ORIGINAL ARTICLE

Determinants of discordant immune response in a cohort of human immunodeficiency virus-infected patients initiating antiretroviral therapy in Nigeria

Umar Abdullahi, Mufutau Muphy Oripelaye[1], Fatai Olatunde Olanrewaju[1], Olaniyi Onayemi[1], Olayinka Abimbola Olasode[1], Olumayowa Abimbola Oninla[1]

Department of Medicine, Dermatology/Infectious Disease Unit, Ahmadu Bello University Zaria, Kaduna State, [1]Department of Dermatology and Venereology, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria

ABSTRACT

Background: The introduction and wide use of highly active antiretroviral therapy (HAART) have significantly resulted in decline in morbidity and mortality from human immunodeficiency virus (HIV) infection and its related complications. These drugs can effectively induce virological suppression of the HIV-RNA replication to below the level of quantification, with eventual rise in the CD4+ cells counts. This is the therapeutic goal of using HAART in HIV-infected patients. However, some HIV-infected patients commencing HAART might have adequate virological suppression without a corresponding rise in CD4+ cells count-a phenomenon referred to as discordant immune response (DIR) or immunological nonresponse. **Objective:** The objective is to determine the factors associated with DIR among HIV-infected patients with adequate virological suppression, after initiating HAART. **Methodology:** This study was a descriptive, retrospective, cross-sectional study that analyzed data from 200 HIV-infected adults that have been on HAART for 12 months descriptive statistics were used to describe the demographic profile of the participants, and binary logistic regression was used to assess the factors predicting DIR among the studied population. **Results:** One hundred and thirty-six (68%) were female with a mean age of 40.5 ± 10.9 years. The mean baseline CD4+ cells count was 162 ± 95.9 cells/mm^3. Twelve months after HAART initiation, 64 (32%) of patients were immunological nonresponders. On multivariate analysis (logistics regression), patients initiating treatment at a higher CD4+ cells count >200 cells/mm^3 (adjusted odds ratio [AOR] 3.89; confidence interval [CI]: 1.64–9.22; $P = 0.002$), the presence of anemia (hemoglobin <11.0 g/dl) (AOR 2.58; CI: 1.11–5.98; $P = 0.027$), and hepatitis C virus (HCV) positivity (AOR 9.84; CI: 3.10–18.12; $P = 0.003$) were independently associated with the development of DIR among the studied population. **Conclusion:** DIR among the studied population was common and associated with high baseline CD4+ cells count, baseline anemia, and HCV positivity from our HIV-infected patients. Thus, there is a need for adequate evaluation and monitoring of at-risk individuals to improve clinical outcomes.

Keywords: Antiretroviral therapy, discordant, highly active antiretroviral therapy, human immunodeficiency virus

Corresponding Author: Dr. Mufutau Muphy Oripelaye, Department of Dermatology and Venereology, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria.
E-mail: mmoripe@yahoo.co.uk

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INTRODUCTION

There has been a dramatic reduction in mortality and morbidity from human immunodeficiency virus (HIV)

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and its related complications since the advent of highly active antiretroviral therapy (HAART) in the mid to late 1990s.[1] The antiretroviral drugs work by effectively suppressing HIV-RNA replication to below the level of quantification, which typically results in a significant rise in CD4$^+$ cells counts. This rise sometimes referred to as immunologic response to HAART, is central to restoration of the integrity of the immune system with eventual reduction in HIV-related morbidity and mortality.[1] Adherence to HAART for at least 6 months should lead to rapid and sustained HIV-RNA virological suppression to undetectable levels (≤400 copies/ml) and subsequently to <50 copies/ml after 12 months.[2] The "Complete" responses (bot virological and immunological) in patient on HAART, are associated with improved clinical outcomes when compared with patients with discordant responses or patients who experience neither a virologic nor immunologic response.[3] Even though there is no agreed definition of discordant immune response (DIR), it is a situation whereby there is a failure to satisfactorily increase CD4$^+$ cells count on HAART despite successful virological control.[4] This paradoxical response is referred to by various terms in the literature including DIR, poor or suboptimal immune reconstitution, incomplete immune recovery (IR) or restoration and immunological nonresponse.[4] DIR is seen in up to 20%–40% of patients on HAART.[2] This condition has been linked with significant increases in the risk of AIDS-related and non-AIDS-related mortality and morbidity, including cardiovascular, hepatic, renal diseases, and malignancies.[2,5,6] The exact pathogenesis of DIR is still not fully understood; however, it may arise either as a result of failed immune reconstitution or the excessive destruction of CD4$^+$ cells.[7] Several risk factors have been put forward to explain this paradoxical phenomenon which includes older age, male sex, poor virologic response, injection drug use as an HIV acquisition risk factor, hepatitis C virus (HCV) coinfection, and lower baseline CD4$^+$ cell count and HIV-RNA viral load.[8]

