DETERMINANTS OF VIROLOGICAL FAILURE IN HIV POSITIVE PATIENTS RECEIVING ANTIRETROVIRAL THERAPY IN HAITI, 2013 - 2017

By

SHANNAN N. RICH

A THESIS PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
MASTER OF SCIENCE

UNIVERSITY OF FLORIDA

2018

ACKNOWLEDGMENTS

I thank the chair and members of my supervisory committee for their mentoring, the staff in the Departments of Epidemiology and Health Outcomes and Biomedical Informatics for their keen research assistance, the participants in my study, the Haitian Ministry of Public Health and Population, and the National Alliance of State and Territorial AIDS Directors for its generous support. I thank my parents and close friends for their loving encouragement, which motivated me to complete my study.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

3TC	Lamivudine
ART	Antiretroviral therapy
AZT	Zidovudine
CI	Confidence interval
EFV	Efavirenz
EMR	Electronic medical records
GHESKIO	Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic Infections
HIV	Human immunodeficiency virus
HIVDR	Human immunodeficiency virus drug resistance
LLV	Low-level viremia
MSPP	Haitian Ministry of Public Health and Population
NVP	Nevirapine
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside-reverse transcriptase inhibitor (NRTIs)
OR	Odds ratio
PIH	Partners in Health
PNLS	National Public Health Laboratory (French acronym)
SALVH	Haitian Active Longitudinal Tracking of HIV database (French acronym)
STI	Sexually transmitted disease
TB	Tuberculosis
TDF	Tenofovir
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization

Abstract of Thesis Presented to the Graduate School
of the University of Florida in Partial Fulfillment of the
Requirements for the Degree of Master of Science

DETERMINANTS OF VIROLOGICAL FAILURE IN HIV POSITIVE PATIENTS RECEIVING ANTIRETROVIRAL THERAPY IN HAITI, 2013 - 2017

By

Shannan N. Rich

August 2018

Chair: Robert Cook
Major: Epidemiology

Studies of early virological failure in human immunodeficiency virus (HIV) positive patients in Haiti are limited. This study aimed to examine the prevalence and determinants of early virological failure among patients initiating first-line antiretroviral therapy (ART) in Haiti between 2013 and 2016.

Electronic medical records data were accessed through the Haitian Active Longitudinal Tracking of HIV database. Patients who initiated ART between January 1, 2013 and December 31, 2016 and who had a viral load test performed within 3 to 12 months after ART initiation were included in the study. Multivariable logistic regression was performed to predict the binary outcome of virological failure, defined as a viral load level greater than or equal to 1000 HIV-1 RNA copies/mL, based on patient demographic and clinical characteristics.

The prevalence of early virological failure in this study population was 67%. In multivariable analysis, virological failure was associated with a CD4 count below 200 cells/mm^3 (Odds ratio [OR]=3.0; 95% Confidence interval [CI] 1.9-4.9), World Health Organization (WHO) clinical stage of IV (OR=2.6; 95% CI 1.2-5.7), ART initiation year of

2015 (OR=1.8; 95% CI 1.2-2.9), ART regimen consisting of lamivudine (3TC), zidovudine (AZT), and nevirapine (NVP) (OR=2.5; 95% CI 1.2-4.9), and months between ART initiation and viral load test (OR=0.9; 95% CI 0.8-0.9). Further, patients who were diagnosed in the Artibonite-Centre and Sud departments were less likely to experience virological failure (OR=0.4; 95% CI 0.3-0.7, OR=0.4; 95% CI 0.2-0.7, respectively), as compared to patients who diagnosed in the Nord department.

In conclusion, this study described, for the first time, differences in early virological outcomes in persons receiving ART in Haiti. Enhanced monitoring of virological outcomes is recommended for younger individuals, individuals with high WHO clinical stages, low CD4 counts, and individuals treated with 3TC-AZT-NVP. Future studies should attempt to explain the departmental differences observed in this study, in addition to studying additional socio-ecological factors that may be at play.

CHAPTER 1
INTRODUCTION

For people living with human immunodeficiency virus (HIV), careful adherence to effective antiretroviral therapy (ART) leads to suppression of plasma viral loads to undetectable levels. The failure to achieve viral suppression is referred to as virological failure and is associated with higher rates of mortality, immunosuppression and the accumulation of resistance mutations [1,2]. Individuals who are not suppressed also have a higher probability of transmitting the virus to others [2]. Virological failure has been linked to individual and ecological factors including treatment nonadherence and pretreatment drug resistance, and hinders the success of HIV programs worldwide [3]. The prevalence of virological failure, accompanied by the emergence of HIV drug resistance (HIVDR), is increasing globally and has recently been termed the fourth HIV epidemic [3]. Virological failure creates an obstacle for the final HIV elimination goal of achieving 90% viral suppression rates among patients receiving ART [3]. Epidemiological monitoring for virological failure, formally defined by the World Health Organization (WHO) as the failure to achieve a plasma viral load level below 1000 HIV-1 RNA copies/mL after three months on antiretroviral therapy (ART) [4], can provide insight into population-level HIVDR development and adherence to ART [5]. As antiretroviral therapy (ART) continues to scale-up, epidemiologic studies are needed to elucidate the correlates and predictors of virological failure.

