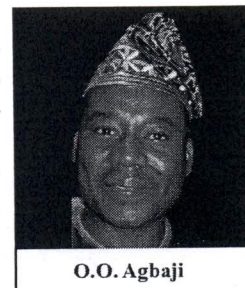


Treatment Discontinuation in Adult HIV-Infected Patients on First-Line Antiretroviral Therapy in Nigeria

O.O. Agbaji¹, I.O. Abah^{*2}, K.D. Falang³, A.O. Ebonyi⁴, J. Musa⁵, P. Ugoagwu⁶, P.A. Agaba⁷, A.S. Sagay⁵, T. Jolayemi⁸, P. Okonkwo⁸, J.A. Idoko⁹ and Phyllis J. Kanki¹⁰

¹Department of Medicine, University of Jos/Jos University Teaching Hospital, Jos, Nigeria; ²Pharmacy Department, Jos University Teaching Hospital, Jos, Nigeria; ³Department of Pharmacology, Faculty of Pharmaceutical Sciences, University of Jos, Nigeria; ⁴Department of Paediatrics, University of Jos/Jos University Teaching Hospital, Jos, Nigeria; ⁵Department of Obstetrics and Gynaecology, University of Jos/Jos University Teaching Hospital, Jos, Nigeria; ⁶Jos University Teaching Hospital, AIDS Prevention Initiative in Nigeria (APIN) Ltd./Gte.-Supported HIV Centre, Jos, Nigeria; ⁷Department of Family Medicine, University of Jos/Jos University Teaching Hospital, Jos, Nigeria; ⁸AIDS Prevention Initiative in Nigeria (APIN) Ltd./Gte., Abuja, Nigeria; ⁹National Agency for the control of AIDS (NACA), Abuja, Nigeria; ¹⁰Harvard School of Public Health, Boston, MA, USA



O.O. Agbaji

Abstract: *Background:* Retention in care and treatment services is critical to health outcomes of individuals diagnosed and living with HIV. We evaluated the incidence of and risk factors for treatment discontinuation (TD) in a large adult HIV population on ART in Nigeria.

Method: A retrospective cohort study of adult HIV patients initiated on first-line ART between 2004 and 2011 at the Jos University Teaching Hospital (JUTH) in Nigeria. Follow up information of participants was retrieved from various sources (patient visit database, pharmacy data and patients charts) up to the end of 2012. The primary study endpoint was TD, defined as discontinuation of ART for any reason, including death or loss to follow-up (lack of pharmacy pick-up for periods ≥ 12 months). The Incidence and hazard for TD were estimated by Kaplan-Meier and Cox proportional regression analysis, respectively.

Result: Overall, 3,362 (28%) patients discontinued treatment during 49,436 person-years (py) of follow-up (incidence rate (IR) 6.8 TD per 100 py). The hazard of treatment discontinuation decreased with increasing age (adjusted hazard ratio (aHR) 0.99; 95% CI 0.98 - 0.99). Other independent risk factors for treatment discontinuation were: being unmarried (aHR 1.24; 95% CI: 1.12-1.38), having primary or secondary level of education as compared to tertiary level education (aHR 1.24; 95% CI: 1.12-1.40) and average percent adherence to drug refill visits $< 95\%$ (adjusted hazard ratio (aHR) 2.13; 95% CI: 1.9-2.40). Compared to tenofovir, greater hazard of TD was noted in patients initiated on ART containing didanosine (aHR) 1.73; 95% CI: 1.03-2.91), but lower in those initiated on zidovudine containing regimen (aHR 0.77; 95% CI: 0.69-0.86).

Conclusion: Long-term treatment discontinuation rate in this study was comparable to estimates in resource-rich countries. Younger patients, as well as patients with lower educational levels and those with poor adherence had significant hazards for treatment discontinuation and should be the target of interventions to reduce treatment discontinuation and improve retention, especially within the first year of ART.

Keywords: ART, HIV, Loss to follow-up, Nigeria, treatment discontinuation.

INTRODUCTION

Global efforts in scaling up antiretroviral therapy (ART) services have resulted in a dramatic increase in the number of people accessing treatment in sub-Saharan Africa (SSA), with about 7.5 million people on treatment by 2012 [1]. Retention in care and treatment services is critical to health outcomes of individuals diagnosed and living with HIV [2].

The benefits of ART are well documented, including reduction in morbidity and mortality, improved life

expectancy, and reduction in HIV transmission [3-6]. Once life-long ART is initiated, a sustained high level of adherence is required to maximize the life-extending benefits of ART [7, 8]. Upon interruption for any reason, the benefits of ART are rapidly reversed, resulting in poorer health outcomes, increased HIV transmission, and emergence of drug resistance, with consequent treatment failure and need for more expensive and difficult-to-implement second-line regimens [9, 10]. Discontinuation of treatment may constitute wastage of scarce treatment resources and negates much of the benefit sought by implementing treatment programs.

Discontinuation of ART or attrition from antiretroviral treatment programs may be attributed to different causes

*Address correspondence to this author at the Pharmacy Department, Jos University Teaching Hospital, Jos, Nigeria; Tel: +234 803 703 5932; E-mail: isaacabah@gmail.com

including: death of the patient, "loss to follow-up"; a general category for patients who miss scheduled clinic appointments or medication pickups for a specified period of time, stopping antiretroviral medication while remaining in care, and transfer to other facilities to continue on ART [11].