Some suggested etiopathogenic mechanisms of DIR include depletion thymic progenitor cells caused by untreated HIV infection, lymphoid tissues fibrosis, especially the gastric associated lymphoid tissues caused by the virus and chronic immune system activation.[9-11] Other factors play an important role in the occurrence of DIR especially in causing T-cell activation include microbial translocation, low-level persistent HIV viral replication within the fibrosed lymph nodes and latent co-infection such as cytomegalovirus and latent tuberculosis.[4,12]

Despite the relative high frequency of DIR among HIV patients on HAART, not much has been published in the literature regarding the prevalence and associated risk factors, especially in our setting (sub-Saharan Africa), where the high burden of HIV infection is characterized by late presentation with advanced disease, delay in HAART initiation, multiple opportunistic infections, and comorbidities such as viral hepatitis. Adequate knowledge about this phenomenon may contribute to their clinical management. This descriptive, retrospective cross-sectional study describes this phenomenon, and factors associated with DIR in a cohort of HIV-infected patients initiating HAART in Nigeria.

METHODOLOGY

Study area

The study was carried out at the Virology research clinic of Obafemi Awolowo University Teaching hospitals Complex (OAUTHC) Ile Ife. A significant number of patients seek medical treatment in this center as a first point of contact. The HIV clinic also receives patients referred to as HIV-positive following screening tests with rapid kits within and outside the hospital and also offers voluntary counseling and testing.

Study design

This was a hospital-based retrospective cross-sectional study.

Study period

The study was conducted over 3 months.

Study population

The study participants comprise of HIV-positive patients aged 18 years and older, receiving treatment and care at the virology clinic of OAUTHC.

Ethical considerations

Ethical approval was obtained from the Medical Research Ethics Committee of OAUTHC before the commencement of this research. The data collected were de-identified, and unique research identification numbers were used instead of patient's names, and patient's records were handled with strict confidentiality.

Study procedure and data collection

We retrospectively reviewed the case folders of 200 HIV-infected patients, who had nadir presuppression CD4$^+$ cells count of <350 cells/mm^3, have been on HAART for 12 months with evidence of good adherence

and has achieved plasma HIV-RNA <20 copies/ml. Data were extracted from the case folders of each participant. Information on socio-demographic characteristics (age, gender, education level, occupation status, and alcohol/cigarette use), medical history including HIV disease stage, history of tuberculosis and HAART information were extracted. Physical examination findings such as body mass index (BMI) and blood pressure were recorded. Laboratory parameters such as hepatitis B and C serology results, hemoglobin (Hb) values, and $CD4^+$ cells count were recorded at HAART initiation (i.e., baseline) and at 12 months' post-HAART initiation as the case may be. In addition, viral load results at 12 months after ART initiation were recorded.

For this study, the following outcomes definitions were adopted; virologic suppression was defined as a viral load value of <20 copies/ml at 12 months after HAART initiation. Immune reconstitution was defined as an absolute increase in the $CD4^+$ cells count value of at least 100 cells/mm^3 at 12 months after ART initiation.[7] This is because the expected rate of $CD4^+$ cells count increase following HAART initiation is 20–30 cells per month in the first 6 months and then 5–10 cells per month between 6 months and 24 months.[4] DIR was defined as a rise of $CD4^+$ cells count of <100 cells/mm^3 at 12 months' following commencement HAART, in patients who have achieved virological suppression.[4] This definition of DIR applies to those commencing HAART with $CD4^+$ cells count <350 cells/mm^3 so as to avoid overdiagnosis of DIR in a population starting with higher CD4 counts.[4] Viral load results obtained at 12 months after HAART initiation was used, in accordance with the 6 and 12 months' follow-up recommendation of the national HIV treatment guidelines, for CD4 cells count and viral load check after HAART initiation.