Drug resistance to non-nucleoside reverse-transcriptase inhibitors (NNRTIs) is increasing across all WHO geographic regions [6]. This is of greatest concern in low-to-middle income countries where NNRTIs, such as nevirapine (NVP) or efavirenz (EFV), are included in most first-line combination ART regimens [7]. Recent studies have

demonstrated a disproportionately higher burden of virological failure in resource-poor settings, as compared to those considered resource-dense [3]. In Haiti, which ranks in 163rd place on the Human Development Index [8], the adult HIV prevalence is the highest in the Western hemisphere [9]. More than 70,000 individuals have been enrolled on ART as of 2016 [10]. While it is estimated that NNRTIs comprise 89% of patient drug regimens in Haiti [11], few studies have been conducted to estimate the prevalence of virological failure or pre-treatment NNRTI drug resistance in this population [12]. Viral load assessments were introduced in 2013 but were not scaled-up nationally until 2016 and not at all treatment facilities [13]. In a study conducted on patients who initiated ART at a large HIV clinic in the capital of Port-au-Prince between 2003 and 2008, virological failure was reportedly detected in 38% of patients tested with resistance to NNRTIs observed in 70% of these individuals [14]. Another study conducted in five hospitals in Port-au-Prince reported that one-third of 2,313 patients failed to achieve virological suppression (<1000 copies/mL) after at least six months on ART [13]. The vast majority of these patients (84%) were receiving ART for more than 12 months, however, and it is unclear whether these patients had experienced any changes to their treatment regimens--an indicator of treatment failure—prior to viral load assessment [13]. That study found male sex, lower CD4 (<500 cells/mm^3), poor adherence to ART, and tuberculosis co-infection were negatively associated with virological suppression [13]. Another study which assessed the risk factors for major regimen changes in Haiti found significant associations with female sex, younger adult age (20 - 39 years old), ART initiation year after 2006, and lower CD4 (<350 cells/mm^3) at ART initiation [15].

Given increasing trends in pre-treatment drug resistance observed worldwide [7], it is becoming increasingly important to understand the indications for treatment failure as early as possible after treatment begins. The prevalence of pretreatment NNRTI resistance in Latin America and the Caribbean was recently estimated to be 9.4% (6.6-13.2), with a predicted annual increase of 0.9% [7]. The WHO recommends countries with a prevalence of pretreatment NNRTI resistance greater than 10% should change their first-line therapies [7]. A study of the early indications for virological failure in Haiti is warranted to inform the Ministry of Public Health and Population (MSPP)'s national treatment guidelines for first-line ART. To our knowledge, no studies have assessed the determinants of early virological outcomes of patients living in Haiti.

This study used the data available from the national HIV case-based surveillance system, called the Haitian Active Longitudinal Tracking of HIV database (SALVH, French acronym), operated by the Ministry of Public Health and Population (MSPP) since 2008 and previously detailed elsewhere [10]. Briefly, there are three main health systems that provide treatment services to persons living with HIV in Haiti and report electronic medical records (EMR) data to SALVH, including the MSPP's associated iSanté clinics (electronically administered by the International Training and Education Center for Health), the Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic Infections (GHESKIO), and Partners in Health's Zanmi Lasante (PIH) [16]. Using the data available from the iSanté clinics, the objectives of the current study were to 1) estimate the prevalence of early virological failure in HIV positive individuals receiving ART, 2) determine key demographic and clinical characteristics associated with virological failure after controlling for covariates, and 3) identify opportunities for

public health action to inform current national treatment guidelines. We hypothesized that the likelihood of virological failure is a function of demographic and clinical characteristics informed by the socio-ecologic model [17]. As a secondary objective and to evaluate potential reporting biases due to many cases with missing lab values, we also sought to compare the demographic and clinical characteristics of patients who had an indication that a viral test was completed but lacked lab results in the surveillance system.

CHAPTER 2
METHODOLOGY

Study Population

This study employed a retrospective cohort design to assess the virological outcomes of treatment-naïve HIV-positive individuals newly-initiated on antiretroviral therapy (ART) in Haiti. The study population included patients who received their first ART prescription at one of the participating iSanté treatment clinics between January 1, 2013 (when the earliest viral load assessments began in Haiti) and December 31, 2016. This date was chosen to allow for lab data to be included until December 31, 2017. Patients must have also had viral load testing performed between 3 to 12 months (90 to 365 days) after ART therapy initiation. Bivariate analyses were performed for all patients meeting this criterion (n=5128) whereas inferential logistic regression analyses were performed only for patients with viral load test results available in the SALVH database (n=1151).

Ethics Approval

This study was reviewed by, and received ethics approval from, the National Bioethics Committee in Haiti and the Institutional Review Board at the University of Florida (IRB201702830).

Virological Failure

Plasma blood samples were collected for every patient across the participating iSanté treatment clinics and transported to the National Public Health Laboratory (PNLS) located in Port-au-Prince. Plasma viral load levels were assessed at PNLS using the Generic HIV Viral Load Assay (Biocentric, Bandol, France) which has a limit of detection of 300 – 10^7 copies/mL. Minimum and maximum functions were performed on

the available viral load results to ensure lab values were within the expected range. Patients whose earliest viral load test, assessed 3 to 12 months after initiation on ART, was ≥1000 HIV-1 RNA copies/mm^3 were classified as failing virologically (or virologically non-suppressed). Patients whose earliest viral load test results were <1000 copies/mm^3 after 3 to 12 months on ART were classified as virologically-suppressed.

Predictors

Demographic characteristics were accessed at the time of the HIV case report and included age, sex, marital status, and clinic department (Haiti is organized into 10 administrative departments). Patient clinical characteristics included dates of diagnosis and ART initiation, months between viral load test date and diagnosis and ART initiation dates, earliest recorded CD4 T-cell count (cells/mm^3), ART drug regimen [combinations of 3 possible drugs, including 1 NNRTI: nevirapine (NVP) or efavirenz (EFV) and 2 nucleoside-reverse transcriptase inhibitors (NRTIs): lamivudine (3TC), zidovudine (AZT), or tenofovir (TDF); or “other” if the regimen comprised less than 3 drugs or contained other less-frequently prescribed drugs], WHO clinical stage of infection severity (I-IV), transmission risk factors identified on the case-report form, history or presence of tuberculosis (TB) or sexually transmitted diseases (STD), and whether patients were prescribed ART by one or multiple clinics during the study period (termed “clinic transfers”). Patients with missing or erroneous data on age (n=16), department (n=3), or ART regimen (n=1) were excluded from the analysis. Large numbers of missing or unknown values were categorized and retained for analysis.