The magnitude and determinants of treatment discontinuation varies substantially across programs and settings. Understanding the magnitude of the problem can help programs to evaluate the effectiveness of ART services and identify opportunities for improvement. Retention on ART potentially takes on an even more important role in Africa than in industrialized settings as the vast majority of HIV-infected people live in SSA where there has been a rapid scaling up of ART services over the past decade [1].

This study assessed the incidence of and hazard for treatment discontinuation in a large adult HIV cohort receiving ART in Jos, Nigeria.

METHOD

Study Design

A retrospective cohort study using one of the largest clinical HIV treatment databases in Nigeria, which included demographic, clinical, and laboratory data on over 14,000 patients initiated on ART collected as part of routine HIV care. Patients enrolled on ART between 2004 and 2011, were considered eligible for this study. Follow-up was until December 31, 2012 to ensure at least 1-year of follow-up time for evaluation. ART experienced patients and those initiated on triple nucleos(t)ide reverse transcriptase (NRTI) ART were excluded from the analysis. The clinical protocol and use of clinical data for research was approved by the ethical committee at JUTH and the institutional review board (IRB) at Harvard School of Public Health (HSPH), Boston, USA. All patients included in the study provided written informed consent for the use of their data for research.

Setting and Study Population

The comprehensive HIV treatment and support program at JUTH, located in North Central Nigeria started in 2002 as part of the Government of Nigeria (GoN) ART initiative. However, in 2004, the collaboration between AIDS Prevention Initiative in Nigeria (APIN) Ltd./Gte., HSPH, the University of Jos and JUTH, with support from the United States President's Emergency Plan for AIDS Relief (PEPFAR) grant, led to rapid scale-up of ART services. The JUTH HIV clinic provides comprehensive HIV care services for the city of Jos and serves as a referral centre for health facilities in Plateau State and other states in the region.

Patient's Eligibility and Standard of Care

Patients included in the study were HIV-1 infected, treatment naive, adults (15 years and above), initiated on first-line non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART (an NNRTI plus two NRTIs) between January 2004 and December 2011. The NNRTIs included efavirenz (EFV) and nevirapine (NVP), and NRTIs included abacavir (ABC), zidovudine (AZT), stavudine (d4T), tenofovir (TDF) and didanosine (DDI). Data were extracted

from an electronic database (FileMaker Pro, FileMaker, Inc. USA) utilized in the clinic for patient care. ART dispensing occurred monthly and at scheduled clinical visits, and pharmacy pick-up data were documented in the pharmacy database developed for this purpose. Adherence was determined using pharmacy dispensing records over the duration of ARV therapy for each patient. Drug refill adherence which had been previously described [12] was calculated as the total number of days behind schedule for drug refill divided by total number of days the patient was assumed to be exposed to ART given the dispensed number of pills multiplied by 100. Patient tracking was well established in the study setting and employs strategies, such as home visits, telephone calls and support groups.

Study End Points

The primary study endpoint was treatment discontinuation, defined as discontinuation of ART for any reason, including death, loss to follow-up; lack of pharmacy pick-up for periods ≥ 12 months or no pharmacy pick-up in the calendar year 2012 with efforts at tracking being done, and self-withdrawal (SW) from ART. Transfer to another ART facility was not regarded as treatment discontinuation; patients who transferred were assumed to still be in care.

Statistical Analysis

All of the analyses were performed using SPSS for windows version 20 (IBM Corp, Armonk, New York, USA). Descriptive analyses included median [interquartile range (IQR)] for continuous variables, and frequencies and proportions for categorical variables. Bi-variate associations of each independent variable with treatment discontinuation were examined using the Pearson's chi-squared test. The medians and interquartile ranges of continuous variables were compared using the Mann Whitney U-test. All tests were two-sided and a p-value of 0.05 was considered significant.

Kaplan-Meier survival analysis was performed using months as the time unit in order to assess the probability of treatment discontinuation among all patients. Observation commenced at first ARV pick-up and observations were censored at the last follow-up date (date of last ARV pick-up or at transfer out to other ART facilities) or at the end of the observation period, which was pre-defined as December 31, 2012. Total time of observation contributed by each patient was summed to obtain total person-years of observation. Variables associated with treatment discontinuation in bi-variate analysis ($p < 0.1$) were included in the Cox regression analysis to adjust for factors associated with treatment discontinuation. To evaluate the contribution of cumulative adherence to treatment discontinuation; given the different time exposure to ART, the multivariate Cox analysis for predictors of treatment discontinuation was performed using separate models with or without the adherence covariate.

RESULTS

A total of 14,040 adults were enrolled on ART within the study period. Of these patients, a total of 2027 patients consisting of 1820 ART experienced at enrollment and 207

initiated on triple nucleoside reverse transcriptase ART were excluded from the analysis. In all 12,013 eligible patients, with median (IQR) duration on ART of 50 (17-78) months were analyzed (Fig. 1). The patients contributed a total of 49,436 person-years (py) of follow-up. Table 1 summarizes patient demographics, and baseline clinical characteristics. The study population was made up of mostly (66%) females, had a median (IQR) age and CD4 cell count of 35 (30-42) years and 145 (72-241) cells/mm³, respectively, at ART initiation.