Data management and data analysis

Study group characteristics were described using descriptive statistics, means and standard deviations for continuous variables when normally distributed, median for skewed data, and frequencies for categorical variables. Means were compared using the student *t*-test for normally distributed data and Chi-square test was used for categorical variables. Associations between the occurrence of DIR and possible risk factors were assessed using logistic regression, adjusted odds ratios (AORs) at 95% confidence intervals (CIs) to express the measure of association. Factors that were significant at $P \leq 0.25$ in the bivariate analysis were considered for inclusion in the logistic regression model.

RESULTS

Baseline characteristics

The socio-demographic characteristics of the study population are shown in Table 1. Among the studied population, 68% ($n = 136$) were female with a mean age of 40.5 ± 10.9 years. The mean baseline $CD4^+$ cells count of the studied population was 162 ± 95.9 cells/mm^3,

Table 1: Demographic characteristics of the study population

Patients' characteristics	Total (*n*=200), *n* (%)	Immunologic response	
		Nonresponders group (*n*=64; 32%)	Responders group (*n*=136; 68%)
Gender			
Males	64 (32)	26 (40.6)	38 (27.9)
Females	136 (68)	38 (59.4)	98 (72.1)
Mean age	40.5±10.9	40.8±9.9	39.7±10.9
Occupation			
Salary employed	32 (16)	13 (20.3)	19 (14)
Self employed	151 (75.5)	43 (67.2)	108 (79.4)
Unemployed	17 (8.5)	8 (12.5)	9 (6.6)
Smoking	12 (6)	2 (3.1)	10 (7.4)
Alcohol intake	48 (24)	19 (29.7)	29 (21.3)
Education level			
Primary	66 (33)	19 (29.7)	47 (34.6)
Secondary	43 (21.5)	18 (28.1)	25 (18.4)
Tertiary	37 (18.5)	14 (21.9)	23 (16.9)
No formal education	54 (27)	13 (20.3)	41 (30.1)
Marital status			
Married	140 (70)	44 (68.8)	96 (70.6)
Single	28 (14)	13 (20.3)	15 (11)
Divorced	8 (4)	2 (3.1)	6 (4.4)
Widowed	16 (8)	3 (4.7)	13 (9.6)
Separated	8 (4)	2 (3.1)	6 (4.4)

median baseline weight was 53.3 kg, 65.5% (n = 131) of the patients were anemic with a mean baseline Hb level of 10.3 ± 1.7 g/dl and 55% (n = 110) of the studied population were commenced on tenofovir-lamivudine-efavirenz/nevirapine based HAART regimen. Twelve months after HAART initiation, 32% (n = 64) of patients are immunological nonresponders (discordant immune responders), compared to 68% (n = 136) who had an optimal immune response. The mean CD4$^+$ cells count of the immunological nonresponders group at HAART initiation was significantly higher at 187 ± 95.8 cells/mm^3 compared to that of the optimal immune responders group with 150 ± 93.9 cells/mm^3 (P = 0.009), and the mean increment in the CD4$^+$ cells count at 12 months for the immunological nonresponders group was significantly lower at 46 ± 28.5 cells/mm^3 compare to the optimal immune responders group which was 251 ± 134.4 cells/mm^3 (P = 0.0001).