Statistical Analysis

Demographic and clinical characteristics of individuals with and without virological failure were compared using Chi-square test for categorical variables and two

sample t-tests or Wilcoxon-Mann-Whitney test for continuous variables with normal and skewed distribution, respectively. Bivariate analyses were also used to assess whether the patients included in the study were systematically different from those who could not be included in the study due to the absence of viral load test results. Logistic regression was used to identify significant predictors of virological failure using variables found to be statistically significant in the bivariate analyses at the $p < 0.05$ level. The full prediction model included the baseline patient demographic factors of continuous age (years), sex (male or female; [reference=female]), marital status (single, cohabiting, married, or divorced/widowed; [reference=single]), and clinic department (Artibonite-Centre, Nord, Nord-Est, Nord-Ouest, Ouest, or Sud; [reference=Nord]). The full prediction model additionally included the clinical factors: WHO clinical stage (I, II, III, or IV; [reference=I]), year of ART initiation (2013, 2014, 2015, or 2016; [reference=2016]), ART regimen (3TC-EFV-TDF, 3TC-AZT-NVP, 3TC-EFV-AZT, or other; [reference=3TC-EFV-TDF]), earliest CD4 count (<200, 200-499, or 500+ cells/mm^3; [reference=500+]), whether a transmission risk factor was identified on the case report form (yes, no, or unknown [reference=no]), and continuous months between viral load test date of ART initiation date. A parsimonious model was also estimated to select variables using a stepwise backwards-elimination procedure. The results of the parsimonious model were similar to the results of the full model, and therefore only the full model results were presented as odds ratios (OR) with their respective 95% confidence intervals (CI). SAS version 9.4 was used for all analyses.

CHAPTER 3
RESULTS

Characteristics of Study Population

Viral load test dates and results were available for 1151 patients. Of those, 774 had evidence of a viral load test ≥1000 HIV-1 RNA copies/mm^3 which indicates prevalence of virological failure in this study population was 67.2%. Descriptive analyses indicated that patients failing to achieve virological suppression were on average younger than patients with suppression (31.9 years vs 35.3 years, p<0.01) and when examining age as a categorical variable, more likely to be under the age of 20 years (6.2% vs 15.3%, p=<0.01) (Table 3-1). Those experiencing virological failure were more likely to be diagnosed in the Ouest Department (37.9% vs 49.9%, p=<0.01), have a more severe WHO clinical stage of HIV at diagnosis (III or IV) (23.6% vs 31.9%, p=0.01), and have a CD4 cell count test result <200 cells/mm^3 (9.0% vs 19.4%, p=<0.01) (Table 3-1). Non-virologically suppressed patients were less likely to be married or cohabitating as compared to suppressed patients (49.8% vs 58.3%, p=0.03) (Table 3-1). Non-virologically suppressed patients were also less likely to have a transmission risk factor identified (58.6% vs 51.0%, p=0.02) on a case-report form (Table 3-1). Non-virologically suppressed patients had longer intervals between viral load test and HIV diagnosis (32.3 vs 27.2 months, p=<0.01) and ART initiation (8.2 months vs 7.5, p=<0.01) (Table 3-1). The majority of patients in both populations were prescribed 3TC-EFV-TDF regimens, however patients experiencing virological failure were more likely to receive an ART regimen other than 3TC-EFV-TDF (12.7% vs 23.0%, p=<0.01) (Table 3-1). Groups did not differ with respect to sex, year of diagnosis, clinic transfer, and history or presence of tuberculosis or sexually transmitted

diseases. Though not statistically significant, the variable sex was retained in the multivariable analyses due to its observed significance in previous studies conducted in this population.

Associations of Demographic and Clinical Characteristic with Virological Failure

In the multivariable analysis, clinic department, WHO clinical stage at diagnosis, year of ART initiation, ART regimen, value of the earliest CD4 count, and time between ART initiation and viral load test remained significant. Patients with virological failure were 59% less likely to be diagnosed in the Artibonite-Centre combined department (Odds Ratio [OR]=0.41; 95% Confidence Interval [CI] 0.25–0.66) and Sud department (OR=0.41; 95% CI 0.24–0.69), as compared to patients who were treated in the Nord department (Table 3-2). Continuous age, sex and marital status were not statistically significantly associated with the outcome of virological failure. Compared to patients with a WHO stage of I at HIV diagnosis, patients who received a WHO clinical stage of IV were 2.6 times more likely to experience virological failure (OR=2.62; 95% CI 1.22–5.66) (Table 3-2). Patients who initiated therapy in 2015 were 1.8 times more likely to experience virological failure (OR=1.84; 95% CI 1.17–2.89), as compared to patients who began treatment in 2016 (Table 3-2). Patients whose treatment regimen consisted of 3TC-AZT-NVP were 2.5 times more likely to experience virological failure (OR=2.45; 95% CI 1.22–4.92), as compared to patients with a treatment regimen consisting of 3TC-EFV-TDF (Table 3-2). Compared to patients in the highest CD4 count category (500+ cells/mm^3), patients in the lowest category (<200 cells/mm^3) had were 3 times more likely to experience virological failure (OR=3.04; 95% CI 1.88–4.94) (Table 3-2). The time between ART initiation and viral load test was inversely correlated with virological failure. For each month increase in time on ART, the odds of virological

failure decreased by 13% (OR=0.87; 95% CI 0.82–0.92) (Table 3-2). The elapsed number of months between the date of HIV diagnosis and the viral load test date was not significantly associated with the outcome. The concordance statistic (c) for the multivariable model was 0.709, indicating that the model could accurately predict a patient's virological status approximately 71% of the time based on the demographic and clinical characteristics included in this study.

