (%) | 2 nd visit, n (%) | 3 rd visit, n (%) | p-value |
|---|------------------------------|------------------------------|------------------------------|-----------|
| CRP – TLD (normal range below < 3 mg/l) | | | | |
| 0.0-3.0 | 123 (67.9) | 127 (70.3) | 145 (80.2) | < 0.00001 |
| 3.1-6.0 | 43 (23.7) | 41 (22.6) | 31 (17.1) | |
| 6.1-10.0 | 15 (8.4) | 13 (7.1) | 5 (2.7) | |
| CRP – TLE (normal range below < 3 mg/l) | | | | |
| 0.0-3.0 | 28 (68.2) | 25 (60.9) | 32 (78.1) | 0.365 |
| 3.1-6.0 | 9 (21.9) | 10 (24.5) | 8 (19.5) | |
| 6.1-10.0 | 4 (9.7) | 6 (14.6) | 1 (2.4) | |
| ESR – TLD (normal range of ESR considered < 20 mm/h for both males and females) | | | | |
| 1-20 | 32 (17.6) | 33 (18.3) | 35 (19.3) | 0.005 |
| 21-40 | 76 (41.9) | 75 (41.4) | 105 (58.1) | |
| 41-60 | 48 (26.7) | 48 (26.5) | 30 (16.5) | |
| > 60 | 25 (13.8) | 25 (13.8) | 11 (6.1) | |
| ESR – TLE (normal range of ESR considered < 20 mm/h for both males and females) | | | | |
| 1-20 | 7 (17.1) | 4 (9.7) | 6 (14.6) | 0.541 |
| 21-40 | 23 (56.2) | 20 (48.7) | 23 (56.1) | |
| 41-60 | 09 (21.9) | 9 (21.9) | 7 (17.1) | |
| > 60 | 2 (4.8) | 8 (19.5) | 5 (12.2) | |

CRP – C-reactive protein, ESR – erythrocyte sedimentation rate, TLD – tenofovir disoproxil fumarate, lamivudine, and dolutegravir, TLE – tenofovir, lamivudine, and efavirenz

were above the age group of 60 years. Around 32 (78.1%) patients were in the age group of 31-45 years who were started on TLE, and 6 (14.6%) were above the age group of 15-30 years (Table 1).

In the study, during the 1st visit, 123 (67.9%) individuals who were started on TLD had normal CRP level, and 58 (32.1%) patients had elevated CRP. At the end of the 3rd visit, 145 (80.2%) patients had normal CRP level, and only 36 (19.8%) patients had elevated CRP. During the 1st visit, 28 (68.2%) individuals who were started on TLE had normal CRP level, and 13 (31.7%) patients had elevated CRP. At the end of 3rd visit, 32 (78.1%) patients had normal CRP, and only 9 (21.9%) patients had elevated CRP. During the 1st visit, 32 (17.6%) individuals who were started on TLD had normal ESR level, and 149 (82.3%) patients had elevated ESR, out of which 25 (13.8%) had ESR > 60 mm/h. At the 3rd visit, 35 (19.3%) individuals on TLD had normal ESR, and 146 (80.7%) patients had elevated ESR, out of which 11 (6.1%) had ESR > 60 mm/h. During the 1st visit, 7 (17.1%) individuals who were started on TLE had normal ESR, and 34 (82.9%) patients had elevated ESR, out of which 2 (4.8%) had ESR > 60 mm/h. At the 3rd visit, 6 (14.6%) individuals on TLE had normal ESR level, and 35 (85.4%) patients had elevated ESR, out of which 5 (12.2%) had ESR > 60 mm/h (Table 2). During the 1st visit, 172 (95.0%) individuals who were started on TLD had normal total cholesterol level, and 9 (5.0%) patients had elevated total cholesterol. At the 3rd visit, 174 (96.1%) patients on TLD had normal total cholesterol level, and 7 (3.9%) patients had elevated total cholesterol. During

