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Patients who present late to HIV care and associated risk factors in Nigeria

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Objectives

Our objectives were to assess trends in late presentation and advanced HIV disease (AHD) and determine associated risk factors.

Methods

We conducted a retrospective cohort analysis of patients who had received care and treatment at the AIDS Prevention Initiative Nigeria Plus (APIN)/Harvard School of Public Health–President's Emergency Plan for AIDS Relief (PEPFAR) programme at the Jos University Teaching Hospital, Jos, Nigeria from 2005 to 2010. We used the European Consensus Definition to assess trends in late presentation (CD4 count < 350 cells/μL or AIDS-defining illness) and AHD (CD4 count < 200 cells/μL or AIDS-defining illness) and evaluated associated risk factors using logistic regression methods.

Results

Among 14 487 eligible patients, 12 401 (85.6%) were late presenters and 9127 (63.0%) presented with AHD. Late presentation decreased from 88.9% in 2005 to 80.1% in 2010 ($P < 0.001$). Similarly, AHD decreased from 67.8% in 2005 to 53.6% in 2010 ($P < 0.001$). In logistic regression models adjusting for sociodemographic and biological variables, male sex [adjusted odds ratio (aOR) = 1.80; 95% confidence interval (CI) 1.60–2.04], older age (aOR = 1.37; 95% CI 1.22–1.54), civil service employment (aOR = 1.48; 95% CI 1.00–2.21), referral from out-patient (aOR = 2.18; 95% CI 1.53–3.08) and in-patient (aOR = 1.55; 95% CI 1.11–2.17) services, and hepatitis B virus (aOR = 1.43; 95% CI 1.26–1.63) and hepatitis C virus (aOR = 1.18; 95% CI 1.02–1.37) coinfections were associated with late presentation. Predictors of AHD were male sex (aOR = 1.67; 95% CI 1.54–1.82), older age (aOR = 1.26; 95% CI 1.16–1.36), unemployment (aOR = 1.34; 95% CI 1.00–1.79), referral from out-patient (aOR = 2.40; 95% CI 1.84–3.14) and in-patient (aOR = 1.97; 95% CI 1.51–2.57) services and hepatitis B virus coinfection (aOR = 1.30; 95% CI 1.19–1.42).

Conclusions

Efforts to reduce the proportion of patients who first seek care at late stages of disease are needed. The identified risk factors should be utilized in formulating targeted public health interventions to improve early diagnosis and presentation for HIV care.

Keywords: advanced HIV disease, HIV, late presentation, Nigeria, risk factors.

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Introduction

Early diagnosis is critical in the prevention and control of the spread of HIV at both an individual and population level. Despite the introduction of highly active antiretroviral therapy (HAART) and its proven benefits, a substantial number of HIV-infected persons are unaware of their serostatus and are at risk of presenting for care when HIV disease is advanced. Patients presenting late to care pose challenges in clinical care and experience a higher burden of HIV-related complications compared with those who are tested and treated earlier. Late presenters have higher rates of hospitalization, opportunistic infections (OIs) and early mortality [1,2]. Late presentation to care is also associated with increased medical care cost, and treatment is usually more complex compared with early presenters [3–6]. Late presenters represent an important group for HIV prevention and control because persistent undiagnosed HIV infection leads to missed opportunities for reducing secondary transmission [7,8].

A number of studies from industrialized countries have described the frequency of late presentation among individuals with newly diagnosed HIV infection [9–14], with estimates ranging from 15 to 55.9%, depending on the definition of late presentation used. In sub-Saharan Africa and some parts of Asia and South America, the prevalence of late presentation has been documented to range between 40 and 55%; most of these studies relied mainly on clinical staging [15–18]. In a multi-country study assessing mortality and morbidity among HIV-infected patients from sub-Saharan Africa and Asia, mortality rates were highest for subjects with CD4 counts < 50 cells/μL, followed by those with counts between 51 and 100 cells/μL. AIDS rates were between 11.5 and 50 per 100 person-years for those with CD4 counts < 100 cells/μL [19]. In the International epidemiological databases to evaluate AIDS (IeDEA) cohort, baseline CD4 count across four regions in sub-Saharan Africa ranged from 126 to 211 cells/μL among patients presenting for care [20].