Comparison of Patients with Known versus Unknown Virological Status

In the analysis of the differences in the demographic characteristics of patients who had tests results available in the SALVH database vs patients who did not, patients included in the study were slightly younger (35.1 vs 33.0 years, p=<0.01) and were more likely to be diagnosed in the Artibonite-Centre department (13.6% vs 8.6%, p=<0.01), compared to patients whose virological status was unknown (Table 3-3). In the comparison of clinical characteristics, patients included in the study were less frequently diagnosed between 2014-2015 (28.3% vs 38.3%, p=0.03), less likely to be initiated on treatment in 2015 (14.5% vs 25.1%, p=<0.01), and more likely to receive an ART regimen other than 3TC-EFV-TDF (19.4% vs 15.0%, p=<0.01), as compared to patients with known virological status (Table 3-3). Additionally, although not clinically significant, patients included in the study had greater average months between diagnosis and viral load test (30.8 vs 29.7 months, p=0.02) and greater average months between ART initiation and viral load test (7.8 vs 7.6 months, p=0.02) (Table 3-3).

Table 3-1. Demographic and clinical characteristics of HIV patients in Haiti by virological status, 2013-2017.

Characteristic	Not virally suppressed (n=774)	Virally suppressed (n=377)	p-for difference
Mean (STD)			
Age at HIV diagnosis (years)	31.9 (14.3)	35.3 (12.8)	<0.001
Frequency (%)			
Age at HIV diagnosis (years)			<0.001
<5	49 (6.3)	7 (1.9)	
5-14	45 (5.8)	6 (1.6)	
15-19	25 (3.2)	10 (2.7)	
20-29	196 (25.3)	106 (28.1)	
30-39	241 (31.1)	129 (34.2)	
40-49	137 (17.7)	66 (17.5)	
50-59	65 (8.4)	38 (10.1)	
60+	16 (2.1)	15 (4.0)	
Sex			0.280
Female	486 (62.8)	249 (66.0)	
Male	288 (37.2)	128 (34.0)	
Marital status			0.030
Single	138 (17.8)	64 (17.0)	
Cohabitating	284 (36.7)	160 (42.4)	
Married	101 (13.1)	60 (15.9)	
Divorced or widowed	74 (9.6)	35 (9.3)	
Missing	177 (22.9)	58 (15.4)	
Clinic department			<0.001
Artibonite-Centre	88 (11.4)	69 (18.3)	
Nord	177 (22.9)	88 (23.3)	
Nord-Est	25 (3.2)	14 (3.7)	
Nord-Ouest	52 (6.7)	18 (4.8)	
Ouest	386 (49.9)	143 (37.9)	
Sud	46 (5.9)	45 (11.9)	
Year of HIV diagnosis			0.644
<2010	51 (6.6)	31 (8.2)	
2010-11	83 (10.7)	43 (11.4)	
2012-13	139 (18.0)	70 (18.6)	
2014-15	229 (29.6)	97 (25.7)	
2016	272 (35.1)	136 (36.1)	
WHO stage at diagnosis			0.011
I	103 (13.3)	49 (13.0)	
II	229 (29.6)	138 (36.6)	
III	195 (25.2)	78 (20.7)	
IV	52 (6.7)	11 (2.9)	
Missing	195 (25.2)	101 (26.7)	

Table 3-1. Continued.

Characteristic	Not virally suppressed (n=774)	Virally suppressed (n=377)	p-for difference
Frequency (%)			
Year of ART initiation			0.009
2013	84 (10.9)	34 (9.0)	
2014	19 (2.5)	14 (3.7)	
2015	129 (16.7)	38 (10.1)	
2016	542 (70.0)	291 (77.2)	
ART regimen			<0.001
3TC-AZT-NVP	68 (8.8)	12 (3.2)	
3TC-EFV-AZT	50 (6.5)	20 (5.3)	
3TC-EFV-TDF	596 (77.0)	329 (87.3)	
Other	60 (7.8)	16 (4.2)	
Earliest CD4 count			<0.001
<200	150 (19.4)	34 (9.0)	
200-499	182 (23.5)	89 (23.6)	
500+	175 (22.6)	111 (29.4)	
Missing	267 (34.5)	143 (37.9)	
History/presence of TB			0.645
No	16 (2.1)	11 (2.9)	
Yes	393 (50.8)	193 (51.2)	
Unknown	365 (47.2)	173 (45.9)	
History/presence of STIs			0.106
No	158 (20.4)	71 (18.8)	
Yes	301 (38.9)	128 (34.0)	
Unknown	315 (40.7)	178 (47.2)	
Any risk factor identified			0.015
No	379 (49.0)	156 (41.4)	
Yes	395 (51.0)	221 (58.6)	
Clinic transfer			0.868
No	729 (94.2)	356 (94.4)	
Yes	45 (5.8)	21 (5.6)	
Mean (STD)			
Months between diagnosis & test	27.2 (29.5)	32.3 (33.0)	0.012
Months between ART & viral test	7.5 (2.6)	8.2 (2.2)	<0.001

Table 3-2. Unadjusted and adjusted model results for association of demographic and clinical characteristics with virological failure in Haiti, 2013-2017.