Predictors of discordant immune response in the studied population

The baseline characteristics of the immunological nonresponders and that of the immunological responders were compared using multivariate analysis and binary logistic regression, as shown in Table 2. Patients initiating treatment at a higher CD4$^+$ cells count >200 cells/mm^3 (AOR 3.89,

Table 2: Factors associated with immunological nonresponse with logistic regressions

Patients' characteristics	Studied population (n=200), n (%)	Immunologic response		P* (bivariate analysis)	AOR (95% CI)	P (logistic regression)
		Nonresponders group (n=64; 32%)	Responders group (n=136; 68%)			
Age (years), mean±SD	40.5±10.9	40.8±9.9	39.7±10.9	0.480		
Age groups (years)						
Young adults (18-35)	82 (41.0)	22 (34.4)	60 (44.1)	0.350		
Mid adults (36-55)	104 (52.0)	36 (56.2)	68 (50.0)			
Older adults (>55)	14 (7.0)	6 (9.4)	8 (5.9)			
Gender						
Males	64 (32)	26 (40.6)	38 (27.9)	0.070	1.15 (0.44-3.05)	0.780
Females	136 (68)	38 (59.4)	98 (72.1)			
WHO clinical stage						
Early disease (1 and 2)	105 (52.5)	28 (43.8)	77 (56.6)	0.097	0.72 (0.32-1.63)	0.424
Advanced disease (3 and 4)	95 (47.5)	36 (56.2)	59 (43.4)		1	
HAART combination						
AZT + 3TC + NVP/EFV	86 (43)	28 (43.8)	58 (42.6)	0.210		
TDF + 3TC + EFV/NVP	110 (55)	36 (56.2)	74 (54.4)			
ABC + 3TC + EFV/NVP	4 (2)		4 (2.9)			
Positive history of tuberculosis	26 (13)	13 (20.3)	13 (9.6)	0.030	1.82 (0.59-5.57)	0.295
Mean baseline CD4 cells count (cells/mm^3)	162±95.9	187±95.8	150±93.9	0.009		
Mean CD4 cells count increase at 12 months	186±147	46.9±28.5	251±134.4	0.0001		
Baseline CD4 cell count (cells/mm^3)						
CD4+ cells <200	127 (63.5)	35 (54.7)	92 (67.6)	0.070	1	0.002
CD4+ cells >200	73 (36.5)	29 (45.3)	44 (32.4)		3.89 (1.64-9.22)	
Mean baseline hemoglobin±SD	10.3±1.7	10.4±1.6	10.2±1.7	0.420		
Hb level (g/dl)						
Normal (≥11)	69 (34.5)	20 (31.2)	49 (36.0)	0.047	1	0.027
Anemic (<11)	131 (65.5)	44 (68.8)	87 (64.0)		2.58 (1.11-5.98)	
Mean baseline weight (kg)	56.4±12.5	56.7±12.5	54.1±12.6	0.680		
BMI						
Normal (18.50-24.99)	64 (32)	21 (32.8)	43 (31.6)	0.390		
Underweight (<18.50)	94 (47)	29 (45.3)	65 (47.8)			
Overweight (25.00-29.99)	37 (18.5)	14 (21.9)	23 (16.9)			
Obese (≥30.00)	5 (2.5)		5 (2.5)			
Positive HCV	15 (7.5)	11 (17.2)	4 (2.9)	0.001	3.9 (3.10-18.12)	0.034
Positive HBV	20 (10)	8 (12.5)	12 (8.8)	0.420		

AQ6,8 *P: P value of bivariate analysis; P: P value for logistic regression, all *P values for bivariate analysis are gotten from Chi-square test except otherwise stated for P values with superscript, #Gotten from students t-test comparing means. CI: Confidence interval; SD: Standard deviation; 3TC: Lamivudine; NVP: Nevirapine; EFV: Efavirenz; AOR: Adjusted odd ratio; BMI: Body mass index; HCV: Hepatitis C virus; HBV: Hepatitis B virus; Hb: Hemoglobin; HAART: Highly active antiretroviral therapy; AZT: ???

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CI; 1.64–9.22, $P = 0.002$), and the presence of anemia (Hb <11.0 g/dl), (AOR 2.58, CI; 1.11–5.98, $P = 0.027$), were significantly associated with immunological nonresponse after adjusting for baseline education level, the WHO clinical stage, and HAART regimen. HCV positivity (AOR 9.84, CI; 3.10–18.12, $P = 0.003$) was also independently associated with the development of immunological nonresponse among the studied population. Other factors such as gender, HBV positivity, HAART type, and BMI were not significant predictors of immunological nonresponse in this study.

