The Epidemiology of Delayed HIV Diagnosis in Ibadan Nigeria

by

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ABSTRACT

Background: Human immunodeficiency virus infection (HIV) is one of the major health burdens in Nigeria. Delayed HIV diagnosis remains a significant driver of HIV transmission. The causes of delayed diagnosis are unknown. This observational study investigated demographic risk factors for delayed HIV diagnosis, time from HIV infection to diagnosis and trends in the rate of positive HIV tests and delayed diagnosis in Ibadan, Nigeria.

Methods: The Acquired immunodeficiency syndrome (AIDS) Prevention Initiative (APIN) database provided data on people living with HIV who enrolled for care between October 2013 and December 2018 at the Antiretroviral Therapy (ART) clinic in the University College Hospital, Ibadan, Nigeria. 3,458 patients aged 15 years or older, diagnosed with HIV for the first time, with available CD_4 counts, were included in this study. Delayed HIV diagnosis was defined as the Cluster of Differentiation 4 (CD_4) counts less than 350 cells/mm^3 at the time of first diagnosis. An assessment of the association between the outcome variable (delayed HIV diagnosis) and the independent variables was conducted using logistic regression analysis to identify the risk factors for delayed HIV diagnosis, and the time interval between HIV infection and diagnosis was calculated based on the average CD_4 decline rate.

Results: A total of 3,458 patients were included. The prevalence of delayed HIV diagnosis was 1,993/3,458 (57.6%). Risk factors significantly associated with delayed HIV diagnosis in the multivariate analysis were older age, retiree, marriage separation, never married and widowed females. Risk factors significantly associated with an early HIV diagnosis were student and

tertiary education. The mean time from infection to diagnosis was 6.3 years. A progressive decline in the rate of positive HIV tests and delayed HIV diagnosis were observed from 2014 to 2018.

Conclusion: The rate of delayed HIV diagnosis was high but is declining with time. HIV testing implementation should focus on groups at risk of delayed diagnosis.

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AIDS Acquired Immune Deficiency Syndrome

APIN AIDS Prevention Initiative in Nigeria

ART Antiretroviral Therapy

CD_4 Cluster of Differentiation 4

CDC Center for Disease Prevention and Control

ELIZA Enzyme-Linked Immunosorbent Assay

FSW Female Sex Workers

HAART Highly Active Antiretroviral Therapy

HIV Human Immunodeficiency Virus

HIVST HIV self-testing

HREB provincial Health Research Ethics Board

HSPH Harvard School of Public Health

IRB Institutional Review board

IDU Injecting Drug Users

MSM Men Who Have Sex with Men

MTCT Mother to child transmission

NL Newfoundland and Labrador

PAPFAR The Presidential's Emergency Plan for AIDS Relief

PMTCT Prevention of Mother to Child Transmission

PLHIV People Living with Human Immunodeficiency Virus

STC Special Treatment Clinic

STI Sexually Transmitted Infection

VCT Voluntary Counselling and Testing

WHO World Health Organization

OUTLINE

Chapter 1 presents the background of this study. Chapter 2 describes the literature related to delayed HIV diagnosis and its relevance to Nigeria. Chapter 3 describes the study methodology, which includes data sources, study population and statistical analysis. Chapter 4 presents the results, including the population's presentation and the results of the logistic regression models, estimation of infection time to diagnosis of HIV and the trends in the HIV incidence and delayed HIV diagnoses between 2014 and 2018. Chapter 5 contains a detailed discussion of the findings in the context of previous related studies in the literature, and a discussion of the strengths and limitations of this research. Chapter 6 provides a conclusion to this study.

CHAPTER 1: INTRODUCTION

1.1 Background

1.1.1 Epidemiology of HIV in Nigeria

HIV continues to be one of the most feared health challenges in the world since 1980 when the first case of AIDS was reported in Los Angeles, USA[1] [2]. HIV is one of the leading causes of morbidity and mortality globally[2] [3]. Since the beginning of the HIV pandemic, an estimated 76.1 million people have been infected, with 35 million deaths from AIDS-related diseases[3]. Globally, 36.7 million people were living with human immunodeficiency virus infection (HIV) at the end of 2018, and it is estimated that Sub-Saharan Africa accounted for 70% of this burden[4] [5]. Nigeria and South Africa account for over 40% of all HIV cases in Sub-Saharan Africa[4]. In 2019, Nigeria recorded the national HIV prevalence in adults aged 15-49 years to be 1.4%, with 1.9 million people currently living with HIV in Nigeria[4]. The HIV prevalence among women in this age group is estimated to be more than double that of men, with an estimated 1.9% prevalence in women versus 0.9% in men[6].

Heterosexual transmission accounts for over 90% of HIV transmission in Nigeria[4]. Mother to child transmission (MTCT) is another mode, and most children less than 15 years old living with HIV in Nigeria acquired HIV through MTCT[4]. Other modes of HIV transmission are not well documented, such as transfusion with infected blood products and contact with piercing tools used for tattoos and scarification[4]. HIV prevalence in men that have sex with men (MSM) and female

sex workers is 23% and 14.4%, respectively, while the prevalence among injected drug users is 3.4% [7]. Socio-cultural attitude towards homosexuality in Nigeria resulted in the stigmatization of MSM and the passage of same-sex marriage prohibition law[8]. Compared to the developed world such as the USA, Canada and countries in Europe[9 10 11], investigating HIV infection among MSM in Nigeria may be challenging due to the antigay law; this means that MSM may have some difficulties accessing HIV care services[7].

1.1.2 HIV Control in Nigeria

Nigeria has the second largest HIV epidemic in the world[12]. In 2014, more than 200,000 Nigerian children were orphans due to the HIV epidemic[2]. In 2018, Nigeria recorded 130,000 new cases, and 53,000 HIV-infected people died from AIDS-related diseases[13]. Nigeria has had significant success in the fight against HIV in the last three years[6 14]. The current prevalence of HIV in adults aged 15 to 49 is 1.4% compared to 2.8% in 2017, and the estimated number of PLHIV has dropped from 3.1 million in 2017 to 1.9 million in 2019[6 14]**.** The reduction of HIV prevalence in Nigeria in recent years is a result of increased access to HIV testing and treatment, which is associated with the decline in HIV transmission rate[6 14 15]. World Health Organization (WHO) report for 2019 showed that only 67% of PLHIV in Nigeria are diagnosed, 53% are on antiretroviral therapy (ART), and only 42% have achieved viral suppression on ART[16]. Therefore, Nigeria has not achieved the 90-90-90 control target recommended by the WHO[17]. Only 15.1% of persons between the ages of 15 and 49 had an HIV test in the last 12 months[7].

Voluntary counselling and testing (VCT) have been the traditional model in Nigeria for HIV testing service delivery in which individuals voluntarily seek HIV counselling and testing[4].

However, this testing strategy has not been proven effective to ensure more people are tested for HIV in Nigeria[18]. In the effort to effectively address the low HIV testing rate in Nigeria, the federal ministry of health adopted provider-initiated testing and counselling (PITC) strategies in 2017 which enables physicians to provide HIV testing with counselling before and after the test[4 18]. The PITC strategies include opt-out and opt-in approaches[19]. Opt-out testing is the prioritized testing strategy in Nigeria, with the opt-in strategy option's availability as part of HIV testing services[4]. The opt-out approach is part of routine screening for infections, but it is required that the physician inform the patients that HIV testing is not considered routine testing, and the patients can decide to opt-out of this test[19]. Whereas an HIV test can only be done in the opt-in approach once the physician obtains written informed consent[19]. However, neither of these approaches achieves a high testing rate[20].

In 2002, Nigeria's government established and funded 25 ART centers, including the ART clinic of the University College Hospital, Ibadan. In 2004, the Presidential Emergency Plan for AIDS Relief (PEPFAR) started providing support for the scale-up of the national ART treatment program. The University College Hospital clinic is supported by the Center for Disease Prevention and Control (CDC) through AIDS Prevention Initiative Public Health, Nigeria.