At present, studies in the literature assessing the degree (or prevalence) of late presentation in Nigeria and reporting detailed analysis of its risk factors are scarce. Two recent studies evaluated late presentation in Nigeria. A prevalence rate of 67.4% was obtained among patients in Lagos using a CD4 count < 350 cells/μL [21], while a rate of 56.7% was reported in Jos among hospitalized HIV-infected patients using the Centers for Disease Control and Prevention (CDC) classification [22]. Recently, a European Consensus Definition of late presentation (CD4 count < 350 cells/mL or clinical AIDS) and presentation with advanced HIV disease (AHD; CD4 count < 200 cells/μL or clinical AIDS) was published to facilitate cross-country comparisons of trends and results of targeted interventions [23,24]. Recent recommendations from the World Health Organization (WHO) advise the commencement of treatment for some patients at a higher CD4 count (350–500 cells/μL) to target HIV transmission [25]. The objectives of this study were to describe the trend in late presentation and presentation with AHD to care and to determine the factors associated with late presentation based on the European Consensus Definition and AHD in a large cohort of HIV-infected adult patients in an urban care centre in Jos, Nigeria.

Methods

Subjects

The study subjects included all patients who attended the Jos University Teaching Hospital (JUTH) adult HIV clinic for the first time between 1 January 2005 and 31 December 2010. During the period covered by this study, the national HIV treatment guidelines were in accordance with the 2006 WHO recommendations, in which the CD4 count cut-off for antiretroviral therapy (ART) initiation was < 200 cells/μL for asymptomatic patients. JUTH is a regional referral hospital that serves a population of about 22 million people [26] in the north central part of Nigeria. As of 31 December 2010, the clinic had cumulatively enrolled 20 193 patients, with 10 069 active in HIV care and 8843 receiving HAART. Patients were included in the study if they were 15 years of age or older with a new HIV diagnosis (obtained using western blot confirmation with the Qualicode HIV-1/2 assay; Immunonetics, Boston, MA), were HAART-naïve and had provided written informed consent. Patients were excluded if they did not have a documented baseline CD4 count result and if their baseline HIV viral load was undetectable (≤400 HIV-1 RNA copies/ml). Hepatitis B virus (HBV) surface antigen (HBsAg) status was determined using an enzyme immunoassay (EIA) (Monolisa HBsAg Ultra3; BioRad, Hercules, CA, USA) based on recommendations in the national guidelines. Anti-hepatitis C virus (HCV) antibody status was determined using a third-generation enzyme immunoassay (DIA.PRO Diagnostic; Bioprobes srl, Milan, Italy) in accordance with the programme protocol. HIV RNA levels were measured using Roche Amplicor HIV-1 monitor test version 1.5 (Roche Diagnostics GmbH, Mannheim, Germany) with a detection limit of 400 copies/ml. Flow cytometry was used to determine CD4 count (Partec GmbH, Munster, Germany).

Data collection

The data used for this study included patient information that is routinely collected at the pre-assessment and entry visits on a standardized form. The pre-assessment and

entry visit forms included sociodemographic, behavioural and clinical information, such as physical symptoms, medication history, prior history of HIV-related illness symptoms, WHO [27] and CDC [28] staging, and HIV treatment plan. Physicians at the pre-assessment and entry visits collected all data on paper. The data from these forms were entered into the electronic data management system, which utilized the FileMaker Pro software (FileMaker Inc, Santa Ana, CA, USA), by data entry clerks.

Definition of terms

The following definitions were used [23].
Late presentation: persons presenting for care with a CD4 count < 350 cells/μL or presenting with an AIDS-defining event, regardless of the CD4 count.

Advanced HIV disease: persons presenting for care with a CD4 count < 200 cells/μL or presenting with an AIDS-defining event, regardless of the CD4 count.

Measurements

Dependent variable
CD4 enumeration is the widely accepted method used for immunological staging of HIV disease, and this staging system reliably predicts survival and disease progression. As our programme had access to CD4 monitoring, we used the European Consensus Definition as our outcome variable. CD4 counts were documented as cells/mm^3.

Independent variables
Independent variables included sociodemographic information such as sex, age (dichotomized as ≤ 35 years and ≥ 36 years), education level, occupation, and marital status, as well as source of referral to care and HIV transmission risk category. The biological variables included HBV and HCV coinfection status. Subjects were defined as having HBV and HCV infection if they tested positive for HBsAg and HCV antibody, respectively, on baseline blood samples.

Statistical analysis

χ^2 or Fisher's exact test, as relevant, was used to analyse categorical variables and the Wilcoxon rank sum test was used to compare the distributions of continuous variables. Median CD4 counts as well as proportions of patients with late presentation and AHD were determined. Temporal trends in the distribution of CD4 counts at presentation, using nonparametric tests, and trends in the proportion of persons diagnosed with CD4 counts < 350 cells/μL and < 200 cells/μL by year of enrolment, using the χ^2 test for trend, were also evaluated. To identify factors associated with late presentation (CD4 count < 350 cells/μL) and presentation with AHD (CD4 count < 200 cells/μL), a multivariate logistic regression analysis was performed using Epi Info version 3.5.3 software (CDC, Atlanta, GA).