Treatment Discontinuation

A total of 3362 patients out of 12013 (28.1%) discontinued treatment [incidence rate (IR) 6.8 treatment discontinuations per 100 person-years (py)]. Treatment discontinuation occurred after a median (IQR) of 12 (4-27) months post ART initiation. The cumulative probability of treatment discontinuation is shown in Fig. (2). A total of 1674 patients discontinued treatment within the first year (50% of total discontinuation), giving the first year crude cumulative incidence of 14% for treatment discontinuation. Incidence of treatment discontinuation showed a steep increase within the first two years of ART initiation compared to subsequent years.

Overall, 25.3% (n= 3038) patients were loss to follow-up (LTFU) (Incidence Rate (IR) 6.1 LTFU per 100 py). LTFU accounted for 90% of the total treatment attrition, while 294

(2.4%) deaths were reported, contributing 8.7% attrition (IR 0.6 deaths per 100 py), and 0.2% (n=33) self-withdrew (SW) from treatment (IR 0.06 SW per 100 py). A total of 1590 (13.2%) patients were transferred to other ART facilities (IR 3.2 transfers per 100 py).

Predictors of Treatment Discontinuation

A bi-variate analysis to evaluate the relationship between baseline demographic and clinical characteristics (Table 1) showed that patients who discontinued treatment had lower median (IQR) age compared to those retained on treatment [34 (29-41) versus 35 (30-42) years, ($p=0.03$)]. Other factors significantly associated with treatment discontinuation were sex, level of education, marital status, and ART regimen. Patients who initiated treatment between June 2004 and December 2005 had a significantly higher retention on ART (72%) compared to those who initiated treatment between 2006 and 2007 (66 and 68% respectively). However a marked improvement in retention was observed from year 2008 onwards, with retention rate up to 92%. Additionally, we found that initial ART regimen was significantly associated with treatment discontinuation. It was higher in patient initiated on EFV compared to NVP ($P= 0.001$), and lowest in AZT containing regimen compared to ABC, d4T, ddi and TDF ($P=0.001$). After adjusting for confounding variables in the Cox regression analysis (Table 3); unmarried patients had about 24% increased hazard of discontinuing

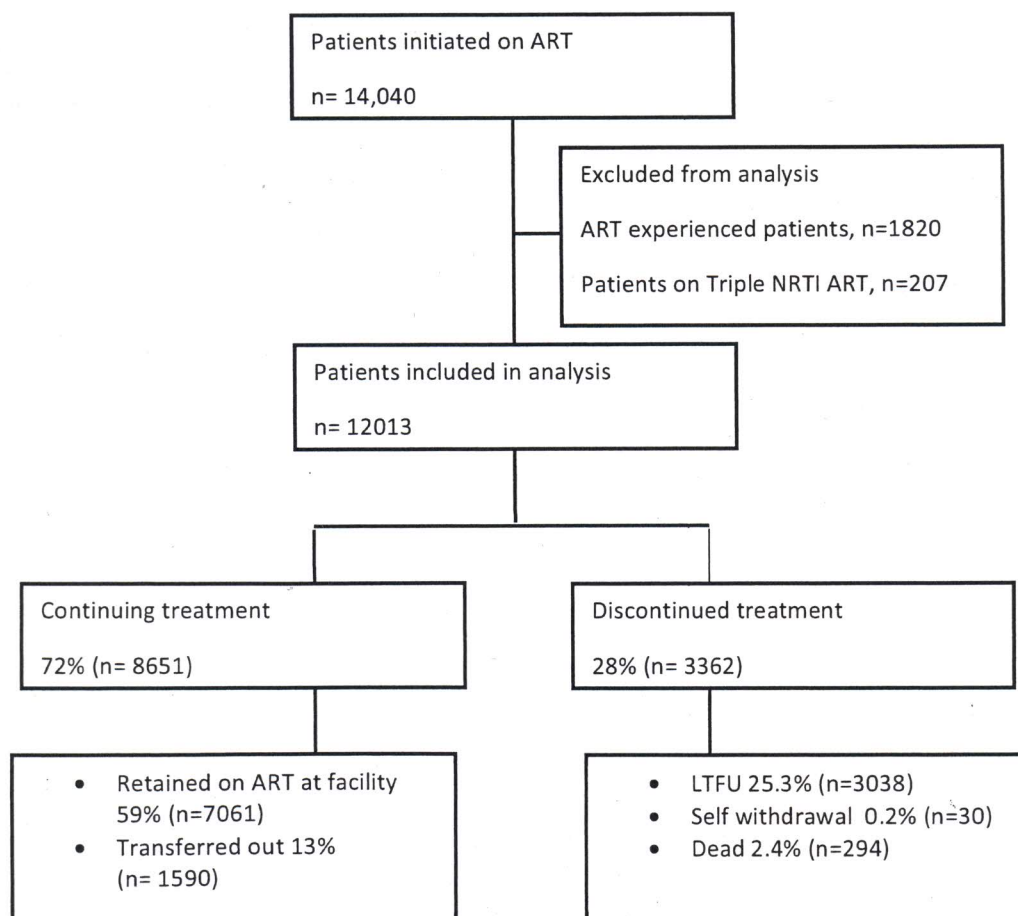


Fig. (1). Disposition of 14,040 patients initiated on ART in Jos University Teaching Hospital, June 2004 to December 2011.

Table 1. Baseline demographic and clinical characteristics of patients on ART in Jos and bi-variate association with treatment discontinuation.