Between 2001 and 2012, Nigeria was among twelve African countries with a stable rate of new HIV infections, defined as less or equal to a 25% change in incidence rate[21]. However, most African countries experienced a drop in incidence by at least 25% and Ghana and the Central Africa Republic observed a decrease in HIV incidence of over 50% [21]. The trend in the incidence of HIV in Nigeria over the years necessitates the need to understand the trends and to predict the

future trends[3 4 22]. Understanding the risk factors for delayed HIV diagnosis is critical in HIV control and preventing its transmission[15]. This may inform an evidence-based plan for effective control of HIV[3 23].

1.1.3 HIV Pathogenesis

The depletion of CD_4 T cells in the peripheral blood, lymphoid, and mucosal tissues is the pathogenesis of HIV infection[24]. HIV binds to CD_4 cells, replicates inside the CD_4 cell, and causes CD_4 cell death, leading to the gradual loss of function of T cell[25 26]. This results in progressive immunosuppression and mortality[27]. Since CD_4 T cells play a major role in the immune defence system against pathogens, patients with HIV are susceptible to opportunistic infections[24]. The level of CD_4 counts is the most important determinant of HIV disease progression and clinical outcome and is a prognostic indicator of the amount of immune function remaining[28]. Fatal opportunistic infections are most common at CD_4 count below 200 cells/mm^3 [28]. HIV has no cure, but it can be controlled by ART, providing PLHIV with a long and healthy life[29]. ART leads to a gradual recovery of CD_4 T-cells[30]. Early initiation of ART reduces mortality[31] and HIV transmission[32]. Current HIV treatment guidelines recommend starting ART immediately at HIV diagnosis[32].

1.1.4 HIV Diagnosis Method

HIV diagnosis is made by demonstrating the presence of the viral antigens and host antibodies in the blood using enzyme-linked immunosorbent assay (ELISA) performed in a laboratory[4 33]. In high-income countries, positive ELISA is confirmed with a second ELISA and a Western blot test[4]. However, in low resource and high HIV prevalence settings where the pre-test probability is high, such an approach is not cost-effective[31]. In Nigeria, rapid point of care or ELISA tests

without a Western blot are used in a diagnostic algorithm[4]. An initial positive rapid or ELISA test will be followed by a second rapid or ELISA test using a different test kit to confirm, while a single negative test requires no further testing[4].

1.1.5 Delayed Diagnosis

Delayed HIV diagnosis among PLHIV who are unaware of their HIV status is a major driver of transmission of HIV since people who are unaware that they are infected do not modify their behaviour or seek treatment, and it is associated with a higher rate of early mortality and cost of treatment[34]. Although older people have been described to be associated with delayed HIV diagnosis in Nigeria and other parts of Africa[15 35 36 37], young individuals are most susceptible to HIV infection, in sub-Saharan Africa, most of the new HIV cases are people aged 15-24 years[38]. HIV is primarily a health burden in Nigeria and a great threat to socio-economic development; given the highest HIV transmission rate among the young adult group, it has a devastating impact on economic productivity in Nigeria[2]. Understanding risk factors for delayed diagnosis may inform targeted testing initiatives to reduce delayed HIV diagnosis, which may subsequently have a favourable impact on the transmission rate of HIV in Nigeria.

As opposed to the developed world, such as the USA and countries in Europe[9 39], literature reporting the prevalence and risk factors for delayed HIV diagnosis in Nigeria are scarce[15]. Identifying these risk factors is a critical first step toward addressing the high rate of delayed HIV diagnosis in Nigeria. This study aimed to understand the risk factors associated with delayed HIV diagnosis in Nigeria. In addition to the detailed analysis of the risk factors for delayed HIV diagnosis, this study will also estimate the time from HIV infection acquisition to diagnosis.

CHAPTER 2: LITERATURE REVIEW

2.1 Definition of Delayed HIV Diagnosis

There is no unified consensus on the definition of late diagnosis of HIV, but several studies define it as a CD_4 count at diagnosis that is less than 200 cells/mm^3 [11]. The European consensus definition of late diagnosis is a CD_4 count of less than 350 cells/mm^3 or clinical AIDS or the presence of opportunistic infection. Several developed countries have described the prevalence of delayed HIV diagnosis ranging from 14 to 55.9% [15]. In Canada, the prevalence of delayed HIV diagnosis is between 8.8 and 30% [11], while in Africa, Asia, and some parts of South America, the prevalence of delayed HIV diagnosis ranges from 49 to 55% [15].

2.2 Delayed HIV diagnosis in Nigeria

Several African countries, including Nigeria, adopted rapid HIV testing kits to provide efficient HIV testing services that are readily available in all health facilities in Nigeria[40]. Home oral HIVST (HIV self-testing) kit has also been introduced in Nigeria[41]. High acceptability of HIVST has been reported in Nigeria and several other African countries[42 43 44]. This promising result can have a favourable effect on the socio-cultural barriers that prevent the utilization of standard facility-based HIV testing services in Nigeria and other parts of Africa[42]. The uptake of oral HIVST can allay the fear of accessing HIV testing due to stigmatization and criminalization among at-risk populations such as MSM[41]; thus, high uptake of HIVST may help reduce delayed HIV diagnosis in this group. Iliyasu et al. (2020) observed high uptake of HIVST compare to HIV counselling and testing strategies among university students in Nigeria[45]. A high rate of acceptability of HIVST among the general population and at-risk groups, including MSM, with

subsequence increase in HIV test coverage, has been reported worldwide[42 46 47]. In a study by Tun et al. (2018) which examined the uptake of the oral HIVST kit among the urban MSM population in Nigeria, high acceptability of HIVST was reported[48]. Although PITC and VCT strategies have recorded some success in many regions of Nigeria, HIV testing coverage is still far below the national target of 95%, as stated in the national HIV/AIDS strategic framework[18 49]. The major drawback of PITC and VCT strategies among the general population is fear of stigmatization if they are HIV positive[48], indicating that many patients often opt out of HIV testing when the physicians offer it. However, these challenges are moderately overcome in few settings, such as STI and antenatal clinics where HIV and other infectious diseases are screened as part of routine general practice[50 51]. An eight months prospective study conducted at the STI clinic of the University College Hospital Ibadan, Nigeria, observed a 21.9% prevalence rate of HIV among patients who visited the clinic within the study period[50].

Given the legal implications around homosexuality and the difficulty gay individuals face in accessing HIV care services in Nigeria[8], the high rate of usage of HIVST among MSM[48] revealed the need to formulate alternative strategies of HIV testing not only among the population at risk but also general population[41]. This strategy can be a great tool in achieving early HIV diagnosis and linkage to ART[41].

2.3 Infection Time to Diagnosis and Delayed HIV Diagnosis in Nigeria

Despite easy access to HIV testing services in Nigeria, most new HIV patients had lived with their infection for years before they were diagnosed, and many people remained undiagnosed[4 34 52]. High mortality due to AIDS and short survival time among PLHIV in Nigeria and most African countries can be linked to delayed diagnosis[52 53]. These findings are consistent with those from other Africa countries such as Uganda and Tanzania[52]. Agaba et al. (2014) observed an 85.6% prevalence of diagnostic delay among 14,000 patients in Jos city, Nigeria, in which 63% presented with advanced HIV disease using the European consensus definition of late HIV diagnosis[15]. Delayed diagnosis of HIV was reported as 67.4% among patients in Lagos, Nigeria, using a threshold CD_4 count of <350 cells/mm^3 [15]. A cross-sectional study conducted in an HIV care clinic of a general hospital in Nigeria observed that the mean time between HIV infection and diagnosis was 6.7 years and 8.1 years for men and women, respectively[54].