Ethical considerations

The Human Research Ethics Committee (HREC) at JUTH and the Institutional Review Board (IRB) at the Harvard School of Public Health, Boston, MA, approved the study. Written informed consent was obtained from all study participants.

Results

General characteristics

Between January 2005 and December 2010, 16 545 treatment-naïve patients enrolled for HIV care at the AIDS Prevention Initiative Nigeria (APIN)/Harvard School of Public Health–President's Emergency Plan for AIDS Relief (PEPFAR)-supported adult treatment programme at JUTH. Of these, 16 322 (98.6%) had CD4 count results documented at their baseline visit and were selected for inclusion. An additional 1835 patients were excluded because their HIV viral loads were ≤ 400 copies/ml at baseline. In total, 14 487 patients were included in this analysis.

Of the patients included, 9556 (66.0%) were female. The median age of our patients was 33 years (range 15–88 years), with male patients being significantly older than female patients (median 38 *vs*. 31 years, respectively; $P < 0.001$). A total of 7855 (54.2%) of the patients were married. Primary education was attained by 2974 patients (20.8%), 4412 (30.8%) had secondary education and 4036 (28.2%) had tertiary education. Of the total cohort, 13 977 (96.5%) reported their primary HIV exposure category as heterosexual, and 11 080 (76.5%) reported being referred from stand-alone HIV counselling and testing (HCT) centres. At enrolment, the median CD4 count was 151 cells/μL [interquartile range (IQR) 1–1660 cells/μL], while the median HIV RNA level was 4.7 log copies/mL (IQR 2.6–7.0 log copies/mL). HBsAg and anti-HCV antibodies were present in 2820 (19.5%) and 1934 (13.3%) patients, respectively. There were significant variations in sociodemographic, risk/referral group and biological parameters across the years of enrolment. The details of sociodemographic and biological parameters by year of enrolment are shown in Table 1.

Prevalence of late presentation and AHD

A total of 12 401 patients (85.6%) met the definition of late presentation, while 9127 (63.0%) presented with AHD.

Table 1 Characteristics of treatment-naïve subjects enrolling for HIV care by year of enrolment in Jos, Nigeria ($n = 14\,487$)