Characteristics	All Patients	Retained on ART	Discontinued ART	P-Value
N (%)	12013	8651 (72)	3362 (28)	
Time in months on ART, median (IQR)	50 (19 - 78)	64 (39 - 85)	12 (4 - 27)	
Age in years, median (IQR)	35 (30 - 42)	35 (30 - 42)	34 (29 - 41)	0.027
Sex, n (%)				
Male	4008 (33.4)	2772 (69.2)	1236 (30.8)	<0.001
Female	8005 (66.)	5879 (73.4)	2126 (26.6)	
Education, n (%)				
Primary / NFE	4123 (35.2)	2874 (69.6)	125 (30.4)	<0.001
Secondary	3589 (30.6)	2573 (71.7)	1016 (28.3)	
Tertiary	4019 (34.2)	3000 (74.6)	1019 (25.4)	
Missing data	277			
Marital status, n (%)				
Married	6454 (55)	4786 (74.2)	1668 (25.8)	<0.001
Single	2342 (20)	1603 (68.4)	739 (31.6)	
Divorced/separated	956 (8.1)	643 (67.3)	313 (32.7)	
Widowed	1984 (16.9)	1415 (72)	569 (28.7)	
Missing data	277			
Employment status, n (%)				
Employed	8648 (72)	6237 (72.1)	2411 (27.9)	0.67
Unemployed	3365 (28)	2414 (71.7)	951 (28.3)	
Missing data	277			
HIV transmission risk, n (%)				
Heterosexual	11179 (96)	8048 (72)	3131 (28)	0.5
Transfusion	312 (2.7)	224 (71.8)	88 (28.2)	
Others	148 (1.3)	113 (1)	35 (23.6)	
Missing data	374			
HBV status at baseline, n (%)				
Negative	8269 (79.4)	5974 (72.2)	2295 (27.8)	0.21
Positive	2146 (20.6)	1521 (70.9)	625 (29.1)	
Missing data	1598			
WHO disease stage, n (%)				
1	3759 (35)	2738 (72.8)	1021 (27.2)	0.142
2	3367 (31.4)	2377 (70.6)	990 (29.4)	
3	2923 (27.2)	2110 (72.2)	813 (27.8)	
4	691 (6.4)	508 (73.5)	183 (26.5)	
Missing data	1273			
CD4 cell count, cells/mm³, n (%)				
≤50	2037 (17.1)	1433 (70.3)	604 (29.7)	0.07
51 – 100	2159 (18.1)	1550 (71.8)	609 (28.2)	
101 – 200	3677 (30.9)	2702 (73.5)	975 (26.5)	
>200	4027 (33.8)	2885 (71.6)	1142 (28.4)	
Missing data	113			

(Table 1) contd.....

Characteristics	All Patients	Retained on ART	Discontinued ART	P-Value
Viral load, copies/mL, n (%)				
<1000	842 (14.2)	672 (79.8)	170 (20.2)	0.001
1000 – 9 999	1044 (17.6)	757 (72.5)	287 (27.5)	
10 000 - 99 999	2207 (37.1)	1659 (75.2)	548 (24.8)	
≥100 000	1851 (31.1)	1363 (73.6)	488 (26.4)	
Missing data	6069			
Year of ART initiation, n (%)				
June 2004 - Dec 2005	2953 (24.5)	2110 (71.5)	843 (28.5)	<0.001
2006	2562 (21.3)	1696 (66.2)	866 (33.8)	
2007	2055 (17.1)	1393 (67.8)	662 (32.2)	
2008	1793 (14.9)	1317 (73.5)	476 (26.5)	
2009	1130 (9.4)	830 (73.5)	300 (26.5)	
2010	747 (6.2)	591 (79.1)	156 (20.9)	
2011	773 (6.4)	714 (92.4)	59 (7.6)	
NNRTI backbone at ART initiation, n (%)				
efavirenz	2459 (20.5)	1702 (69.2)	757 (30.8)	0.001
nevirapine	9554 (79.5)	6949 (72.7)	2605 (27.3)	
NRTI backbone at ART initiation*, n (%)				
Abacavir + 3TC	268 (2.3)	180 (67.2)	88 (32.8)	<0.001
Zidovudine + 3TC	5652 (47.5)	4187 (74.1)	1465 (25.9)	
Stavudine + 3TC	1978 (16.6)	1424 (72)	554 (28)	
Didanosine + 3TC	237 (2)	134 (56.5)	103 (43.5)	
tenofovir+ 3TC	3758 (31.6)	2644 (70.4)	1114 (29.6)	

Missing data were excluded from the analysis. Abbreviations: ART: antiretroviral therapy, IQR: Interquartile range, NFE: No formal education, TB: tuberculosis, HBV: hepatitis B virus, WHO: World Health Organization, NNRTI: nucleoside reverse transcriptase inhibitor, NRTI: nucleos(t)ide reverse transcriptase inhibitor, 3TC: lamivudine, * 120 patients on abacavir/zidovudine NRTI excluded.

treatment compared to the married. Similarly, compared to those with tertiary education, patients with primary or no formal education, and those with secondary education had 24% higher hazard of treatment discontinuation. The hazard of treatment discontinuation decreased by 1% with every year increase in age. Compared to tenofovir, greater hazard of treatment discontinuation was noted in patients initiated on ART containing didanosine (aHR) 1.73; 95% CI: 1.03-2.91), but lower in those initiated on zidovudine containing regimen (aHR) 0.77; 95% CI: 0.69-0.86).