Even with the international support and the introduction of voluntary counselling and testing for HIV, Nigeria still experience low test coverage[17 18 55]. About 40-90% of new HIV infections in Nigeria are associated with symptoms[18], indicating diagnosis is delayed. The fear of being stigmatized is a major barrier to HIV diagnosis in Nigeria[4]; thus, this may negatively impact regular HIV testing among the general population, making the information on most individual last HIV tests to be impracticable in Nigeria.

2.4 Risk Factors for Delayed HIV diagnosis

Demographic factors have been described as predictors of early and delayed HIV diagnosis[11]. In Nova Scotia, Canada, older age was observed as the demographic characteristic that significantly

predicts a delayed HIV diagnosis[11]. In a European study consisting of 34 countries, the prevalence of delayed HIV diagnosis was 62.4% among heterosexual men, 52.2% among heterosexual women and 39% among MSM[9]. Older age, heterosexuality, MSM and IDU were predictors of delayed HIV diagnosis in most countries[9].

2.5 Factors Associated with Delayed HIV Diagnosis in Nigeria

Only one study reporting the prevalence of delayed diagnosis in Nigeria with analysis of the risk factors was found[15]. Risk factors for delayed HIV diagnosis in Nigeria include male sex, older age, being a civil servant, Hepatitis C and Hepatitis B virus coinfection, widowed or divorced, unemployment, poverty, and fear of discrimination[15]. Identifying risk factors for delayed HIV diagnosis may result in a focused effort to move diagnosis to earlier in infection[15 52 56].

2.6 Study Objectives

The study objectives of the thesis projects are:

1. To measure the prevalence of delayed diagnosis of HIV in a single HIV clinic in Ibadan, Oyo State, Nigeria, and identify the risk factors for delayed diagnosis from 2013 to 2018.
2. To estimate the time from HIV infection acquisition to the diagnosis of HIV in patients diagnosed between 2013 and 2018.
3. To examine the trends in the rate of positive HIV tests and delayed HIV diagnoses from 2014 to 2018.

CHAPTER 3: METHODS

3.1 Study Design, Setting and Population, Data Source

This study was an observational design involving the data of people with HIV infection who enrolled for care between January 2013 and December 2018 at the ART clinic in the University College Hospital, Ibadan, Nigeria. The ART clinic is under Special Treatment Clinic (STC) and a regional center of excellence in infectious disease training, research, and treatment of STD, including HIV, and one of the two designated STCs in the state. The clinic is located in Ibadan city center and serves as a walk-in clinic and referral center for HIV patients in Ibadan city, Oyo state and the region. Ibadan is the capital and largest city of Oyo State, with a population of over 5 million, the third most populous city in Nigeria.

Patient information was collected at the first clinic visit by the attending physicians using a standardized preassessment form and entered to the electronic data management system. Information collected from the time of HIV diagnosis included clinical and socio-demographic variables, such as age at diagnosis, gender, marital status, leader in a religious organization, educational status, occupation, and employment status.

This study made secondary use of data that was made available by APIN Public Health Initiatives database. APIN Public Health Initiative Nigeria is a program of the Harvard School of Public Health, in partnership with non-governmental agencies, the Nigerian governmental and the University College Hospital. APIN Public Health Initiatives Nigeria is supported by the Center for Disease Prevention and Control (CDC) and Bill and Melinda Gates.

Inclusion criteria were patients with HIV infection, aged 15 years or older, with a documented CD_4 count at diagnosis. Of the 3,559 patients in the data provided for this study, 58 were excluded for lack of CD_4 counts at diagnosis. Of the remaining 3,501, 30 were excluded because of missing data, and 13 patients were excluded because their age was less than 15 years. A total of 3,458/3,559 patients (97.2%) of available patients were included in the study.

3.2 Ethics Statement

Ethics approval was given by the APIN Institutional Review Board (IRB) in Nigeria (Approved February 26, 2020, IRB reference IRB033-SD) and the Health Research Ethics Board (HREB) of Newfoundland and Labrador (Approved March 12, 2020, HREB reference 2019.229). Data was collected without identifiers to protect patient identity. Raw data was kept locked in Dr. Peter Daley's office and destroyed at the end of the analysis.

3.3 Power Analysis

Power analysis was conducted to determine if the sample size for this study would be sufficient to detect statistically significant associations between delayed HIV diagnosis and the risk factors of interest. Analysis of power was performed considering the prevalence of delayed HIV diagnosis in the reference group ranging from 40% to 60% with the assumption of two equal-size groups and the odds ratio ranging from 1.3 to 1.8 (see the sample size calculation in table 1). If the prevalence of delayed HIV diagnosis in the reference group is 60%, we need at least 1,964

individuals to detect an OR of 1.3 at 0.05 level with 80% power. The analysis of power confirmed that 3,458 subjects will provide enough power for this study.

Table 1: Sample Size Calculation

Index	Reference Proportion	Odds Ratio	Actual Power	N power
1	0.4	1.3	0.800	1864
2	0.4	1.4	0.800	1130
3	0.4	1.5	0.800	776
4	0.4	1.6	0.801	578
5	0.4	1.7	0.802	454
6	0.4	1.8	0.802	370
7	0.5	1.3	0.800	1838
8	0.5	1.4	0.800	1122
9	0.5	1.5	0.800	776
10	0.5	1.6	0.801	582
11	0.5	1.7	0.800	458
12	0.5	1.8	0.801	376
13	**0.6**	**1.3**	**0.800**	**1964**
14	0.6	1.4	0.800	1208
15	0.6	1.5	0.801	842
16	0.6	1.6	0.801	634
17	0.6	1.7	0.802	504
18	0.6	1.8	0.800	414

3.4 Study Variables

The CD_4 count at diagnosis reflects the state of the immune system and an excellent predictor of the progression of the disease process in HIV[24]. In this study, the outcome variable is the delayed diagnosis of HIV, which is the CD_4 count of less than 350 cells/ mm^3. Risk factors known to be associated with delayed HIV diagnosis in Nigeria[15] were collected as predictor variables, including socio-demographic information such as gender, age at diagnosis, employment status, marital status, educational status, occupation, leader in a religious organization.

All variables are categorical, except CD_4 count, which is a continuous variable with a normal reference range of 500-1500 cells/ mm^3. Each categorical variable was classified; accordingly, age was categorized as 15–39 years or 40years and above. Gender was categorized as male or female. Education was categorized as none, primary, secondary, or tertiary. Occupation was categorized as trader, student, commercial driver, civil servant, retiree, or other. Leader in a religious organization was categorized as yes or no. Marital status was categorized as single, married, separated, or divorced. Employment status was categorized as employed or unemployed.

3.5 Data Analysis

The socio-demographic characteristics were described as mean and frequency/percentage for continuous and categorical variables, respectively. Differences in percentage for categorical variables and means for continuous variables between groups were examined by t-test and chi-square tests, respectively. The associations between delayed HIV diagnosis and presumed risk factors of delayed HIV diagnosis were examined using logistic regression models in both

univariate and multivariate analyses. Using SAS 9.4 (SAS System for Windows copyright © 2019 SAS Institute Inc) was used in all the analyses in this study.

3.5.1 Risk Factors for Delayed HIV diagnosis

An assessment of the association between the outcome variable (delayed HIV diagnosis) and the independent variables of interest (see table 3) was conducted using univariate and multivariate logistic regression models. Firstly, the association between each of the independent variables and the outcome variable was examined by univariate logistic regression models. Follow by a multivariate logistic regression model involving the statistically significant variables at $p>0.20$ level in the univariate models. All the independent variables that were significant at $p>0.50$ level in the first multivariate model were included in the second multivariate model with relevant interaction terms. The final model consists of the significant variables and significant interaction term.

In addition to the multivariate logistic analysis with the main effect, possible effect modification was also examined in the final model. The strength of association between the independent variables and delayed HIV diagnosis was reported as odds ratios, 95% confidence interval and p-value. A linear trend test was performed using the Cochran-Armitage test to test a linear relationship between delayed HIV diagnosis and age group and between delayed HIV diagnosis and educational level.