Characteristic	Total	2005	2006	2007	2008	2009	2010	*P*-value
Patients enrolled [*n* (%)]	14 487 (100.0)	3052 (21.1)	4128 (28.5)	3090 (21.3)	2008 (13.9)	1429 (9.9)	780 (5.4)	
Age (years) (median)	33	34	33	33	32	33	33	0.009
Age ≥ 50 years [*n* (%)][a]	860 (5.9)	178 (5.8)	246 (6.0)	175 (5.7)	124 (6.2)	85 (5.9)	52 (6.7)	0.92
Sex [*n* (%)]								
Female	9556 (66.0)	2011 (65.9)	2788 (67.5)	2021 (65.4)	1287 (64.1)	939 (65.7)	510 (65.4)	0.35
Male	4931 (34.0)	1041 (34.1)	1340 (32.5)	1069 (34.6)	721 (35.9)	490 (34.3)	270 (34.6)	
Marital status [*n* (%)]								
Married	7855 (54.2)	1637 (53.6)	2187 (53.0)	1631 (52.8)	1168 (58.2)	793 (55.5)	439 (56.3)	0.0006
Single	3047 (21.0)	580 (19.0)	859 (20.8)	618 (20.0)	481 (24.0)	327 (22.9)	182 (23.3)	0.0002
Widowed	2316 (16.0)	554 (18.2)	706 (17.1)	531 (17.2)	229 (11.4)	201 (14.1)	95 (12.2)	<0.001
Divorced	670 (4.6)	171 (5.6)	214 (5.2)	180 (5.8)	48 (2.4)	29 (2.0)	28 (3.6)	0.001
Separated	599 (4.1)	110 (3.6)	162 (3.9)	130 (4.2)	82 (4.1)	79 (5.5)	36 (4.6)	0.07
Educational status [*n* (%)]								
No formal education	2899 (20.2)	620 (20.6)	898 (21.7)	617 (20.2)	365 (18.4)	264 (18.7)	146 (19.1)	0.01
Primary	2974 (20.8)	602 (20.0)	805 (19.7)	619 (20.3)	435 (21.9)	337 (23.9)	176 (23.0)	0.006
Secondary	4412 (30.8)	907 (30.1)	1233 (30.1)	956 (31.3)	638 (32.1)	427 (30.3)	251 (32.8)	0.44
Tertiary	4036 (28.2)	883 (29.3)	1166 (28.5)	863 (28.2)	551 (27.7)	381 (27.0)	192 (25.1)	0.19
Occupation [*n* (%)]								
Civil servant	3318 (22.8)	722 (23.5)	969 (23.5)	736 (23.8)	427 (21.2)	293 (20.4)	171 (21.9)	0.05
Artisan	2309 (15.9)	460 (15.1)	608 (14.7)	459 (14.9)	369 (18.4)	280 (19.6)	133 (17.1)	<0.001
Trader	2477 (17.1)	538 (17.6)	668 (16.2)	512 (16.5)	360 (17.9)	246 (17.2)	153 (19.6)	0.21
Farmer	2008 (13.9)	462 (15.1)	608 (14.7)	451 (14.6)	230 (11.4)	174 (12.2)	83 (10.6)	<0.001
Unemployed	3047 (21.0)	611 (20.0)	916 (22.2)	631 (20.4)	422 (21.0)	294 (20.6)	173 (22.2)	0.24
Student	1126 (7.8)	220 (7.2)	313 (7.6)	255 (8.3)	162 (8.1)	120 (8.4)	56 (7.2)	0.54
Soldier	80 (0.6)	18 (0.6)	21 (0.5)	16 (0.5)	11 (0.5)	10 (0.7)	4 (0.5)	0.97
Retiree	112 (0.8)	20 (0.7)	21 (0.5)	28 (0.9)	25 (1.2)	11 (0.8)	7 (0.9)	0.05
Other	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.77
HIV exposure category [*n* (%)]								
Heterosexual	13977 (96.6)	2921 (95.7)	3937 (95.4)	2963 (95.9)	1978 (98.6)	1410 (98.8)	769 (98.7)	<0.001
Heterosexual/transfusion	354 (2.4)	88 (2.9)	130 (3.1)	99 (3.2)	20 (1.0)	7 (0.5)	7 (0.9)	0.54
Transfusion	21 (0.1)	5 (0.2)	5 (0.1)	3 (0.1)	3 (0.1)	4 (0.3)	1 (0.1)	0.77
Heterosexual/MSM	3 (0.0)	2 (0.1)	0)0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0.81
Heterosexual/IDU	1 (0.0)	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.76
MSM	6 (0.0)	0 (0.0)	3 (0.1)	1 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0.43
Unknown	118 (0.8)	34 (1.1)	51 (1.2)	24 (0.8)	3 (0.1)	4 (0.3)	2 (0.3)	<0.001
MTCT	2 (0.0)	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.83
Source of referral [*n* (%)]								
Stand-alone HCT	11089 (76.6)	2188 (71.7)	2995 (72.6)	2194 (71.0)	1764 (87.8)	1254 (87.8)	694 (89.2)	<0.001
Out-patient service	1599 (11.0)	446 (14.6)	586 (14.2)	480 (15.5)	42 (2.1)	34 (2.4)	11 (1.4)	<0.001
In-patient service	1523 (10.0)	353 (11.6)	450 (10.9)	350 (11.3)	180 (9.0)	127 (8.9)	63 (8.1)	0.001
PMTCT programme	169 (1.2)	37 (1.2)	59 (1.4)	44 (1.40	13 (0.6)	9 (0.6)	7 (0.9)	0.02
STI service	48 (0.3)	11 (0.0)	24 (0.6)	11 (0.4)	1 (0.0)	1 (0.1)	0 (0.0)	0.002
TB clinic	31 (0.2)	13 (0.4)	5 (0.1)	7 (0.2)	4 (0.2)	1 (0.1)	1 (0.1)	0.08
Transfer-in	25 (0.2)	4 (0.1)	9 (0.2)	4 (0.1)	4 (0.2)	2 (0.1)	2 (0.3)	0.89
Advanced WHO stage (3 and 4) [*n* (%)][a]	3306 (22.8)	684 (22.4)	895 (21.7)	630 (20.4)	502 (25.0)	381 (26.7)	214 (27.4)	<0.001
CD4 count (cells/μL) (median)	151	139	138	141	191	181	189	<0.001
HIV RNA (log copies/ml) (median)	4.7	4.8	4.7	4.7	4.6	4.6	4.6	<0.001
High viral load (> 100 000 copies/ml) [*n* (%)][a]	5322 (36.7)	1195 (39.2)	1621 (39.3)	1138 (36.8)	635 (31.6)	469 (32.8)	264 (33.8)	<0.001
HBsAg positive [*n* (%)]	2820 (21.0)	597 (20.4)	830 (20.9)	621 (21.0)	386 (22.9)	257 (21.1)	129 (19.5)	0.29
Anti-HCV Ab positive [*n* (%)]	1934 (14.3)	388 (13.3)	554 (14.0)	422 (14.3)	261 (15.1)	195 (15.6)	114 (16.8)	0.88
Late presenters [*n* (%)]*[a]	12401 (85.6)	2712 (88.9)	3642 (88.2)	2692 (87.1)	1604 (79.9)	1126 (78.8)	625 (80.1)	<0.001
Advanced HIV disease [*n* (%)]†[a]	9127 (63.0)	2069 (67.8)	2773 (67.2)	2013 (65.1)	1064 (53.0)	790 (55.3)	418 (53.6)	<0.001