the 1st visit, 179 (98.7%) individuals who were started on TLD had normal LDL cholesterol level, and 2 (1.3%) patients had elevated LDL cholesterol. At the 3rd visit, 178 (98.4%) individuals on TLD had normal LDL cholesterol level, and 3 (1.6%) patients had elevated LDL cholesterol. During the 1st and 3rd visits, 27 (15.1%) individuals who were started on TLD had normal HDL cholesterol level, and 154 (84.1%) patients had low HDL cholesterol. During the 1st visit, 140 (77.4%) individuals who were started on TLD had normal TGs level, and 41 (22.6%) patients had borderline high TGs level. At the 3rd visit, 164 (90.7%) individuals on TLD had normal TGs level, and 17 (9.3%) patients had borderline high TGs level. Maximum patients had normal range of TGs level (Table 3).

During the 1st visit, 39 (95.2%) individuals who were started on TLE had normal total cholesterol level, and 2 (4.8%) patients had elevated total cholesterol. At the 3rd visit, 40 (97.6%) individuals on TLE had normal total cholesterol, and 1 (2.4%) patient had elevated total cholesterol. During the 1st visit, 40 (97.5%) individuals who were started on TLE had normal LDL cholesterol level, and 1 (2.5%) patient had elevated LDL cholesterol. At the 3rd visit, 38 (92.6%) individuals on TLE had normal LDL cholesterol, and 3 (7.4%) patients had elevated LDL cholesterol. During the 1st visit, 5 (12.3%) individuals who were started on TLE had normal HDL cholesterol level, and 36 (87.7%) patients had low HDL cholesterol. At the 3rd visit, 6 (14.8%) individuals on TLE had normal HDL cholesterol level, and 35 (85.2%) patients had low HDL cholesterol. During the 1st visit, 34 (82.9%) individuals who were started on TLE had normal TGs level, and 7 (17.1%) patients had borderline high TGs level.

Table 3. Comparison of lipid profiles among subjects on TLD (tenofovir disoproxil fumarate, lamivudine, and dolutegravir) during 1st, 2nd, and 3rd visits

| Variable | 1 st visit, n (%) | 2 nd visit, n (%) | 3 rd visit, n (%) | p-value |
|--|------------------------------|------------------------------|------------------------------|---------|
| Total cholesterol | | | | |
| 120-150 | 19 (10.4) | 17 (9.3) | 17 (9.3) | 0.952 |
| 151-180 | 116 (64.3) | 120 (66.5) | 126 (69.6) | |
| 181-200 | 37 (20.4) | 37 (20.4) | 31 (17.3) | |
| > 200 | 9 (4.9) | 7 (3.8) | 7 (3.8) | |
| LDL (normal range < 100 mg/dl) | | | | |
| 50-80 | 99 (54.6) | 97 (53.6) | 96 (53.1) | 0.985 |
| 81-100 | 80 (44.1) | 82 (45.3) | 82 (45.3) | |
| 101-140 | 2 (1.3) | 2 (1.1) | 3 (1.6) | |
| HDL (normal range > 60 mg/dl) | | | | |
| 30-45 | 74 (40.8) | 70 (38.6) | 69 (38.1) | 0.999 |
| 46-60 | 80 (44.1) | 84 (46.3) | 85 (46.8) | |
| > 60 | 27 (15.1) | 27 (15.1) | 27 (15.1) | |
| Triglycerides (normal range < 150 mg/dl) | | | | |
| 25-100 | 50 (27.7) | 50 (27.7) | 58 (32.2) | 0.009 |
| 101-150 | 90 (49.8) | 92 (50.8) | 106 (58.5) | |
| 151-200 | 41 (22.6) | 39 (21.5) | 17 (9.3) | |