3.5.2 Estimation of Time from HIV Infection to HIV Diagnoses Using CD_4 Count Depletion Model

Time from infection to diagnosis was estimated in years using the CD_4 count depletion model. The CD_4 depletion model contains two constants: 847 cells/mm^3, the average CD_4 counts among healthy Nigerians[54] and 80 cells/mm^3/year, the average CD_4 rate of decline in the absence of treatment [57]. The depletion rate was applied to the first observed CD_4 count to estimate the time between infection and diagnosis. Using the formula $t = (N – n)/80$, where t is the approximate time between infection and diagnosis, N is the reference mean CD_4 counts among healthy Nigerians, and n is the mean CD_4 counts at diagnosis. This model has been used in previous studies[52 54 58].

3.5.3 Trends in the Rate of Positive HIV Tests and Delayed HIV Diagnoses Between 2014 and 2018

Annual observation of the rate of positive HIV tests and rate of delayed HIV diagnosis within the cohort were compared annually between 2014 to 2018. Data from October 1, 2013, to December 31, 2013, were not included in this analysis.

CHAPTER 4: RESULTS

4.1 Descriptive Statistics

Table 2 describes the included cohorts. Of all the patients, 55.7% were diagnosed between the age of 15 and 39 years, and 44.3% were diagnosed at 40 years or more. The percentage of married patients was 52.6%, which was higher than those who were divorced (1.9%), separated (8,7%), widowed (11.8%), and single (25%). Of all the patients, patients who attained a secondary school education were 36.5%, 19.8% of patients had primary school education, 27.3% had tertiary education, and 16.4% had no formal education. Traders accounted for more than one-third (37.4%) of all the patients, which was higher than students, commercial drivers, civil servants, and retirees, while other occupations made up 45.4% of all the patients. Most of the patients were employed and were not leaders in a religious organization, with 97.9% and 98.9%, respectively. The percentage of delayed HIV diagnosis was 57.6%. Delayed diagnosis was more common among female patients (66.0%) than male patients (34.0%).

Table 2: Descriptive Analysis

Variables	Labels	Total (%) (N=3458)
Delayed HIV	Yes No	57.6 42.4
Age	15-39 years ≥40 years	55.7 44.3
Gender	Male Female	34.0 66.0
Marital status	Single Married Separated Divorced Widowed	25.0 52.6 8.7 1.9 11.8
Educational level	None Primary Secondary Tertiary	16.4 19.8 36.5 27.3
Occupation	Trader Student Commercial driver Civil servant Retiree Other	37.4 7.2 5.3 3.0 1.7 45.4
Employment Status	Employed Unemployed	97.9 2.1
Leader in a religious organization	Yes No	1.1 98.9
Enrollment year	2013 2014 2015 2016 2017 2018	6.3 25.9 19.1 19.3 15.7 13.8

4.2 Univariate Analysis

Table 3 presents the results of the univariate analysis. The odds of delayed HIV diagnosis in patients aged 40 years or more was 1.74 times more than those aged 15-39 years (OR 1.74; 95% CI 0.59–0.92). Male patients had a 1.5 times higher odds of delayed HIV diagnosis than female patients (OR 1.50; 95% CI 1.30–1.73). Compared with married patients, patients who were separated were 2.29 times more likely to be diagnosed late (OR 2.29; 95% CI 1.74–3.02), the odds of delayed HIV diagnosis were 1.85 times higher in patients who were divorced (OR 1.85; 95% CI 1.09–3.15), and the odds of delayed HIV diagnosis was 1.36 times higher in the patients who were widowed (OR 1.36; 95% CI 1.09–1.70). However, the odds of delayed HIV diagnosis in patients who were single was 0.86 times less than married patients (OR 0.84; 95% CI 0.72–0.99).

The odds of delayed HIV diagnosis in patients who had a tertiary education was 0.64 times less than patients with no formal education (OR 0.64; 95% CI 0.52–0.79). Compared with other occupations, patients who were retired were 4 times more likely to have a delayed HIV diagnosis (OR 4.20; 95% CI 2.50–8.61), commercial drivers were 2 times more likely to have a delayed diagnosis of HIV (OR 2.28; 95% CI 1.61–3.23), whereas in patients who were students, the odds of delayed HIV were 0.5 times lesser (OR 0.50; 95% CI 3.38–0.66). The odds of delayed HIV diagnosis in patients who were leaders in a religious organization was 2.47 times more than patients who were not (OR 2.47; 95% CI 1.17–5.22).

Table 3: Univariate Analysis of Delayed HIV Diagnosis

Variable	% of delayed HIV diagnosis	Odds ratio	95% Cl		P-value	Type 3 P-value
			Lower	Upper		
Age						
≥40 years	65.01	1.73	1.51	1.99	<0.0001	
15-39 years	51.77	1				
Gender						
Male	64.06	1.50	1.30	1.73	<0.0001	
Female	54.32	1				
Marital status						<0.0001
Single	51.68	0.84	0.72	0.99	0.0385	
Separated	74.42	2.29	1.74	3.02	<0.0001	
Divorced	70.15	1.85	1.09	3.15	0.0232	
Widowed	63.33	1.36	1.09	1.70	0.0065	
Married	55.94	1				
Educational level						<0.0001
Primary	65.06	1.24	0.99	1.56	0.0673	
Secondary	59.03	0.96	0.78	1.17	0.6864	
Tertiary	48.94	0.64	0.52	0.79	<0.0001	
None	60.04	1				
Occupation						<0.0001
Trader	59.00	1.11	0.96	1.29	0.1717	
Student	39.52	0.50	0.38	0.66	<0.0001	
Commercial driver	74.73	2.28	1.61	3.23	<0.0001	
Civil servant	56.73	1.01	0.68	1.51	0.9571	
Retiree	84.48	4.20	2.05	8.61	<0.0001	
Other	56.46	1				
Employment status						
Unemployed	58.33	1.03	0.64	1.65	0.9037	
Employed	57.62	1				
Leader in a religious organization						
Yes	76.92	2.47	1.17	5.22	0.0177	
No	57.41	1				

4.3 Multivariate Analysis

Table 4 presents the results of multivariate analysis. The odds of delayed HIV diagnosis in patients aged 40 years or older were 1.29 times more than those aged 15 to 39 years (OR 1.29; 95% CI 1.10–1.51). In the linear trend test between delayed HIV diagnosis and age groups (15-40, 21-40, 41-60, and 61 years or more), a linear relationship was observed (trend test: p-value <0.0001), thus the probability of delayed HIV diagnosis increases with increasing age. The odds of delayed HIV diagnosis in patients with a tertiary education were 0.71 times less than those with no formal education (OR 0.71; 95% CI 0.56–0.88). A linear relationship between delayed HIV diagnosis and educational level was observed (trend test: p-value <0.0001), thus the probability of delayed HIV diagnosis decreases with the order of educational level from none to tertiary education**.** Compared with other occupations, the odds of delayed HIV diagnosis in retirees were 3.24 times higher (OR 3.24; 95% CI 1.56–6.74), and the odd of delayed HIV diagnosis in students was 0.61 times lesser (OR 0.61; 95% CI 0.45–0.82).

A statistically significant interaction term between gender and marital status was observed in the final multivariate model (p-value = 0.0249). The odds of delayed HIV diagnosis in male patients who were separated was 2.16 times more than married male patients (OR 2.16; 95% CI 1.21–3.88). Compared to married female patients, the odds of delayed HIV diagnosis in single female patients were 1.36 times higher (OR 1.36; 95% CI 1.09–1.71), the odds of delayed HIV diagnosis in female patients who were separated was 2.17 times higher (OR 2.17; 95% CI 1.57–2.99), whereas the odds of delayed HIV diagnosis in female patients who were widowed were 1.37 times higher (OR 1.37; 95% CI 1.06–1.77).