HBsAg, hepatitis B virus surface antigen; HCT, HIV counselling and testing; HCV Ab, hepatitis C virus antibody; IDU, injection; TB, tuberculosis; MSM, men who have sex with men; MTCT, mother-to-child transmission; PMTCT, prevention of mother-to-child transmission; STI, sexually transmitted infection; WHO, World Health Organization.
*CD4 count < 350 cells/μL or presenting with an AIDS-defining illness regardless of CD4 count.
†CD4 count < 200 cells/μL or presenting with an AIDS-defining illness regardless of CD4 count.
[a]*P*-values for trend.

Overall, 3306 patients (22.8%) presented with a WHO stage 3 or 4 condition (advanced WHO stage or CDC clinical stage C). Figure 1a shows trends in CD4 count categories at entry into care. There was a trend towards a decreasing frequency of late presentation over the years. The proportion of patients presenting late decreased from 88.9% in 2005 to 80.1% in 2010 ($P < 0.001$). This trend was also observed for the proportion of those presenting with AHD,

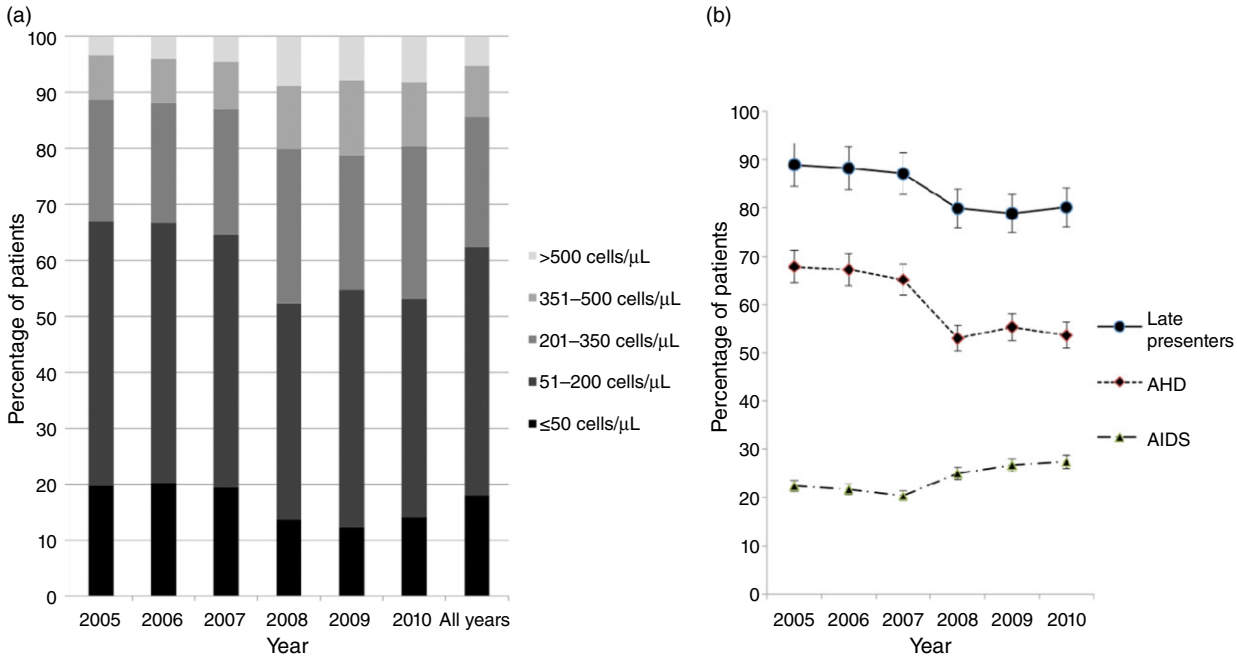

Fig. 1 Summary of trends in baseline status of patients included in the study. (a) CD4 count (cells/μL) distribution for the overall cohort by year of enrolment. (b) Trends in late presentation, advanced HIV disease (AHD) and AIDS by year of enrolment.

with a decrease from 67.8% in 2005 to 53.6% in 2010 ($P < 0.001$). Trends in the frequency of late presentation, AHD and clinical AIDS over 6 years are shown in Figure 1b.