HDL – high-density lipoprotein, LDL – low-density lipoprotein

Table 4. Comparison of lipid profiles among subjects on TLE (tenofovir, lamivudine, and efavirenz) during 1st, 2nd, and 3rd visits

| Variable | 1 st visit, n (%) | 2 nd visit, n (%) | 3 rd visit, n (%) | p-value |
|--|------------------------------|------------------------------|------------------------------|---------|
| Total cholesterol | | | | |
| 120-150 | 4 (9.7) | 6 (14.6) | 6 (14.7) | 0.920 |
| 151-180 | 30 (73.4) | 26 (63.4) | 26 (63.4) | |
| 181-200 | 5 (12.1) | 17 (17.2) | 8 (19.5) | |
| > 200 | 2 (4.8) | 2 (4.8) | 1 (2.4) | |
| LDL (normal range < 100 mg/dl) | | | | |
| 50-80 | 23 (56.1) | 20 (48.7) | 20 (48.7) | 0.832 |
| 81-100 | 17 (41.4) | 18 (43.9) | 18 (43.9) | |
| 101-140 | 1 (2.5) | 3 (7.4) | 3 (7.4) | |
| HDL (normal range > 60 mg/dl) | | | | |
| 30-45 | 12 (29.2) | 10 (24.3) | 10 (24.3) | 0.982 |
| 46-60 | 24 (58.5) | 25 (60.9) | 25 (60.9) | |
| > 60 | 5 (12.3) | 6 (14.8) | 6 (14.8) | |
| Triglycerides (normal range < 150 mg/dl) | | | | |
| 25-100 | 7 (17.1) | 5 (12.3) | 6 (14.8) | 0.519 |
| 101-150 | 27 (65.8) | 22 (53.6) | 25 (60.9) | |
| 151-200 | 7 (17.1) | 14 (34.1) | 10 (24.3) | |

HDL – high-density lipoprotein, LDL – low-density lipoprotein

At the 3rd visit, 31 (75.7%) individuals on TLE had normal TGs level, and 10 (24.3%) patients had borderline high TGs level. Maximum patients had normal range of TGs level (Table 4).

In the current study, during the 1st visit, 89 (49.2%) individuals who were started on TLD had normal CD4 count, and 92 (50.8%) patients had low CD4 count. At the 3rd visit,

Table 5. Comparison of CD4 counts among subjects during 1st, 2nd, and 3rd visits

| Variable | 1 st visit, n (%) | 2 nd visit, n (%) | 3 rd visit, n (%) | p-value |
|---|------------------------------|------------------------------|------------------------------|---------|
| CD4 count – TLD (normal range 500-1,200 cells/mm ³) | | | | |
| 100-300 | 23 (12.7) | 17 (9.3) | 11 (6.1) | 0.778 |
| 301-500 | 69 (38.1) | 67 (37.2) | 71 (39.3) | |
| 501-700 | 67 (37.1) | 75 (41.4) | 77 (42.5) | |
| 701-900 | 18 (9.9) | 18 (9.9) | 18 (9.9) | |
| > 900 | 4 (2.2) | 4 (2.2) | 4 (2.2) | |
| CD4 count – TLE (normal range 500-1,200 cells/mm ³) | | | | |
| 100-300 | 6 (14.6) | 7 (17.3) | 6 (14.6) | 0.999 |
| 301-500 | 15 (36.5) | 17 (41.4) | 17 (41.4) | |
| 501-700 | 17 (41.7) | 15 (36.5) | 16 (39.2) | |
| 701-900 | 2 (4.8) | 2 (4.8) | 2 (4.8) | |
| > 900 | 1 (2.4) | 0 (0.0) | 0 (0.0) | |

TLD – tenofovir disoproxil fumarate, lamivudine, and dolutegravir, TLE – tenofovir, lamivudine, and efavirenz

99 (54.6%) individuals on TLD had normal CD4 count, and 82 (45.4%) patients had low CD4 count. During the 1st visit, 20 (49.9%) individuals who were started on TLE had normal CD4 count, and 21 (50.1%) patients had low CD4 count. At the 3rd visit, 18 (44.0%) individuals on TLE had normal CD4 count, and 23 (56.0%) patients had low CD4 count (Table 5).