Table 4: Multivariate analysis of delayed HIV diagnosis

Variables	Odds ratio	95% Cl		P-value	Type 3 p-value
		Lower	Upper		
Age					
≥40 years	1.29	1.10	1.51	0.0016	
15-39 years	1				
Educational status					<0.0001
Primary	1.18	0.93	1.50	0.1706	
Secondary	1.01	0.82	1.24	0.9614	
Tertiary	0.71	0.56	0.88	0.0021	
None	1				
Occupation					<0.0002
Trader	1.09	0.92	1.29	0.3018	
Student	0.61	0.45	0.82	0.0012	
Commercial driver	1.35	0.93	1.97	0.1151	
Civil servant	1.10	0.73	1.67	0.6466	
Retiree	3.24	1.56	6.74	0.0017	
Other	1				
Interaction Between Gender and Marital Status					0.0249
Male					
Single	0.77	0.57	1.04	0.0857	
Separated	2.16	1.21	3.88	0.0096	
Divorced	2.02	0.67	6.11	0.2122	
Widowed	0.93	0.54	1.61	0.7952	
Married	1				
Female					
Single	1.36	1.09	1.71	0.0073	
Separated	2.17	1.57	2.99	<0.0001	
Divorced	1.73	0.93	3.24	0.0856	
Widowed	1.37	1.06	1.77	0.0179	
Married	1				

4.4 Estimation of Time from HIV Infection to HIV Diagnoses

Table 5 presents the results of the time from infection to diagnosis. The overall mean estimate of the time to diagnosis was 6.3 years. Time to diagnosis for patients aged 40 years or older was longer than younger patients aged 15-39 years, and the time was 6.9 years and 5.9 years, respectively. Time to diagnosis was longer in males than in females (male; 6.8 versus female; 6.1). In comparison to other marital statuses (married: 6.24 years, widowed: 6.71 years, divorced: 7.31 years, and separated: 7.42 years), being single revealed a moderately shorter time to diagnosis (5.80 years). Compared to other educational levels (None: 6.43 years, primary: 6.90 years, secondary: 6.35 years), having a tertiary education showed a moderately shorter infection time to diagnosis of HIV (5.75 years). In the occupation category, being students revealed a substantially shorter infection time to diagnosis (4.91 years) than all other patients in the occupation categories (retiree: 7.79 years, commercial driver: 7.45 years, civil servant: 6.17 years, trader: 6.38 years). The calculation revealed that students and patients with tertiary education have the shortest time to diagnosis.

Table 5: Estimation of Time from HIV Infection to HIV Diagnoses

Variables	Mean CD_4 counts at diagnosis (n)	Mean CD_4 counts difference (N-n)	Infection time to diagnosis in years [t=(N-n)/80]
Age			
≥40 years	298.98	548.02	6.85
15-39 years	376.67	470.33	5.88
Gender			
Male	302.09	544.91	6.80
Female	362.98	484.02	6.05
Marital status			
Single	383.36	463.64	5.80
Separated	253.12	593.88	7.42
Divorced	261.88	585.12	7.31
Widowed	310.18	536.82	6.71
Married	347.67	499.33	6.24
Educational level			
Primary	295.23	551.77	6.90
Secondary	338.78	508.22	6.35
Tertiary	386.79	460.21	5.75
None	332.55	514.45	6.43
Occupation			
Trader	336.64	510.36	6.38
Student	454.60	392.40	4.91
Commercial driver	250.96	596.04	7.45
Civil servant	353.54	493.46	6.17
Retiree	223.50	623.50	7.79
Other	343.36	503.64	6.30

N=847 cells/mm³, the average CD_4 counts in healthy Nigeria Adults, **n** is the average CD_4 counts at diagnosis in each category of the variables in the data examined, and 80 (cells/mm³) is the CD_4 counts that deplete per calendar year in untreated HIV infected individuals.

4.5 Trends in the Rate of Positive HIV tests and Delayed HIV Diagnosis in Ibadan Between 2014 and 2018.

As presented in Figure 1, there was a progressive decline in the rate of positive HIV tests and the rate of delayed HIV diagnosis between 2014 and 2018. Of the 3247 new HIV diagnoses from 2014 to 2018, the rate of positive tests among tests performed dropped from 28% in 2014 to 20% in 2015 and then to 17% in 2017, and 15% in 2018, a 13% decrease over four years**.**

Furthermore, from 2014 to 2018, the annual rate of delayed HIV diagnosis was 15.24% in 2014, while in 2015, the trend in the delayed HIV diagnosis per annum presented a steady decline, which was sustained until 2018, the end of the study period. The percentage of delayed HIV diagnosis dropped from 15.2% in 2014 to 11.8% in 2015, increased to 12.2% in 2016, then decreased to 9.6% in 2017 and 9.2% in 2018. Figure 2 shows a progressive trend in decline in the rate of annual cases of delayed HIV diagnoses with a percentage decrease of 6.06% from 2014 to 2018.