Factors associated with late presentation and AHD

The results of the analyses to identify factors associated with late presentation and AHD are shown in Table 2. Male patients had higher rates of late presentation (90.1% *vs.* 83.3% for women; $P < 0.001$) as well as AHD (70.4% *vs.* 59.2%, respectively; $P < 0.001$) when compared with female patients, and this trend was also observed throughout the study period. For late presenters, being male, older, a civil servant, unemployed, widowed or divorced was associated with increased risk. Other factors associated with late presentation included being referred from hospital in-patient or out-patient services, and coinfection with HBV or HCV. The same factors were also observed to be associated with increased risk of presenting with AHD.

The factors that retained significance as independent predictors of late presentation in a logistic regression model were male sex, older age, being a civil servant, in-patient and out-patient referral source and being HBV and HCV coinfected. Similarly, the independent predictors of AHD were male sex, older age, being unemployed, in-patient and out-patient referral source and HBV coinfection.

Discussion

Individuals who present late to HIV care or present with AHD are often ill, have high early mortality risk, are less likely to respond well to ART and have higher rates of adverse events. In addition, late presentation increases the risk of onward transmission of HIV. This study, which examined data on over 14 000 patients, is one of the first in West Africa to use the European Consensus Definition of late presentation and AHD and provides information on the trends and risk factors for both late presentation and AHD over a 6-year period in Nigeria. In an era and location where HAART was not only free, but widely available, we observed an alarmingly high rate of late presentation (85.6%) as well as high rates of patients presenting with AHD (63.0%). Furthermore, 22.8% of our patients had developed AIDS by the time of presentation. Despite high rates of both late presentation and AHD, we observed a significant downward trend in the frequency of both conditions over the years covered by the study. Independent predictors of both late presentation and AHD were similar among our patients.

It is difficult to compare prevalence rates in earlier studies because a standardized definition was not available until the European Consensus Definition became operational. To our knowledge, this is the first report from a high-burden country on late presentation using the

Table 2 Risk factors and independent predictors of late presentation and advanced HIV disease (AHD) among adults in Jos, Nigeria

	Late presentation							AHD						
	Univariate analysis				Multivariate analysis			Univariate analysis				Multivariate analysis		
Variable	*n* (%)	OR	95% CI	*P*-value	aOR	95% CI	*P*-value	*n* (%)	OR	95% CI	*P*-value	aOR	95% CI	*P*-value
Sex														
Female	7958 (83.3)	1	1.64–2.03	< 0.001	1	1.60–2.04	< 0.001	5657 (59.2)	1	1.52–1.76	< 0.001	1	1.54–1.82	< 0.001
Male	4443 (90.1)	1.82			1.80			3470 (70.4)	1.64			1.67		
Age														
15–35 years	7163 (83.2)	1	1.51–1.84	< 0.001	1	1.22–1.54	< 0.001	5120 (59.4)	1	1.36–1.57	< 0.001	1	1.1.16–1.36	< 0.001
≥ 36 years	5238 (89.2)	1.67			1.37			4007 (68.2)	1.46			1.26		
Marital status														
Married	6620 (84.3)	1			1			4788 (61.0)	1			1		
Single	2597 (85.2)	0.96	0.86–1.07	0.24	4.46	0.00– > 1.0E	1.00	1909 (62.7)	0.98	0.90–1.06	0.52	0.39	0.00– > 1.0E	1.00
Other	3184 (88.8)	1.45	1.29–1.63	< 0.001	5.13	0.00–1.0E	1.00	2396 (66.8)	1.30	1.20–1.41	< 0.001	0.44	0.00– > 1.0E	1.00
Education														
No formal education	2446 (85.3)	1			1			1813 (63.3)	1			1		
Primary/secondary	6311 (85.4)	0.97	0.88–1.06	0.23	0.77	0.47–1.25	0.29	4633 (62.7)	0.97	0.91–1.04	0.35	1.26	0.94–1.70	0.11
Tertiary	3464 (85.8)	1.02	0.92–1.13	0.32	0.73	0.44–1.20	0.22	2558 (63.4)	1.02	0.94–1.10	0.49	1.25	0.91–1.70	0.15
Occupation														
Student	892 (79.3)	1						614 (54.6)	1			1		
Unemployed	2566 (84.3)	0.87	0.78–0.97	0.009	1.42	0.95–2.12	0.08	1870 (61.4)	0.91	0.84–1.00	0.05	1.34	1.00–1.79	0.04
Civil servant	2906 (88.3)	1.34	1.19–1.51	< 0.001	1.48	1.00–2.21	0.04	2176 (66.1)	1.19	1.09–1.29	0.001	1.25	0.94–1.66	0.11
Other	5834 (85.9)	1.05	0.95–1.15	0.15	1.28	0.87–1.90	0.20	4314 (63.5)	1.04	0.97–1.11	0.23	1.19	0.90–1.58	0.20
HIV risk category														
Heterosexual	11941 (85.5)	1			1			8759 (62.7)	1			1		
Blood transfusion	20 (95.2)	3.36	0.45–25.1	0.17	2.44	0.31–18.85	0.39	17 (81.0)	2.49	0.84–7.42	0.05	1.94	0.63–5.97	0.24
Unknown	104 (88.1)	1.25	0.71–2.19	0.22	0.96	0.49–1.86	0.91	87 (73.3)	1.65	1.09–2.49	0.006	1.34	0.83–2.17	0.22
Source of referral														
Stand-alone HCT	9382 (84.6)	1			1			6811 (61.4)	1			1		
In-patient	1336 (87.7)	1.22	1.04–1.43	0.005	1.55	1.11–2.17	0.009	1025 (67.3)	1.23	1.10–1.38	0.0001	1.97	1.51–2.57	< 0.001
Out-patient	1464 (91.6)	1.93	1.61–2.32	< 0.001	2.16	1.53–3.07	< 0.001	1158 (72.4)	1.62	1.44–1.81	0.0001	2.40	1.84–3.14	< 0.001
HBV coinfection														
Negative	9892 (84.8)	1	1.27–1.64	< 0.001	1	1.26–1.63	< 0.001	7209 (61.8)	1	1.20–1.43	0.0004	1.30	1.19–1.42	< 0.001
Positive	2509 (89.0)	1.44			1.43			1918 (68.0)	1.31					
HCV coinfection														
Negative	10696 (85.2)	1	1.11–1.49	0.0002	1	1.02–1.37	0.02	7859 (62.6)	1	1.02–1.25	0.006	1	0.96–1.18	0.21
Positive	1705 (88.2)	1.29			1.18			1268 (65.6)	1.13			1.06		