Characteristic	Unadjusted ORs (95% CI)	Adjusted ORs (95% CI)
Age at HIV diagnosis (years)	0.98 (0.97;0.99)	0.99 (0.97;1.00)
Sex		
Female	Reference	Reference
Male	1.15 (0.89;1.49)	1.19 (0.90;1.57)
Marital status		
Single	Reference	Reference
Cohabitating	0.82 (0.58;1.17)	1.04 (0.71;1.54)
Married	0.78 (0.51;1.21)	0.94 (0.58;1.54)
Divorced/widowed	0.98 (0.60;1.62)	1.15 (0.66;2.03)
Clinic department		
Nord	Reference	Reference
Artibonite-Centre	0.63 (0.42;0.95)	0.41 (0.25;0.66)
Nord-Est	0.89 (0.44;1.79)	0.74 (0.35;1.57)
Nord-Ouest	1.44 (0.79;2.60)	1.01 (0.54;1.90)
Ouest	1.34 (0.98;1.85)	0.84 (0.55;1.28)
Sud	0.51 (0.31;0.83)	0.41 (0.24;0.69)
WHO stage at diagnosis		
I	Reference	Reference
II	0.79 (0.53;1.18)	0.82 (0.54;1.26)
III	1.19 (0.77;1.83)	1.26 (0.80;2.00)
IV	2.25 (1.08;4.69)	2.62 (1.22;5.66)
Year of ART initiation		
2013	1.33 (0.87;2.03)	0.78 (0.46;1.32)
2014	0.73 (0.36;1.48)	0.58 (0.26;1.27)
2015	1.82 (1.24;2.69)	1.84 (1.17;2.89)
2016	Reference	Reference
ART regimen		
3TC-EFV-TDF	Reference	Reference
3TC-AZT-NVP	3.13 (1.67;5.86)	2.45 (1.22;4.92)
3TC-EFV-AZT	1.38 (0.81;2.36)	1.37 (0.75;2.49)
Other	2.07 (1.17;3.65)	1.61 (0.86;3.03)
Earliest CD4 count		
<200	2.80 (1.80;4.35)	3.04 (1.88;4.94)
200-499	1.30 (0.92;1.84)	1.42 (0.96;2.08)
500+	Reference	Reference
Any risk factor identified		
No	Reference	Reference
Yes	0.74 (0.57;0.94)	0.81 (0.61;1.07)
Months between diagnosis and test	1.00 (0.99;1.00)	0.99 (0.99;1.00)
Months between ART and test	0.90 (0.85;0.94)	0.87 (0.82;0.92)

Table 3-3. Comparative analysis of associations of demographic and clinical characteristics with virological failure in Haiti, 2013-2017.

Characteristic	Virologic status known (n=1151)	Virologic status unknown (n=3977)	p-for difference
Mean (STD)			
Age at HIV diagnosis (years)	33.0 (13.9)	35.1 (13.5)	<0.001
Frequency (%)			
Age at HIV diagnosis (years)			0.001
<5	56 (4.9)	117 (2.9)	
5-14	51 (4.4)	128 (3.2)	
15-19	35 (3.0)	113 (2.8)	
20-29	302 (26.2)	941 (23.7)	
30-39	370 (32.2)	1279 (32.2)	
40-49	203 (17.6)	825 (20.7)	
50-59	103 (9.0)	423 (10.6)	
60+	31 (2.7)	151 (3.8)	
Sex			0.254
Female	735 (63.9)	2466 (62.0)	
Male	416 (36.1)	1511 (38.0)	
Marital status			0.088
Single	202 (17.6)	663 (16.7)	
Cohabitating	444 (38.6)	1482 (37.3)	
Married	161 (14.0)	580 (14.6)	
Divorced or widowed	109 (9.5)	491 (12.4)	
Missing	235 (20.4)	761 (19.1)	
Clinic department			<0.001
Artibonite-Centre	157 (13.6)	341 (8.6)	
Nord	265 (23.0)	971 (24.4)	
Nord-Est	39 (3.4)	187 (4.7)	
Nord-Ouest	70 (6.1)	161 (4.1)	
Ouest	529 (46.0)	1879 (47.3)	
Sud	91 (7.9)	438 (11.0)	
Year of HIV diagnosis			<0.001
<2010	82 (7.1)	324 (8.2)	
2010-11	126 (11.0)	235 (5.9)	
2012-13	209 (18.2)	594 (14.9)	
2014-15	326 (28.3)	1523 (38.3)	
2016	408 (35.5)	1301 (32.7)	
WHO stage at diagnosis			0.032
I	152 (13.2)	602 (15.1)	
II	367 (31.9)	1238 (31.1)	
III	273 (23.7)	1029 (25.9)	
IV	63 (5.5)	154 (3.9)	
Missing	296 (25.7)	954 (24.0)	

Table 3-3. Continued.