Figure 1: Trends in the Rate of Positive HIV Tests Between 2014 and 2018

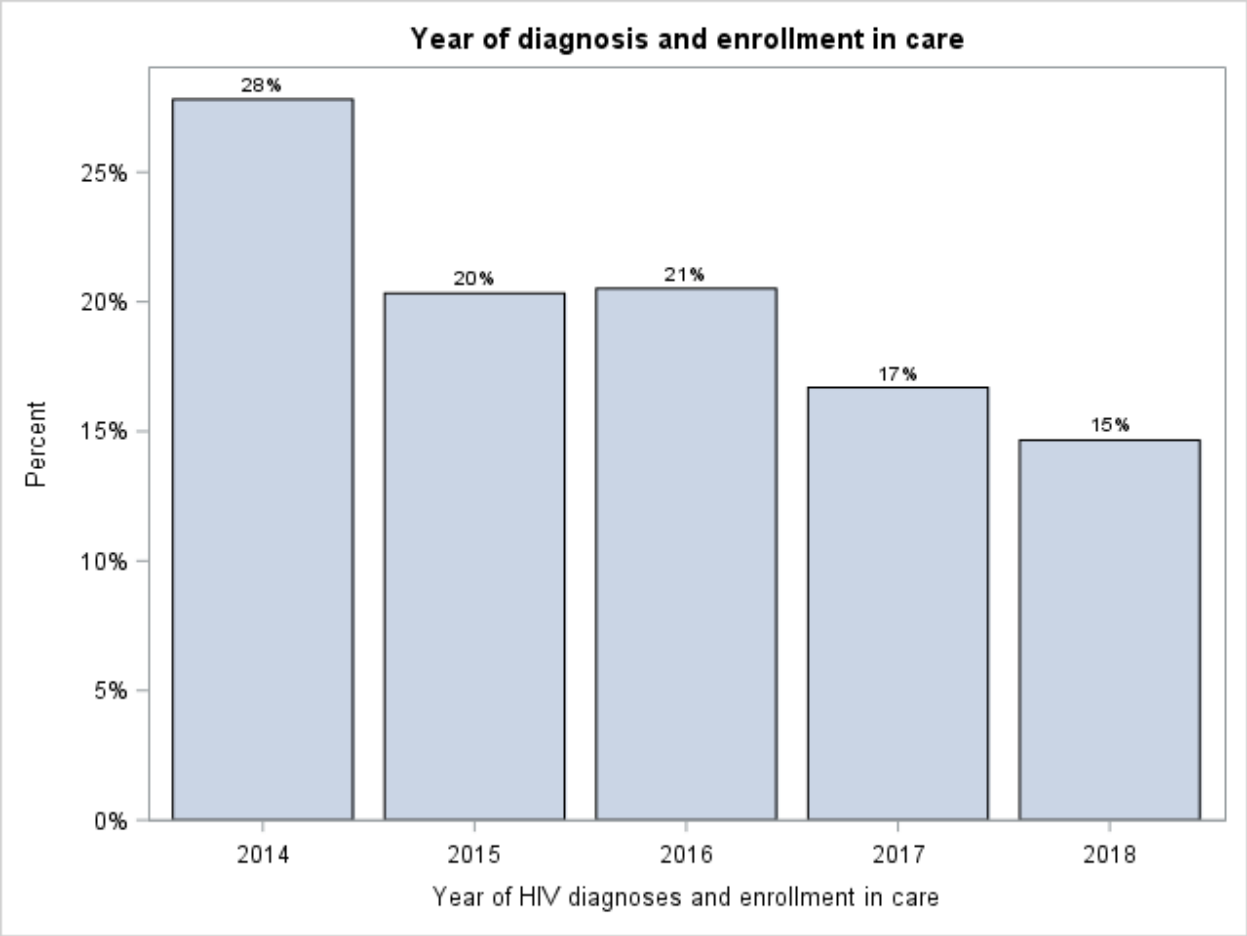
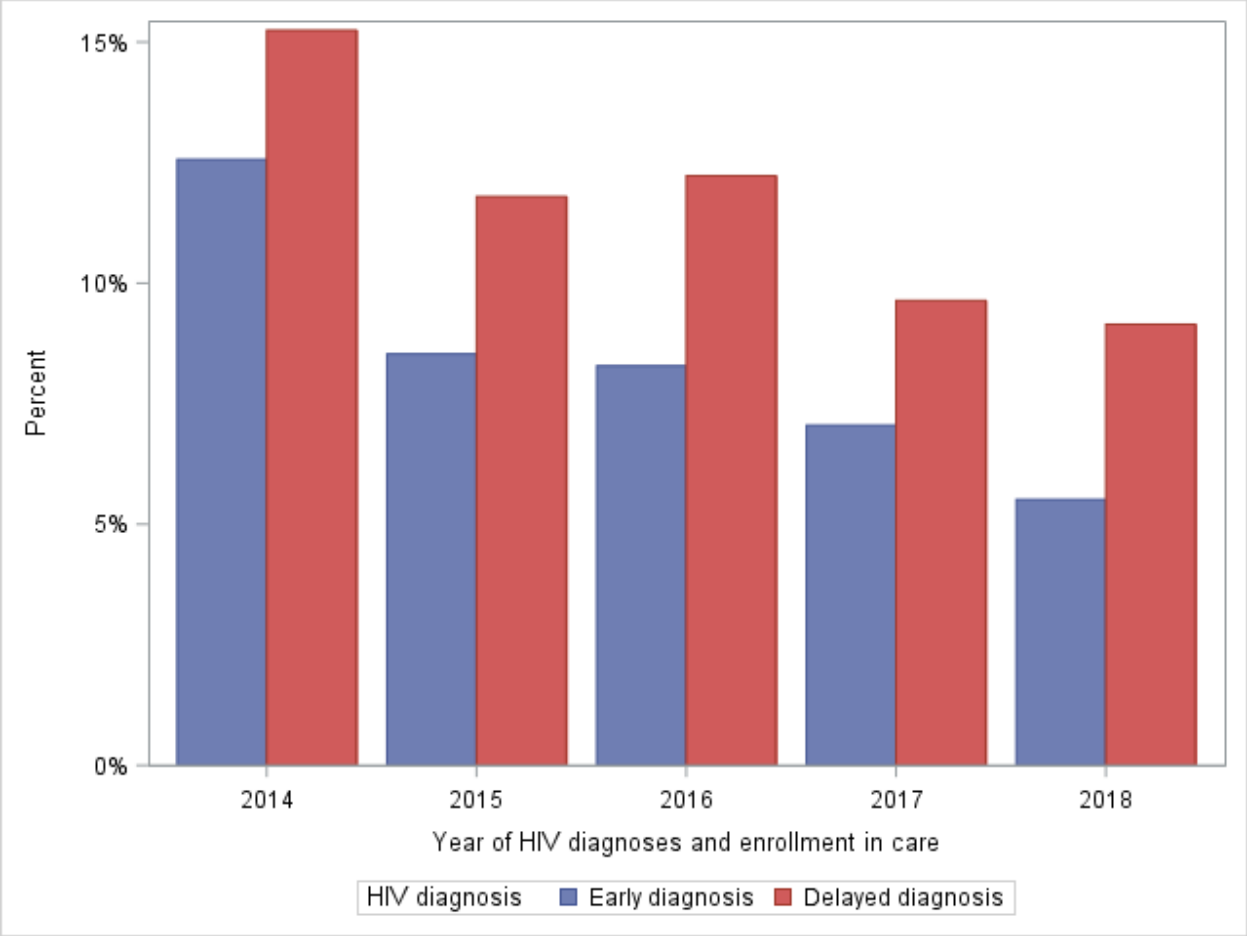


Figure 2: Trends in the Rate of Delayed HIV Diagnosis Between 2014 and 2018



CHAPTER 5: DISCUSSION

In the last two decades, evidence has demonstrated that early diagnosis of HIV infection is fundamental to its successful treatment and prevention of its onward transmission[59 60 61]. Before the inception of Highly Active Antiretroviral Therapy (HAART), HIV-infected individuals would eventually die of AIDS due to progressive loss of immune function[61]. Early diagnosis of HIV with immediate initiation of ART and retention in care will not only result in viral suppression and reduced mortality but also reduced the risk of transmission[61 62]. Delayed HIV diagnosis means the opportunity to minimize transmission either by high-risk behavioural modification or by immediate linkage to HIV care and ART initiation are missed[63]. Identifying the risk factors responsible for delayed HIV diagnosis in millions of HIV patients in Nigeria and other countries in Africa and establishing the time delay or the infection time to diagnosis is of utmost importance. Delayed HIV diagnosis is a major contributing factor to the challenges most African countries face in the effective control of the onward transmission of HIV infection[15 64 65]. Identifying the factors associated with delayed HIV diagnosis and determining the estimates of the time interval between acquisition of infection to the time patients were diagnosed may be a game-changer in HIV control in Nigeria and encourage the adoption of a focused HIV screening policy.

In this study, a retrospective analysis of data on 3458 patients was conducted on HIV patients who were diagnosed at the ART clinic of the University College Hospital Ibadan, Nigeria, between 2013 and 2018. The risk factors of delayed HIV diagnosis were studied to identified factors associated with delayed HIV diagnosis in Nigeria. The findings in this study indicate that risk factors such as older age, tertiary education, being students, retirees were associated with delayed

HIV diagnosis. More so, both separated males and females were more likely to have delayed HIV diagnosis compared to those married within their gender. Compared with married female patients, widowed and single females were more likely to have delayed HIV diagnosis. The marital status effect on the risk of delayed HIV diagnosis was greater among females than males. However, in the multivariate analysis without the interaction term between marital status and gender, male patients were more likely to have delayed HIV diagnosis compared to females. Additionally, compared to other factors, the calculation for the infection time to diagnosis showed that retirees have the longest time to diagnosis, while students and patients with a tertiary education showed a shorter infection time to diagnosis. Moreover, the analysis of trends in the rate of positive HIV tests and delayed diagnosis between 2014 and 2018 showed a progressive decline in both the annual rate of positive HIV tests and delayed HIV diagnosis.

This study found that older patients were more likely to have delayed HIV diagnosis compared to younger patients, and this is consistent with previous studies in Nigeria and other parts of the world. The older age group has been well described as a risk factor for delayed HIV diagnosis[15] [66] [56]. In a Nigerian study by Agaba et al. (2014), older patients compared to younger patients were significantly associated with delayed HIV diagnosis[15]. A similar association between older age and the risk of delayed HIV diagnosis was reported in a cross-European study involving 34 countries[9]. Older age was also found to be associated with delayed HIV diagnosis in previous studies in Canada[67] [59]. The association observed in the older patients may be due to the perception as being a low-risk group by the primary health care physicians, as a result, this group of people may miss the opportunity to be diagnosed early for HIV[68].