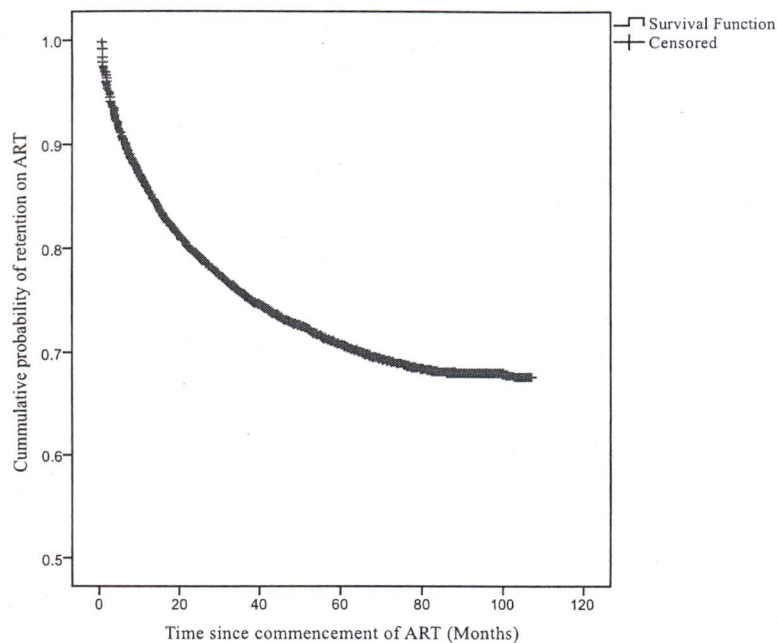
Adherence and Treatment Discontinuation

Retention on ART increased proportionately with increased adherence to drug refill visits for the entire duration of ART. However the greatest difference was observed at adherence levels ≥95% (Fig. 3). When adherence was included in the final multivariate Cox regression model, there was a 2-fold increase in the hazard of treatment discontinuation in patients' with <95% adherence to pharmacy refill visits compared with those with ≥ 95% adherence.

DISCUSSION

The purpose of this study was to estimate the incidence of and risk factors for treatment discontinuation to ART in our adult HIV treatment program. During the 8.5-year study period about 72% of our initial cohort were retained on ART, suggesting high patient retention in ART programs in our setting. Age, marital status, education, NRTI backbone and adherence to pharmacy drug refill were significant predictors of treatment discontinuation in our setting.

Our analysis showed a one and two years treatment discontinuation incidence of 14% and 20% respectively comparable to that reported in US cohorts [13-16], and lower than percentages in other cohorts in SSA where on average of up to 40% discontinuation from treatment have been reported after two years of treatment initiation [17]. Interestingly, over half of the treatment discontinuation in this study occurred within the first year of ART, and by the third year up to 90% of the treatment discontinuation had accrued. Our finding is suggestive of improved retention on ART over time. This finding corroborates with a recent study by Meloni *et al.* [18], which reported that the majority of loss occurs within the first 12–18 months of treatment in the



Time (months)	12	24	36	48	60	72	84	96
Cumulative probability of TD*	0.14	0.20	0.25	0.27	0.29	0.31	0.32	0.32
Number of events	1674	2394	2810	3053	3229	3320	3359	3362
Number remaining	9997	8510	7285	6251	4902	3608	2402	1028
Cumulative % of total TD*	49.79	71.21	83.58	90.81	96.04	98.75	99.91	100

*TD, treatment discontinuation

Fig. (2). Kaplan-Meier estimates of time to treatment discontinuation of patients (n=12013) on first-line ART in Jos, Nigeria.

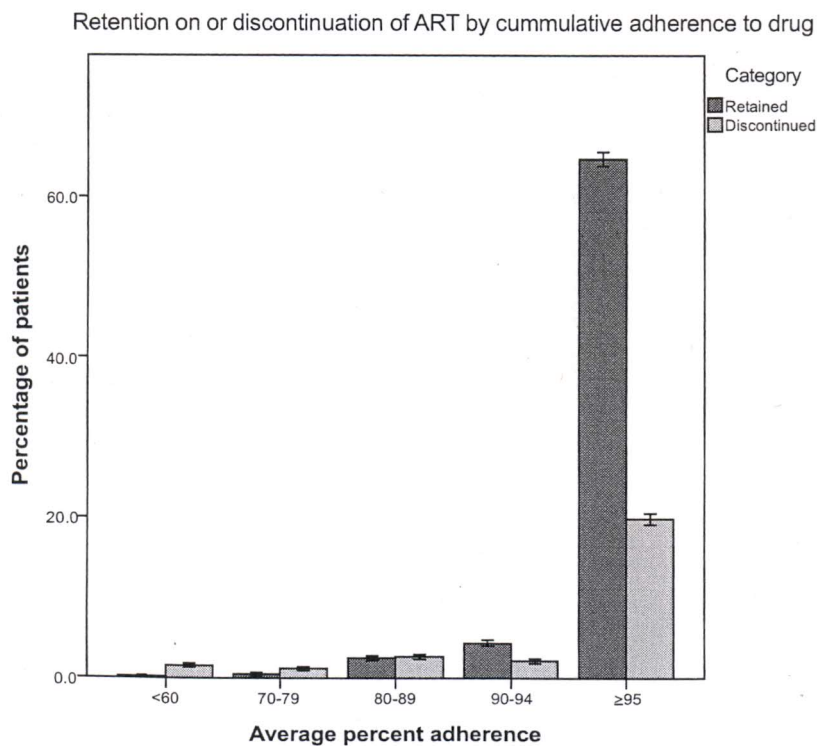


Fig. (3). Association between cumulative percent adherence to drug refill and retention on or discontinuation of ART.