aOR, adjusted odds ratio; CI, confidence interval; HBV, hepatitis B virus; HCT, HIV counselling and testing; HCV, hepatitis C virus; OR, odds ratio.

European Consensus Definition. By this definition, rates of late presentation have been reported to range from 40 to 68.7% [22,27–31]. These rates differed significantly from the 85.4% we obtained among our patients. The reasons for late presentation vary from place to place and depend on sociocultural and economic factors. These have been reported to include fear of stigma, financial constraints, faith in herbal/spiritual treatment and a lack of belief in orthodox HIV treatment coupled with the fact that many people are unaware of their HIV-positive status [24,25,32]. The implications of the high rates of late presentation are that these patients are already qualified to initiate ART at the time of presentation according to existing local and international treatment guidelines. As expected, patients who present late for care are more likely to have an AIDS-defining condition (or develop one shortly thereafter), have higher short-term mortality and account for higher proportions of health care resource utilization [5,27]. In addition to the obvious benefits of early presentation to the individual, the main advantage of earlier diagnosis is the opportunity it provides to reduce onward transmission and community-level incidence either by encouraging safer sexual behaviour or by reducing individual infectiveness through the timely use of HAART. Interestingly, even in countries where there is near-universal ART coverage, late presentation is still a common occurrence [33].

The 2013 WHO guidelines recommend that national HIV programmes provide ART to all people with a confirmed HIV diagnosis with a CD4 count of ≤ 500 cells/μL, giving priority to initiating ART among those with severe/advanced HIV disease. These recommendations are based on evidence that early treatment initiation is associated with clinical and HIV prevention benefits, improving survival and reducing the incidence of HIV infection at the community level [25]

As our treatment programme matured, HIV testing services became more widespread and provider-initiated testing was introduced within the health facility and there was uninterrupted supply of drugs and commodities. In addition, persons living with HIV were engaged both in our clinic to promote adherence and in the community to reduce stigma and discrimination. These programme-level factors, in synergy with patient factors, are likely explanations for the downward trend in late presentation that we observed.