Association of delayed HIV diagnosis and male gender, and delayed HIV diagnosis and marital status have been well documented in many studies[15 59 65 66 67 69 70]. However, a critical analysis assessing the effect of marital status on delayed HIV diagnosis among males and females has not been reported. Several previous studies revealed a significant association between delayed HIV diagnosis and being divorced and widowed[15 70 71]. Findings in this study showed that both separated male and female patients are associated with delayed HIV diagnosis; a differential in the risk of delayed HIV diagnosis was observed based on gender, with female patients having a greater effect than males. Separated male patients were two times more likely to be associated with delayed HIV diagnosis, and separated female patients were also two times more likely to be associated with delayed HIV diagnosis than married men or women. As revealed by this study, married women are less likely to get a delayed HIV diagnosis compared to females patients who were single, separated, or divorced and widowed. This observation may be linked to routine mandatory screening for HIV offered to pregnant women during their first antenatal visit[15]. The mandatory HIV screening for all pregnant women is a strategic policy to prevent Mother-To-Child Transmission (MTCT) in Nigeria and other African countries[15 72]. In comparison to married female patients, female patients who were single or widowed were more likely to be associated with delayed HIV diagnosis; this association was not observed in male patients. The finding of a differential effect of marital status on delayed HIV diagnosis based on gender might be related to the lower utilization of health care services by unmarried women compared to married women [72].

This study found that patients who had a tertiary education are less likely to have a delayed HIV diagnosis compared to patients with no formal education; this finding is consistent with previous studies[36]. Additionally, lower educational levels were observed to be associated with delayed HIV

diagnosis in several other studies[71 73 74]. People with higher education are often financially independent and are empowered to make well-informed decisions, especially those related to their health and wellbeing[75]. However, individuals with no formal education or lower educational level are less informed about the need for HIV testing[76]. The privilege of decision power and sufficient knowledge of the importance of HIV testing may explain the lower probability of delayed HIV diagnosis observed in patients with tertiary education.

This study found a significant association between delayed HIV diagnosis and retiree, and also among students. These findings of a greater risk of late HIV diagnosis among retirees and a lower risk among students have not been reported in the literature. However, the findings may be related to the other findings in this study, namely a significant positive association between delayed HIV diagnosis and older age and a significant negative association between delayed HIV diagnosis and having tertiary education. It may be logical to link these findings; for instance, retirees and students are related to the older age group and having a tertiary education, respectively. Retirees and older people are one of the most vulnerable populations in Nigeria due to the lack of a national plan for social welfare for the senior citizens, which has resulted in widespread poverty and diminished health among the senior citizens[77 78]. Additionally, poor pension programs and insufficient health insurance coverage had contributed to the difficulty faced by senior citizens to access health care services in Nigeria[77]. All these may explain the higher probability of delayed HIV diagnosis observed in the retiree and the older age group. Several targeted screening programs have been conducted among students in various higher institutions in Nigeria[79 38]. This countrywide awareness among Nigeria students about the need to diagnoses HIV early and several

opportunities to do so may contribute to the low risk of delayed HIV diagnosis observed among students.

The infection time to diagnosis was longer in male patients than in female patients, also longer in older patients than younger patients, and these findings are consistent with a previous study conducted in Nigeria[54]. Despite the current emphasis on conventional HIV treatment, traditional medical practices are a popular alternative therapy in Nigeria and most other African countries because of lower cost and easier access to services compared to conventional medicine[80 81]. Oreagba et al. (2020) observed a high prevalence of traditional herbal medicine usage of 66.8% and a low rate of health care services utilization in a Nigerian population[81]. Traditional herbal medicine usage is consistent with other African countries[81 82]. This high prevalence of traditional medical services patronage with a low rate of health care services utilization and subsequent lack of opportunity to be tested for HIV may explain the unfortunate prolonged time to diagnosis observed in this study.

Additionally, a greater percentage of male herbal medicine users than females, a lower rate of utilization of health care services among men than women, and a low rate of health care services utilization among older Nigerian citizens have been widely reported[81]. Therefore, these may explain a longer time to diagnosis observed in males as well as in older patients. Conversely, the shorter infection to the diagnosis observed in patients who were students and younger patients may result from more opportunities to be tested for HIV than other demographic groups.

This study found a progressive decline in the rate of positive HIV tests per year from 2014 to 2018. A previous population study in Nigeria revealed a progressive decline in the annual incidence of HIV infection[7]. Previous national HIV treatment guidelines in Nigeria advised delaying ART until CD_4 counts declined to 350 cells/mm^3 or less[83]. However, in 2016, the Nigeria Ministry of Health updated its HIV treatment guidelines to 'treat all approach,' which made all newly diagnosed HIV patients eligible for ART regardless of their CD_4 counts[84]. In a study by Stafford et al. (2019) that evaluated the clinical outcome of the test and treat guidelines in five Nigeria states, among patients with documented serial viral load measurement for 6 months and 12 months, 79% and 78% were suppressed at six months and at 12 months respectively[84]. Thus, the observed reduction in the positive test rate may be attributed to the policy of treating all cases adopted in Nigeria in 2016. This observed reduction in test positivity rate may also have been caused by increased testing rate. Figure 1 summarizes the rate of positive HIV tests per year in the population examined in this study; it showed a progressive decline in the rate of positive HIV tests from 2014 to 2018. This decline was especially more pronounced from 2016 to 2018 (figure 1). This finding revealed a sharp drop in the rate of positive HIV tests from 2016, which corresponds to the year Nigeria adopted a test and treat policy (Treat All guidelines). The observed decline trend in HIV test positivity rate may be further evidence that early diagnosis of HIV and the immediate initiation of ART are essential in effectively controlling HIV and maybe a great interventional tool in preventing its onward transmission.

The overall percentage of delayed HIV diagnosis observed in the population examined in this study was 57.2%. This finding was consistent with previous population studies conducted in different regions of Nigeria. Daniyam et al. (2011) observed a 56.7% delayed HIV diagnosis in a hospital

in-patients' population, while Akinbami et al. (2012) reported 67.4% delayed HIV diagnosis among patients in Lagos city Nigeria[85 86]. Additionally, this study found a progressive decline in the annual percentage of delayed HIV diagnoses. Although Nigeria has no information on national trends in delayed HIV diagnosis in the last decades and studies on the delayed HIV diagnosis trends in the literature are scarce. However, research in other parts of the world revealed a decline in the annual percentage of delayed HIV diagnosis. A steady decline in delayed HIV diagnosis was observed within five years in a United States study, and a European study also reported a similar trend[87 88]. Awareness about the need for timely diagnosis of HIV has been improved in Nigeria and other African countries in the past decades. VCT is being practiced in Nigeria, especially in the most vulnerable communities and at-risk demographic groups[18]. VCT has been widely advocated in Nigeria in order to provide HIV testing at every opportunity. VCT is being offered at STI clinics, hospital general outpatient clinics and HIV mobile testing has been strategically put in place[89], and increased access to testing may explain the decline in delayed diagnosis observed.

The findings of this study are based on a population tested in a single clinic. These findings should also be considered in terms of its strength and weakness. The ART clinic where the data examined in this study was collected is at the university college hospital in Ibadan city, Nigeria's largest city by geographical area. The clinic provides HIV care and treatment to most people living with HIV in Oyo state and other parts of Nigeria; thus, the data represents the broader population of people living with HIV in Oyo state Nigeria, which is an important strength of this study. This study's sample size was adequate to detect a statistically significant association between delayed HIV diagnosis and the risk factors of interest. Another strength of this research is that the attending

physician collected the data at the first clinic visit of the individual patients during which they were first diagnosed with HIV. The database's quality where the data was saved and the physician data collection at first visits would be more reliable than interviewing HIV patients or searching through their medical records.