Table 3. Multivariate Cox regression analysis of hazards for treatment discontinuation in patients on first-line ART in Jos, Nigeria (n=12,013).

Variable	Unadjusted Cox Analysis			Adjusted Cox Model A			Adjusted Cox model B		
	HR	95% CI	p Value	aHR	95% CI	p Value	aHR	95% CI	p Value
Sex									
Male	1.18	1.10-1.26	<0.001	1.16	1.00-1.35	0.06	1.12	0.96-1.30	0.15
Female	Ref			Ref			Ref		
Age, years	0.99	0.99-1.0	0.09	.990	0.98-0.99	0.01	.99	0.98-0.99	0.02
Marital status									
Unmarried	1.22	1.13-1.30	<0.001	1.28	1.16-1.42	<0.001	1.24	1.12-1.38	<0.001
Married	Ref			Ref			Ref		
Highest Education									
Primary/Secondary	1.23	1.14-1.32	<0.001	1.30	1.16-1.46	<0.001	1.24	1.12-1.40	<0.001
Tertiary	Ref			Ref			Ref		
Viral load, copies/mL									
<1000	0.72	0.81-0.86	<0.001	0.76	0.64-0.92	<0.001	.77	0.64-0.92	<0.001
1000 – 9 999	1.03	0.89-1.20	0.66	1.08	0.93-1.26	0.32	1.10	0.95-1.28	0.21
10 000 - 99 999	0.94	0.83-1.06	0.31	1.00	0.88-1.13	0.98	1.02	0.90-1.15	0.77
≥100 000	Ref			Ref			Ref		
NNRTI backbone									
Nevirapine	0.79	0.73-0.86	<0.001	0.86	0.73-1.01	0.071	0.89	0.76-1.05	0.18
Efavirenz	Ref			Ref			Ref		
NRTI backbone									
abacavir + 3TC	0.94	0.76-1.17	0.62	0.96	0.51-1.83	0.91	0.97	0.52-1.84	0.94
zidovudine + 3TC	0.78	0.73-0.85	<0.001	0.77	0.69-0.87	<0.001	0.77	0.69-0.86	<0.001
stavudine + 3TC	0.73	0.66-0.81	<0.001	0.97	0.74-1.27	0.82	0.92	0.70-1.20	0.54
didanosine + 3TC	1.37	1.11-1.68	<0.001	1.76	1.04-2.97	0.04	1.73	1.03-2.91	0.04
tenofovir + 3TC	Ref			Ref			Ref		
Year of ART initiation									
Jun 2004 - Dec 2005	Ref			Ref			Ref		
2006	1.31	1.20-1.45	<0.001	0.86	0.65-1.15	0.32	0.82	0.61-1.09	0.18
2007	1.35	1.22-1.49	<0.001	1.24	1.02-1.50	0.03	1.26	1.04-1.53	0.02
2008	1.12	0.99-1.25	0.05	1.03	0.85-1.24	0.77	1.07	0.89-1.29	0.47
2009	1.24	1.09-1.42	0.001	1.05	0.85-1.29	0.66	1.05	0.56-1.29	0.62
2010	1.06	0.89-1.26	0.52	0.91	0.72-1.16	0.46	0.90	0.71-1.14	0.38
2011	0.45	0.34-0.59	<0.001	0.35	0.25-0.50	<0.001	0.35	0.25-0.50	<0.001
average % adherence									
<95%	2.82	2.62-3.04	<0.001	-	-	-	2.13	1.90-2.40	<0.001
≥ 95%	Ref						Ref		

Model B; average % adherence included as covariate, HR: hazard ratio, aHR: adjusted hazard ratio, CI: confidence interval, NNRTI: non-nucleoside reverse transcriptase inhibitor, NRTI: nucleos(t)ide reverse transcriptase inhibitor, 3TC: lamivudine, ART: antiretroviral therapy.

Harvard/APIN PEPFAR program in Nigeria. Other findings from Vietnam [19], and other African countries [20, 21], have also observed similar trends. The improved retention

over time in our program may be due to the robust adherence counseling and overall improvement in HIV care and treatment services instituted as a result of support enjoyed

from PEPFAR. Other quality improvement initiatives that might have contributed to improved retention in our program include simplification of patients appointment system, use of electronic database to track and flag missed appointments, enhanced patient tracking through a tracking team, health education, formation of support groups of people living with HIV, and improved laboratory monitoring to identify patients at risk of treatment failure.

Of concern in this study is the disposition of patients who discontinued treatment. While mortality accounted for less than 10% of the treatment attrition, the majority of treatment discontinuation was due to loss to follow-up. The findings reported here highlight the importance of further evaluating and improving patient tracking strategies in the program, especially within the first two years of treatment initiation. More efficient and active patient tracking systems are critically needed within ART programs in Nigeria.