DISCUSSION

DIR in HIV-positive patients still remains a common phenomenon affecting up to 20%–40% of patients on HAART, which has been linked to increase morbidity and mortality in the affected patients.[2] The observed proportion of HIV-infected patients from this study having DIR following HAART falls within the above range. Factors that were found to predict DIR from this study include initiating HAART at a higher $CD4^+$ cells count >200 cells/mm^3, initiating HAART with mild anemia and HCV coinfection. However, this study did not observe any significant associations between DIR and age, gender, BMI, or HAART regimen, even though these were previously reported as risk factors by other studies.[7,13]

The findings of an association between commencing HAART at a higher baseline $CD4^+$ cells count >200 cells/mm^3 and DIR from this study was similar to reports from South Africa, Uganda, and some other western countries.[4,7,13-16] This can be explained by the nonlinear nature of $CD4^+$ cells count increase following HAART initiation across the different baseline $CD4^+$ cells count strata, in that commencing HAART at higher CD4 cell counts limits the scope for further rise in the $CD4^+$ cells.[7,14,16] Furthermore, patients with baseline $CD4^+$ cells counts <50 cells/mm^3 tend to have a steeper gradient of $CD4^+$ cells count increase compare to patients with baseline $CD4^+$ cells counts between 50 and 199 cells/mm^3 as was reported by large HIV treatment programs in South Africa.[17] Nakanjako *et al*.[13] in a study that described patterns of suboptimal (SO-IR) and associated HIV-related-illnesses during the first 5 years' following first-line antiretroviral therapy (HAART) initiation across seven HIV treatment sites in East Africa, reported SO-IR in 40% of adults initiated on HARART with $CD4^+$ cells counts <350 cells/ml after 5 years. Factors that were reported to predict SO-IR in that study were older age, male sex, and anemia.[13] They also found that patients with an advanced stage of HIV disease (WHO stage three and four, and baseline $CD4^+$ cells counts <100 cells/mm^3) were less likely to have SO-IR.[13]

However, it is contrary to several studies conducted in resource-rich settings that have reported low baseline $CD4^+$ cells count at initiation of HAART to be associated with DIR.[18-21]

This study also found that anemia at the initiation of HAART is associated with DIR, a finding that was reported by similar studies.[7,14,20] HIV-related anemia is often anemia of chronic illness which can be caused by many factors. The mechanisms of cytokine-induced bone marrow stem cell suppression caused by continuous immune system activation, and membrane changes in both erythrocytes and $CD4^+$ T-lymphocytes could explain the association between anemia when starting HAART and a subsequent DIR.[22] Some studies have also shown that anemia in HIV-infected patients is associated with $CD4^+$ cells depletion and progression to AIDS, and is one of the strongest predictors of HIV mortality and poor response to HAART.[23,24]

Finally, DIR was also found to be associated with HCV co-infection in HIV patients from our study. This is similar to the findings in studies conducted in developed countries to determine the effects of $CD4^+$ cells recovery in patients with HIV/HCV coinfection following initiation of HAART, where it was found that presence of HCV coinfection significantly affects $CD4^+$ cells recovery without any effect on the viral load.[25,26] HCV/HIV coinfection is known to result in a higher level of immune activation.[27] This persistent immune activation makes the $CD4^+$ cells to be trapped in secondary lymphoid organs, as well as die by apoptosis.[28] This has been linked with incomplete $CD4^+$ cells regeneration in HIV/HCV coinfection following initiation of HAART.

Limitations of the study

It is possible that some of the observed risk factors may be absent, as well as reduced percentage of the immune discordant subjects, if the outcomes were assessed after a longer period on HAART like 2–5 years. The multicenter study would have given a better picture of the factors associated with DIR in Nigeria.

CONCLUSION

The findings from this study suggest that 32% of patients initiating HAART in Nigeria have a DIR after 12 months on HAART, despite adequate virological suppression. Factors that were found to be significantly associated with DIR in these patients were baseline $CD4^+$ cells count >200 cells/mm^3, anemia, and HCV coinfection. While further multicenter studies are required, to involve a large cohort of HIV-infected patients from different parts of the country to examine these associations, these data may assist in the early identification of patients that are likely to have DIRs on HAART.

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Conflicts of interest

There are no conflicts of interest.

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