Characteristic	Virologic status known (n=1151)	Virologic status unknown (n=3977)	p-for difference
Frequency (%)			
Year of ART initiation			<0.001
2013	118 (10.3)	176 (4.4)	
2014	33 (2.9)	145 (3.7)	
2015	167 (14.5)	1000 (25.1)	
2016	833 (72.4)	2656 (66.8)	
ART regimen			0.001
3TC-AZT-NVP	80 (7.0)	185 (4.7)	
3TC-EFV-AZT	70 (6.1)	223 (5.6)	
3TC-EFV-TDF	925 (80.4)	3381 (85.0)	
Other	76 (6.6)	188 (4.7)	
Earliest CD4 count			<0.001
<200	184 (16.0)	681 (17.1)	
200-499	271 (23.5)	1030 (25.9)	
500+	286 (24.9)	1138 (28.6)	
Missing	410 (35.6)	1128 (28.4)	
History/presence of TB			0.273
No	586 (50.9)	2069 (52.0)	
Yes	27 (2.4)	123 (3.1)	
Unknown	538 (46.7)	1785 (44.9)	
History/presence of STIs			0.003
No	429 (37.3)	1601 (40.3)	
Yes	229 (19.9)	894 (22.5)	
Unknown	493 (42.8)	1482 (37.3)	
Any risk factor identified			0.875
No	535 (46.5)	1859 (46.7)	
Yes	616 (53.5)	2118 (53.3)	
Clinic transfer			0.084
No	1085 (94.3)	3798 (95.5)	
Yes	66 (5.7)	179 (4.5)	
Mean (STD)			
Months between diagnosis and test	28.9 (30.8)	26.6 (29.7)	0.016
Months between ART and test	7.8 (2.5)	7.6 (2.5)	0.018

CHAPTER 4
DISCUSSION

The purpose of this study was to estimate the prevalence and determine the demographic and clinical characteristics associated with virological failure in this population of HIV-positive individuals receiving ART in Haiti. As a result, we identified opportunities for public health action to inform current treatment guidelines. The prevalence of virological failure in this study was 67% which differs markedly from previous studies in this population on ART. The Joint United Nations Programme on HIV/AIDS (UNAIDS) reported in 2016 that among those who were diagnosed and receiving therapy, 31% were reported to be virologically failing [18]. Further, another study found that virological failure was detected in 32% of patients tested [13]. Comparisons of these estimates are difficult because case definitions of treatment failure differ (viral load level ≥1000 copies/mL after 6 to 60 months or more on ART vs ≥1000 copies/mL after 3 to 12 months on ART applied in this study) [13]. Most patients in the study conducted by Jean Louis et al. (84%) were receiving ART for at least 12 months before their viral loads were assessed, and it is unknown whether patients had experienced any changes to their initial treatment regimens during the follow-up period, which could indicate virological failure [13]. The number of months on ART was negatively correlated with the outcome of virological failure in the current study, inferring that patients were more likely to achieve viral suppression the longer they are on ART. This suggests that patients in the current study population may have been prematurely classified as failing therapy in this study, because of the case definition applied. However, previous studies have reported that earlier indications of high viral load results are positively correlated with virological failure [19,20]. According to a study conducted

in India, 83% of cases of virological failure were identified at the time of the initial viral load test (assessed within 6 to 12 months after ART initiation) [19]. Further, a study conducted on low-level viremia (LLV = viral load levels between 50 and 1000 copies/mL) in South Africa found that patients with any previous result of LLV after 5 months on ART had 2.8 times increased risk of confirmed virological failure and 5.2 times increased risk of switching to second-line therapy [20]. Further, studies have shown that rates of virological suppression tend to decline with each subsequent year on first-line ART [21], potentially due to increasing drug resistance mutations [22]. Earlier detection of virological failure and switch to second-line therapy was previously found to increase the probability of survival in this population from 88% to 93% [23].

Demographic Characteristics

The demographic factor most strongly associated with virological failure in this study was diagnosis at clinics located outside of the Artibonite-Centre and Sud departments. There was no association between age, sex, or marital status with virological failure in the multivariable analysis. It is unclear why patients who were diagnosed in the Artibonite-Centre and Sud departments were more likely to achieve viral suppression than patients in some of the other departments. It is possible that since these departments border the Ouest department, where the capital Port-au-Prince is located, that the clinics located in these departments may have access to better resources (e.g. medications, testing services) and therefore have more robust HIV care services.

The lack of a statistically significant difference in the outcome of virological failure between males and females varies from previous studies in this population. In Jean Louis et al., males were 20% less likely to be virologically suppressed after at least 6

months on ART [13] and in McNairy et al., male sex was associated with higher HIV mortality after 12 months on ART [9]. While it is possible that males may have poorer health outcomes in the long-term due to issues such as adherence or loss to follow-up [9,13], this study found no difference in earlier virological outcomes by sex.

Clinical Characteristics

The patient clinical factors most strongly associated with virological failure in this analysis were a WHO stage of IV, a CD4 count <200 cells/mm^3, an ART regimen consisting of 3TC-AZT-NVP, and an ART initiation year of 2015. The finding that virological failure was associated with lower CD4 counts and higher WHO clinical stage of HIV at diagnosis is consistent with previous studies in this population [13,15] and with a study conducted in a similarly low-resource population [24]. The first-line ART regimen found to be associated with increased odds of failure in this study (3TC-AZT-NVP) was similarly associated with reduced odds of virological suppression in another study conducted in this population [13]. In another study conducted in Haiti, 31% of people treated with this first-line regimen eventually switched to a second-line regimen, although this result was not statistically significant at the 0.05 level [23]. Patients who initiated treatment in 2015 were more likely to experience virological failure, suggesting a time-varying effect. However, patients who initiated ART in 2015 were also more likely to have unknown virological status, suggesting that this significance may be attributed to stastical artifact due to the smaller frequency of patients in this category.

The results of the analysis indicate that ART treatment initiatives should be targeted at younger individuals, individuals with more severe infection stages, and individuals with significant immune status decline. Most patients in this study were receiving the current recommended ART regimen: 3TC-EFV-TDF. Patients who were

not receiving this regimen were more likely to be non-virologically suppressed. In particular, the ART regimen: 3TC-AZT-NVP was linked to the greatest odds of virological failure in this study when compared to the 3TC-EFV-TDF regimen, potentially due to NVP which is an NNRTI. In a systematic review of the effectiveness of EFV vs NVP (both NNRTIs), researchers reported little to no difference in viral suppression, however, the development of drug resistance was slightly higher for patients who received NVP [25].