Consistent with a number of studies in Western, Eastern, and Southern Africa [18, 22, 23], we observed increased hazard of treatment discontinuation with younger age. Increased risk of treatment discontinuation in younger persons; who constitute the majority of people living with HIV in Nigeria [1], and those who would have the longest life expectancy on successful ART, underscores the need to urgently identify risk factors for treatment discontinuation in this population. This will help the development of targeted interventions to increase treatment retention among young people.

Lower educational levels were associated with greater risk of treatment discontinuation in our study. Our findings are consistent with reports from Uganda [23], whereas a study from Kenya found no association between educational status and loss to follow-up [24]. While the causal relationship is not clear, it is expected that more educated people have better understanding of HIV disease process which could reflect on their attitude to care and potentially more resources to facilitate care. Education and counseling intensification are useful strategies that could improve retention in care in our setting, since the majority of our patients have a low level of education.

An important finding in this study is the variability in risk of treatment discontinuation according to NRTI backbone. Surprisingly, the risk of discontinuing treatment was higher in patients who initiated treatment with TDF containing regimen compared to AZT. There is a shift towards the use of TDF in combination with lamivudine in the more recent WHO guideline for treatment and prevention of HIV in adults and adolescents [25]. Other studies [18] have reported similar risk of lost to follow-up with use of TDF and therefore merits further investigation.

Consistent with established evidence linking poor adherence to poor health outcomes in patients on ART [18, 26, 28], our analysis found that patients with poor adherence to pharmacy drug pick up visits were at greater risk of treatment discontinuation. The adherence threshold of greatest impact was average percent adherence < 95%. Since adherence is a modifiable risk factor, adherence interventions could improve retention in care in our setting.

A major strength of this study is the large sample of our cohort and the length of follow up. We analyzed one of the

largest databases in a single centre providing ART in Nigeria, with longitudinal data of up to 8.5 years, the longest so far of the published studies on patient retention in an African setting [17, 18, 20-23]. Using carefully collected clinical data; we learnt that interventions to improve retention on ART should include enhanced counseling for younger patients, the unmarried and those with lower levels of education. ART regimen should be carefully selected at treatment initiation with preference to simplified regimens to achieve maximal adherence and ease of usage at all levels of health care. In addition, a system to track patient's adherence to treatment should be put in place to enable early identification of patients at risk of treatment discontinuation. This study had a few notable limitations. First, this was a single institutional, retrospective study; hence the generalization of the study results should be done cautiously. Secondly, there was little or no information on the disposition of patients lost to follow up. A number of these patients might have died without notification to the clinic, hence underestimating the true mortality rate in our patient cohort. Thirdly, patients transferred to other ART facilities are presumed to be retained in care without adequate linkage information between our treatment facility and other ART facilities to ensure that these patients are in care. Fourthly, the association of patients geographic location with treatment discontinuation; which would have been interesting to consider in decentralizing HIV/AIDS treatment services was not investigated. Finally, though our analysis revealed a trend in treatment discontinuation with changing levels of adherence to drug refill visits, our determination of average percent adherence did not consider the different duration of therapy and might be a bit biased towards those on treatment for longer period.

CONCLUSION

About 7 out of 100 adults initiated on ART in our setting discontinued treatment per year. The rate of treatment discontinuation was comparable to estimates in resource rich countries. More efficient interventions are needed, particularly within the first year of ART, to reduce the incidence of treatment discontinuation and improve retention in antiretroviral programs, with a special focus on younger patients, those with lower educational status and poor adherence.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

The authors are thankful to the patients and staff of the HIV clinic at JUTH for their cooperation and support.

FUNDING

1. This work was funded in part by the US Department of Health and Human Services, Health Resources and Services Administration (U51HA02522) and the Centers for Disease Control and Prevention (CDC)

through a cooperative agreement with APIN (PS 001058). The contents are solely the responsibility of the authors and do not represent the official views of the funding institutions.

2. This study was supported in-part by the Medical Education Partnership Initiative in Nigeria (MEPIN) project funded by Fogarty International Center, the Office of AIDS Research, the National Human Genome Research Institute of the National Institute of Health, the Health Resources and Services Administration (HRSA) and the Office of the U.S. Global AIDS Coordinator under Award Number R24TW008878.