One of the limitations of this study is a retrospective design. The data did not include qualitative data or other factors that may contribute to delayed HIV diagnoses, such as proximity of health facilities to where patients live, level of awareness about the need for HIV tests, and the last HIV test before they were diagnosed. These data may provide more information regarding delayed HIV diagnosis in Nigeria and the time delay from HIV infection to diagnosis. All this may further help understand strategic HIV control and guide interventional policy that will address the challenges and barriers to early testing of HIV in different regions of Nigeria and other Africa countries.

CHAPTER 6: CONCLUSION

This study examined risk factors of delayed HIV diagnosis in Nigeria, the estimation of time from HIV infection to HIV diagnoses, and trends in the rate of positive HIV tests and the rate of delayed HIV diagnoses. Delayed diagnosis is common, but the rate of delayed diagnosis is declining. Studies examining the risk factors for delayed HIV diagnosis in Nigeria and the trend in the rate of positive HIV tests in the literature are very scarce. This study presented an important understanding of the demographic risk factors for delayed HIV diagnosis in Ibadan, Nigeria.

Early diagnosis of HIV with immediate ART initiation is critical in reducing the health burden of HIV, improving HIV survival rate, and reducing transmission. The findings in this study suggest that a significant expansion to the existing testing strategies (PITC and VCT), with emphasis on the population at risk, needs to be effectively legislated in Nigeria to yield better output in terms of testing rate. Additionally, comprehensive advocacy regarding the usage of HIVST may motivate more people to be tested, especially the at-risk groups such as MSM and FSW who may fear discrimination if their tests are positive. Finally, anonymous HIV testing and proper linkage to care governed by clear legislation may favourably change the way people perceive HIV testing in Nigeria.

The assurance of confidentiality may overcome clients' hesitancy to be tested for HIV. Testing for HIV in regular clinics or health facilities with blood draw sent to the laboratory coded without a name may encourage more people to be tested. All these testing strategies should be made

available not only in primary health care centres and all other health care facilities but also in places such as pharmacies and religious centers, and organizations. HIV testing is an essential component of HIV care. A widespread awareness campaign may play a major role in achieving greater results of the aforementioned testing strategies. Promoting HIV testing among all demographic and at-risk groups, including residents in rural communities and less-educated populations, will complement these testing strategies. Consequently, effective HIV testing strategies may significantly reduce delayed HIV diagnosis and HIV transmission in Nigeria and other African countries.

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Appendix A: Newfoundland and Labrador-Health Research Ethics Board.

Research Ethics Office
Suite 200, Eastern Trust Building
95 Bonaventure
Avenue St. John's, NL

A1B 2X5

March 12, 2020

Dear Mr. Oluwalana:

Researcher Portal File # 20201077
Reference # 2019.229

RE: The Epidemiology of HIV Diagnosis in Nigeria

Your application was reviewed by a subcommittee under the direction of the HREB and your response was reviewed by the Chair and the following decision was rendered:

X	Approval
	Approval subject to changes
	Rejection

Ethics approval is granted for one-year effective March 20, 2020. This ethics approval will be reported to the board at the next scheduled HREB meeting.

This is to confirm that the HREB reviewed and approved or acknowledged the following documents (as indicated):

- Application, approved
- Research proposal, approved
- Data abstraction form, approved
- Approval document from Nigeria ethics, acknowledged

Please note the following:

- This ethics approval will lapse on March 21, 2021. It is your responsibility to ensure that the Ethics Renewal form is submitted prior to the renewal date.
- This is your ethics approval only. Organizational approval may also be required. It is your responsibility to seek the necessary organizational approvals.
- Modifications of the study are not permitted without prior approval from the HREB. Request for modification to the study must be outlined on the relevant Event Form available on the Researcher Portal website.
- Though this research has received HREB approval, you are responsible for the ethical conduct of this research.
- If you have any questions please contact info@hrea.ca or 709 777 6974.

The HREB operates according to the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2), ICH Guidance E6: Good Clinical Practice Guidelines (GCP), the Health Research Ethics Authority Act (HREA Act) and applicable laws and regulations.

We wish you every success with your study.

Sincerely,

Dr B, Chairperson
Health Research Ethics Board

You Have Received Ethics Approval, Now What?: HREB Reporting Requirements

Once a study has received ethics approval from the Health Research Ethics Board (HREB), there are still associated reporting requirements. In the conduct of approved research researchers are required to report to the HREB, in a timely manner, proposed changes from approved research that affect participants at any stage of the process. This includes, but is not limited to, changes to the consent form, changes to the tasks or interventions involved in the research, or changes to measures to protect privacy and confidentiality.

Any substantive change to the research should not be implemented prior to documented approval by the HREB, except when necessary to eliminate an immediate risk(s) to the participants. Below are examples of post approval documentation that must be submitted to the HREB:

Amendments

Any proposed change in the conduct of a study must be submitted to the HREB, and approved, before the change may be implemented. Such changes might include modification of recruitment procedures, inclusion or exclusion criteria, revised sample size, addition or deletion of study sites, changes to an intervention, consent forms, questionnaires or scripts, etc. If there are changes in project team members

or changes to funding source(s)/sponsor(s), there are specific forms to complete to report this to the HREB.

Adverse Events

Serious and unanticipated adverse events that occur within Newfoundland and Labrador are required to be reported to the HREB. Such events may occur in both clinical trials and in other types of research, e.g. collapse during a rehabilitation program, emotional breakdown requiring follow up care during an interview, or breach of privacy during correspondence. Serious adverse events that are fatal or life-threatening are required to be reported to the HREB as soon as the research team is aware of the event.

Protocol Deviations

Deviations from an approved study protocol must be reported to the HREB. Changes that eliminate immediate hazards to participants do not require prior approval, but must be reported soon as reasonably possible.

Safety Reports

Safety reports providing information on all serious adverse events (SAEs) occurring in a clinical trial must be provided by the sponsor to the HREB, normally on a three or six monthly basis (i.e. in accordance with the specified reporting timelines that were outlined in the approved ethics application).

Investigator Brochure (IB) and Product Monograph (PM)

Throughout the course of a clinical trial, changes may be implemented to study documents. All revisions to approved study documents must be submitted to the HREB to ensure the record is up to date. If the revisions include new risk or safety information there may be a requirement to notify research participants.

Ethics Renewal/Study Closure

Ethics approval lasts for one year. Ethics renewal is required annually, on the anniversary of the date of the HREB notification of approval. Once data collection is no longer ongoing, a study closure form is required to be submitted to the HREB for the study to remain active or to be closed in good standing.

Appendix B: AIDS Prevention Initiative Review Board, Nigeria.

Institutional Review Board
OHRP IRB# IRB00011406

Secondary Use of Data

EFFECTIVE:	February 26, 2020
TO:	Michael Oluwalana
INSTITUTION:	College of Medicine, University of Ibadan
REVIEW TYPE:	Secondary Use of Data
IRB REF:	IRB033-SD
STUDY TITLE:	The Epidemiology of HIV Diagnosis in Nigeria

IRB APPROVAL

Dear Michael Oluwalana

The above referenced application has been reviewed and approved by the APIN Institutional Review Board via Expedited Review for the use of Human Subjects Data in Research Projects (45 CFR 46). The risks in this research are deemed minimal, and the potential benefits to the subject outweigh those associated risk.

No further submission to the APIN IRB is required.

This approval is good for 1 one year from February 26, 2020 to January 16, 2021 at which when due, you must either submit a termination report or request IRB cover continuation.

Juliet Adeola copied with this notification will provide the required data set in line with the approved study application. Please feel free to contact her at jadeola@apin.org.ng or by phone on +234 703 837 5653

For further guidance or questions about this notification, please contact the APIN IRB Administrator at +234 802 944 5112 or by email at irb@apin.org.ng.

I wish you all the best with your work.

Sincerely,

Professor B, MON. IRB Committee Chair,
APIN Institutional Review Board