Strengths and Limitations

This study had several strengths. It was the first to assess the virological outcomes of individuals living with HIV outside of the capital of Port-au-Prince and identified regions (departments) associated with increased odds of virological failure. Associations of virological failure with low CD4 cell counts and high WHO clinical stages are consistent with previous studies. Although not statistically significant, there was an upward trend observed in the strength of the associations with each increasing WHO HIV infection stage category and a downward trend in the strength of the associations with each increasing CD4 count category. The study also had some limitations worth noting. First, most patient records that were queried had unknown virological status, excluding them from the primary analysis and calling into question potential selection bias. Patients included in the study were slightly younger, more likely to be diagnosed in the Artibonite-Centre department, less frequently diagnosed between 2014 and 2015 or initiated on ART in 2015, and more likely to receive an ART regimen other than 3TC-EFV-TDF. Additionally, patients included in the study also had a greater mean number of months between viral load test and diagnosis and ART initiation. While, an ART regimen other than 3TC-EFV-TDF, and ART initiation in 2015 were associated with

increased odds of virological failure in the primary analysis, treatment in the Artibonite-Centre department and more time on ART were associated with reduced odds. Therefore, the results of the bias assessment indicate that though the populations differed with respect to some demographic and clinical characteristics, these characteristics did not appear to be related to virological status. A second limitation of the current analysis was the use of only a single viral load measurement to classify virological failure. Repeated viral load assessments (at least two) are more precise and increase statistical power [26], however, they were not sufficiently available for consideration in this analysis. Further, the proportion of missing data on some covariates ranged from 20.4% to 46.7% which limited their utility in the analyses but represent opportunities to improve reporting. Of note, data on the history or presence of tuberculosis and sexually transmitted diseases was significantly under-reported (46.7% and 42.8% respectively). This likely explains the lack of an association between virological outcomes and comorbid tuberculosis, which is a known risk factor for virological failure. Additionally, CD4 count data was missing for approximately 35.6% of patients which is much higher than previous studies conducted in this population. This may be due to its decreased use as an eligibility screener in recent years, as it is no longer required for ART eligibility. Further, no data was available to consider treatment adherence or prior treatment exposure, both of which are linked to virological failure.

CHAPTER 5
CONCLUSION AND FUTURE DIRECTIONS

In conclusion, this study was the first to describe the differences in early virological status in Haiti. Virological status differed by age, clinic department, year of ART initiation, WHO clinical stage, CD4 counts, ART regimen, and time on ART. Patients diagnosed in the Artibonite-Centre and Sud departments were less likely to experience virological failure. Future studies should confirm these findings and attempt to explain the departmental differences in virological response to identify underlying factors. The alternative ART regimen: 3TC-AZT-NVP was strongly associated with poorer virological outcomes in the present study and in another recently conducted study [14]. It is therefore recommended that the Ministry of Public Health and Population (MSPP) enhance their monitoring of virological outcomes in patients receiving these first-line regimens. This study included patients who were treated in 76 of 164 (46%) HIV treatment clinics in Haiti. While there are three main electronic medical records (EMR) systems that report data to SALVH (iSanté, GHESKIO, and PIH), only iSanté clinics could be included in the study due to lack of data availability for the other systems. The MSPP should encourage better reporting from the other EMR systems moving forward. Continued escalation of viral load testing is recommended, however the turnaround time for reporting of test results should be minimized. Lastly, future studies should be conducted to evaluate the role of ART adherence and pre-treatment NNRTI drug resistance on virological outcomes in Haiti.

LIST OF REFERENCES

1 Lynen L, Van Griensven J, Elliott J. **Monitoring for treatment failure in patients on first-line antiretroviral treatment in resource-constrained settings.** *Curr Opin HIV AIDS* 2010; **5**:1–5.

2 Chun HM, Obeng-Aduasare YF, Broyles LN, Ellenberger D. **Expansion of Viral Load Testing and the Potential Impact on Human Immunodeficiency Virus Drug Resistance.** *J Infect Dis* 2017; **216**:S808–S811.

3 Laborde-Balen G, Taverne B, Ndour CT, Kouanfack C, Peeters M, Ndoye I, *et al.* **The fourth HIV epidemic.** *Lancet Infect Dis* 2018; **18**:379–380.

4 World Health Organization (WHO), 'Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach, 2013', http://www.ncbi.nlm.nih.gov/books/NBK195400/ [Accessed 21 June 2018].

5 World Health Organization (WHO). 'Consolidated Strategic Information Guidelines for HIV in the Health Sector. WHO Guidelines Approved by the Guidelines Review Committee, 2015', http://apps.who.int/iris/bitstream/10665/164716/1/9789241508759_eng.pdf [Accessed 22 May 2018].

6 Haile-Selassie H, World Health Organization (WHO), Department of HIV/AIDS, Centers for Disease Control and Prevention (U.S.), Global Fund to Fight AIDS T and Malaria, *et al.* 'WHO HIV drug resistance report 2017', http://apps.who.int/iris/bitstream/10665/255896/1/9789241512831-eng.pdf [Accessed 21 June 2018].

7 Gupta RK, Gregson J, Parkin N, Haile-Selassie H, Tanuri A, Andrade Forero L, *et al.* **HIV-1 drug resistance before initiation or re-initiation of first-line antiretroviral therapy in low-income and middle-income countries: a systematic review and meta-regression analysis.** *Lancet Infect Dis* 2018; **18**:346–355.