Our findings are similar to those of other studies, where being male or of older age was associated with an increased risk of late presentation and presenting with AHD. Diagnoses in older subjects missed by primary care providers in primary care settings because of low levels of clinical suspicion and a perception of a low risk of HIV infection, coupled with less frequent opportunities to access HIV testing in organized care settings, are the main drivers of late presentation in older patients [27,34]. Women and younger subjects seem less likely to present late, and this could be attributable to free access to care and testing offered to women routinely in antenatal care settings and the targeted interventions to reduce harmful practices and promote testing among young people. Moreover, a large proportion of newly infected HIV-positive women, being sexual partners of men already known to be HIV-positive or at risk of acquiring HIV infection, have higher perception of risk themselves. Although not applicable to our cohort, other risk factors associated with late presentation and AHD in resource limited settings (RLS) include being single (i.e. unmarried) or unemployed, living in a household with others (as opposed to alone), lack of spousal HIV status disclosure, not having a permanent house and frequent alcohol use [23,25,35]. The differences in factors associated with late presentation among our patients and other cohorts RLS may be attributable to the fact that sociocultural and economic differences that affect health-seeking behaviour and health indices vary from country to country among the countries most affected by the HIV epidemic.

We found that some biological factors were also associated with increased risk of late presentation and AHD. Late presenters and patients presenting with AHD were more likely to be coinfected with HBV and have circulating anti-HCV antibodies. Hepatitis coinfection in HIV-infected persons has been documented to impact treatment responses to HAART and end-stage liver disease (ESLD) and has become a leading cause of mortality among coinfected subjects [36–38]. Furthermore, HBV, HCV and HIV share similar routes of transmission and patients with hepatitis infection should also be offered screening for HIV. Screening for hepatitis and the use of drugs with dual activity among HIV-coinfected patients with active hepatitis B as integral components of HAART should be encouraged as part of standard of care for HIV-infected persons, in line with existing guidelines. Sociodemographic factors found to be protective against late presentation and AHD were younger age and being a student or a soldier. Young students and military personnel have been identified as high-risk groups for HIV infection, and it is possible that they receive more targeted interventions for HIV prevention and potentially have better opportunities to access testing and enroll into care at earlier stages of the disease. Unemployment and the consequent lack of income often limit the ability of such persons to access health care services early, leading to late presentation.

One of the strengths of our study was the large patient numbers included in our analysis. Our treatment programme draws patients from various states within the

north central zone of Nigeria and reflects a large proportion of the target population. Another strength was that 98.6% of the evaluated patients had CD4 assessment at entry into care, thereby limiting the potential for bias. Despite these strengths, the study had some limitations. Our programme did not capture qualitative data on the reasons why patients present late for HIV care. These data may have provided useful information to support our findings and also to guide policy and interventions for more effective HIV prevention and programming aimed at reducing the barriers to early testing and presentation in our various communities. In addition, because this was not a cohort that had been followed prior to entry at the clinic, we were unable to provide information on the duration of HIV infection prior to diagnosis and subsequent presentation for care. The CD4 count at presentation was, therefore, used as a surrogate. Various authors have used different imputation methods to estimate the probable date of HIV seroconversion [39]. Some surrogates previously used include down-regulation of CD127 on CD4 cells and the degree of immune activation. A recent study from Nigeria estimated the time between HIV seroconversion and diagnosis to be 6.1 years for men and 7.3 years for women [40–43]. Using the formula derived in that study, the probable time from seroconversion to presentation for care among our patients would be 2.3 years for men and 2.6 years for women. As with most cross-sectional studies, causality cannot usually be attributed. That said, the causal factors for this cohort would be sociodemographic factors, while the effect of late presentation would be high viral load and clinical AIDS.

In order to ensure early presentation to care, many countries have adopted provider-initiated testing and counselling (PITC) in health facilities and routine testing for high-risk groups. The use of rapid test kits and same-day disclosure of results has also encouraged early referrals and linkages to minimize pre-ART attrition. The use of point-of-care CD4 testing is also being encouraged in RLS and the assessment of the need for ART initiation immediately after HIV testing. The revision of the CD4 count cut-off for ART initiation to < 350 cells/μL from <200 cells/μL by many countries is also expected to help reduce morbidity and mortality from late ART initiation. In the USA, the test-and-treat approach was recently adopted. As desirable as that scenario may be, it may not be possible to implement such initiatives in sub-Saharan Africa because of the cost implications.

In conclusion, we found that, among patients entering care, almost two-thirds were diagnosed with AHD, and an overwhelming majority were late presenters, with CD4 counts below the threshold at which initiating ART is recommended. These findings should raise concerns. Prompt HIV diagnosis and entry into care and timely initiation of ART are critical for reducing the risk of both opportunistic and nonopportunistic disease, prolonging survival, and reducing onward HIV transmission. Our findings also suggest that expanding testing and reducing late HIV diagnosis need to be a priority, if the programmes related to improving linkage to care and earlier ART initiation are to reach patients and potentially alter the trajectory of the HIV epidemic in Nigeria. It is only under such circumstances that late-stage or illness-triggered HIV diagnoses will be reduced.

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