Discussion

There is outstanding development in the diagnosis of PLWHA, and with a better infrastructure for diagnosis, HIV/AIDS burden in India has been reduced drastically, with the reason being availability of more reliable population-based data [1].

Decreases in total cholesterol and HDL levels in newly diagnosed PLWHA are seen more with decreasing CD4 counts [9], which was not evident in the present study. HDL, known as a marker of disease development, shows a negative relation with TNF- α and interferon gamma (IFN- γ) [9-11]. HDL decreased in the current study, but due to limited resources, TNF- α and IFN- γ could not be performed. The study shows that lower HDL levels occur in asymptomatic PLWHA, even in the absence of other infections, which confirms previous data showing that disturbances in cholesterol metabolism precede hypertriglyceridemia in asymptomatic PLWHA [12], as HDL provides cholesterol for peripheral cells involved in the immune response [9], and ApoA1 inhibits HIV virus-induced CD4 syncytium formation [13].

Paraoxonase detoxifies biologically active lipids, and its activity decreases during acute phase response (APR) [14]. Increased lipid peroxidation occurs in PLWHA [15, 16], which induces apoptosis of T cells showing HIV-associated glutathione peroxidase deficiency caused by TNF- α and NF- κ B [17-19].

Hypertriglyceridemia in PLWHA has been shown to be related with several factors, such as severe wasting, secondary infections, and derangement of the immune system [20]. Our study had only a few patients showing TGs derangement, 17 (9.3%) cases had borderline high TGs level who were on TLD, and 10 (24.3%) patients on TLE had borderline high TGs level at 6 months follow-up. IFN- α levels are correlated with significant level of serum TGs concentrations in PLWHA. Hepatic production of VLDL, due to more lipogenesis in liver and delayed clearance mediated by a decrease in LPL, contribute to an increase in TGs [21-23]. In the current study, due to limited resources, IFN- α level was not evaluated, but derangement of TGs was found not correlating with CD4, as its improvement after 6 months of ART in many patients. No significant differences were found for CRP and ESR among the studied groups. Also, no significant correlation was observed for lipids level with inflammatory markers. It has been found that HIV promotes fractional and absolute synthesis rates of positive APRs [24].

Grunfeld *et al.* [25] reported higher plasma concentrations of CRP in a group of HIV patients compared with healthy controls. Monet *et al.* [26] reported that β_2 -microglobulin of the 3 studied positive APPs (CRP, β_2 -microglobulin, and α_1 -glycoprotein) had a higher plasma value in HIV patients. Jahoor *et al.* [24] found that the asymptomatic HIV group presented significantly increased CRP, fibrinogen, and haptoglobin levels than the control group.

Increased CRP and ESR levels were associated with disease progression, independent of CD4 lymphocyte counts. Regardless of progression to AIDS, PLWHA had significant increase in CRP and ESR over time, but in the study at 6 months, we could not find a significant increase in CRP and ESR. A declining trend was found after the start of ART, which suggest new ARTs are much more effective in stopping the progression of disease and cardiovascular risk. CRP is useful for diagnosis and monitoring in HIV-1 patients. In individuals without

intercurrent infection, its values greater than that of the general population, reflect a sustained APRs because of HIV.

Conclusions

From our study, it can be concluded that significant number of patients showed improvement in inflammatory markers, more among those with recently added TLD regimen compared with TLE, which was evident due to normalization of ESR and CRP levels in most of the patients. Lipid parameters were not significantly altered, especially HDL, and is presumed to be low in almost all patients because of its consumption by peripheral tissue sites. Possible explanation for this non-alteration of HDL may be short duration of the study; longer follow-up of our patients is needed for some conclusion statements.

Disclosures

1. Institutional review board statement: The study was approved by Mahatma Gandhi Memorial Medical College, Indore, India (approval number: EC/MGM/MAY-20/94).
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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