8 United Nations Development Programme (UNDP), 'Human Development Indicators Haiti, 2016', http://hdr.undp.org/en/countries/profiles/HTI [Accessed 22 May 2018].

9 McNairy ML, Joseph P, Unterbrink M, Galbaud S, Mathon J-E, Rivera V, *et al.* **Outcomes after antiretroviral therapy during the expansion of HIV services in Haiti.** *PLOS ONE* 2017; **12**:e0175521.

10 Auld AF, Pelletier V, Robin E, Shiraishi RW, Dee J, Antoine M, *et al.* **Retention throughout the HIV Care and Treatment Cascade: from Diagnosis to Antiretroviral Treatment of Adults and Children Living with HIV – Haiti, 1985-2015.** *Morb Mortal Wkly MMWR*

11 Wolff MJ, Giganti MJ, Cortes CP, Cahn P, Grinsztejn B, Pape JW, *et al.* **A decade of HAART in Latin America: Long term outcomes among the first wave of HIV patients to receive combination therapy.** *PloS One* 2017; **12**:e0179769.

12 Rebeiro PF, Cesar C, Shepherd BE, De Boni RB, Cortés CP, Rodriguez F, *et al.* **Assessing the HIV Care Continuum in Latin America: progress in clinical retention, cART use and viral suppression.** *J Int AIDS Soc* 2016; **19**. doi:10.7448/IAS.19.1.20636

13 Jean Louis F, Buteau J, François K, Hulland E, Domerçant JW, Yang C, *et al.* **Virologic outcome among patients receiving antiretroviral therapy at five hospitals in Haiti**. *PloS One* 2018; **13**:e0192077.

14 Charles M, Noel F, Leger P, Severe P, Riviere C, Beauharnais CA, *et al.* **Survival, plasma HIV-1 RNA concentrations and drug resistance in HIV-1-infected Haitian adolescents and young adults on antiretrovirals.** *Bull World Health Organ* 2008; **86**:970–977.

15 Cesar C, Jenkins CA, Shepherd BE, Padgett D, Mejía F, Ribeiro SR, *et al.* **Incidence of virological failure and major regimen change of initial combination antiretroviral therapy in the Latin America and the Caribbean: an observational cohort study.** *Lancet HIV* 2015; **2**:e492-500.

16 Delcher C, Puttkammer N, Arnoux R, Francois K, Griswold M, Zaidi I, *et al.* **Validating Procedures used to Identify Duplicate Reports in Haiti's National HIV/AIDS Case Surveillance System.** *J Regist Manag* 2016; **43**:10–15.

17 Hare AQ, Ordóñez CE, Johnson BA, del Rio C, Kearns RA, Wu B, *et al.* **Gender-Specific Risk Factors for Virologic Failure in KwaZulu-Natal: Automobile Ownership and Financial Insecurity.** *AIDS Behav* 2014; **18**:2219–2229.

18 UN Joint Programme on HIV/AIDS (UNAIDS). 'Haiti: HIV and AIDS Estimates, 2015', http://www.unaids.org/en/regionscountries/countries/haiti/ [Accessed 22 May 2018]

19 Alvarez-Uria G, Naik PK, Pakam R, Midde M. **Early HIV viral load determination after initiating first-line antiretroviral therapy for indentifying patients with high risk of developing virological failure: data from a cohort study in a resource-limited setting.** *Trop Med Int Health TM IH* 2012; **17**:1152–1155.

20 Hermans LE, Moorhouse M, Carmona S, Grobbee DE, Hofstra LM, Richman DD, *et al.* **Effect of HIV-1 low-level viraemia during antiretroviral therapy on treatment outcomes in WHO-guided South African treatment programmes: a multicentre cohort study.** *Lancet Infect Dis* 2018; **18**:188–197.

21 Hassan AS, Nabwera HM, Mwaringa SM, Obonyo CA, Sanders EJ, Rinke de Wit TF, *et al.* **HIV-1 virologic failure and acquired drug resistance among first-line antiretroviral experienced adults at a rural HIV clinic in coastal Kenya: a cross-sectional study.** *AIDS Res Ther* 2014; **11**:9.

22 Stadeli KM, Richman DD. **Rates of emergence of HIV drug resistance in resource-limited settings: a systematic review.** *Antivir Ther* 2012; **18**:115–123.

23 Charles M, Leger PD, Severe P, Guiteau C, Apollon A, Gulick RM, *et al.* **Virologic, clinical and immunologic responses following failure of first-line antiretroviral therapy in Haiti.** *J Int AIDS Soc* 2012; **15**:17375.

24 Rupérez M, Pou C, Maculuve S, Cedeño S, Luis L, Rodríguez J, *et al.* **Determinants of virological failure and antiretroviral drug resistance in Mozambique.** *J Antimicrob Chemother* 2015; **70**:2639–2647.

25 Mbuagbaw L, Mursleen S, Irlam JH, Spaulding AB, Rutherford GW, Siegfried N. **Efavirenz or nevirapine in three-drug combination therapy with two nucleoside or nucleotide-reverse transcriptase inhibitors for initial treatment of HIV infection in antiretroviral-naïve individuals.** *Cochrane Database Syst Rev* 2016; **12**:CD004246.

26 Rose CE, Gardner L, Craw J, Girde S, Wawrzyniak AJ, Drainoni M-L, *et al.* **A Comparison of Methods for Analyzing Viral Load Data in Studies of HIV Patients.** *PLOS ONE* 2015; **10**:e0130090.

BIOGRAPHICAL SKETCH

Shannan majored in epidemiology. While simultaneously working for the Departments of Epidemiology and Health Outcomes and Biomedical Informatics, she received her master's degree in the summer of 2018.