REFERENCES

- [1] UNAIDS. Access to antiretroviral therapy in Africa. Status report on progress towards the 2015 targets http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2013/20131219_AccessARTAfricaStatusReportProgressTowards2015Targets_en.pdf
- [2] Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. *Clin Infect Dis*. 2011;52(6):793-800.
- [3] Dieffenbach CW, Fauci AS. Thirty years of HIV and AIDS: future challenges and opportunities. *Ann Intern Med* 2011; 154: 766-71.
- [4] Gulick RM, Mellors JW, Havlir D, *et al.* Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. *N Engl J Med* 1997; 337: 734-9.
- [5] Palella FJ Jr, Delaney KM, Moorman AC, *et al.*; for the HIV Outpatient Study investigators. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998; 338: 853-60.
- [6] Cohen MS, Chen YQ, McCauley M, *et al.* Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011; 365:493-505.
- [7] Paterson DL, Swindells S, Mohr J, *et al.* Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med* 2000; 133: 21-30.
- [8] Moore DM, Hogg RS, Yip B, *et al.* Discordant immunologic and virologic responses to highly active antiretroviral therapy are associated with increased mortality and poor adherence to therapy. *J Acquir Immune Defic Syndr* 2005; 40: 288-93.
- [9] Oyugi JH, Byakika-Tusiime J, Ragland K, *et al.* Treatment interruptions predict resistance in HIV-positive individuals purchasing fixed-dose combination antiretroviral therapy in Kampala, Uganda. *AIDS* 2007; 21: 965-71.
- [10] Nachega JB, Hislop M, Dowdy DW, *et al.* Adherence to highly active antiretroviral therapy assessed by pharmacy claims predicts survival in HIV-infected South African adults. *J Acquir Immune Defic Syndr*. 2006; 43:78-84.
- [11] Rosen S, Fox MP, Gill CJ. Patient retention in antiretroviral therapy programs in sub-Saharan Africa: A systematic review. *PLoS Med* 2007;4(10): e298. doi:10.1371/journal.pmed.0040298.
- [12] Abah IO, Ojeh VB, Musa J *et al.* Clinical Utility of Pharmacy-Based Adherence Measurement in Predicting Virologic Outcomes in an Adult HIV-Infected Cohort in Jos, North Central Nigeria. *Journal of the International Association of Providers of AIDS Care*. 2014; 1-7. doi: 10.1177/2325957414539197.
- [13] Ellen M, Tedaldi, James T. Richardson *et al.*, and the HOPS Investigators. Retention in Care within 1 Year of Initial HIV Care Visit in a Multisite US Cohort: Who's in and Who's Out? *Journal of the International Association of Providers of AIDS Care*. 2014. doi: 10.1177/2325957413514631.
- [14] Mugavero MJ, Amico KR, Westfall AO, *et al.* Early retention in HIV care and viral load suppression: implications for a test and treat approach to HIV prevention. *J Acquir Immune Defic Syndr* 2012; 59(1): 86-93.
- [15] Dombrowski JC, Kent JB, Buskin SE, *et al.* Population-based metrics for the timing of HIV diagnosis, engagement in HIV care, and virologic suppression. *AIDS* 2012; 26(1): 77-86.
- [16] Marks G, Gardner LI, Craw J, Crepaz N. Entry and retention in medical care among HIV-diagnosed persons: a meta-analysis. *AIDS* 2010; 24(17): 2665-78.
- [17] Rosen S, Fox MP, Gill CJ. Patient retention in antiretroviral therapy programs in sub-Saharan Africa: A systematic review. *PLoS Med* 2007; 4(10): e298. doi:10.1371/journal.pmed.0040298.
- [18] Meloni ST, Chang C, Chaplin B, *et al.* Time-Dependent Predictors of Loss to Follow-Up in a Large HIV Treatment Cohort in Nigeria. *Open Forum Infectious Diseases*. Vol. 1. No. 2. Oxford University Press, 2014.
- [19] Tran DA, Ngo AD, Shakeshaft A, *et al.* Trends in and Determinants of Loss to Follow Up and Early Mortality in a Rapid Expansion of the Antiretroviral Treatment Program in Vietnam: Findings from 13 Outpatient Clinics. *PLoS ONE* 2013; 8(9): e73181. doi:10.1371/journal.pone.0073181.
- [20] Nglazi MD, Lawn SD, Kaplan R, *et al.* Changes in Programmatic Outcomes During 7 Years of Scale-up at a Community-Based Antiretroviral Treatment Service in South Africa. *JAIDS Journal of Acquired Immune Deficiency Syndromes*. 2011; 56 [1]: e1-e8 doi: 10.1097/QAI.0b013e3181ff0bdc.
- [21] Brinkhof M, Dabis F, Myer L, *et al.* Early loss of HIV-infected patients on potent antiretroviral therapy programmes in lower-income countries. *Bulletin World Health Organization*. 2008;86 (7):559-67.
- [22] W K Poole, R Perritt, K B Shah, *et al.* and the Pulmonary Complications of Immunodeficiency Virus Infection Study Group. A characterization of patient drop outs in a cohort of HIV positive homosexual/bisexual men and intravenous drug users. *J Epidemiol Community Health*. 2001; 55: 66-67.
- [23] Mills EJ, Funk A, Kanters S, *et al.* Long-term health care interruptions among HIV-positive patients in Uganda. *J Acquir Immune Defic Syndr*. 2013;63(1):e23-7. doi: 10.1097/QAI.0b013e31828a3fb8.
- [24] Hassan SA, Fielding LK, Thuo MN, *et al.* Early loss to follow-up of recently diagnosed HIV-infected adults from routine pre-ART care in a rural district hospital in Kenya: a cohort study. *Tropical Medicine and International Health*. 2012;17(1):82-93.
- [25] WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach, June 2013. Available from: http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf. Accessed 6May 2014.
- [26] Charurat M, Oyegunle M, Benjamin R, *et al.* Patient Retention and Adherence to Antiretrovirals in a Large Antiretroviral Therapy Program in Nigeria: A Longitudinal Analysis for Risk Factors. *PLoS ONE* 2010; 5 (5):e10584.
- [27] Keiser O, Chi BH, Gsponer T, *et al.* Outcomes of antiretroviral treatment in programmes with and without routine viral load monitoring in southern Africa. *AIDS* 2011; 25 (14):1761-9 doi: 10.097/QAD.0b013e328349822f.
- [28] Rougemont M, Stoll B, Elia N, Ngang P. Antiretroviral treatment adherence and its determinants in Sub-Saharan Africa: a prospective study at Yaounde Central Hospital Cameroon. *AIDS Research and Therapy* 2009; 6:21.