Developing a predictive model to identify sub-optimal antiretroviral therapy adherence in Namibia

A thesis

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Nadi Nina Kaonga

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Advisors:

Thesis Chair: Christine Wanke, MD

Project Mentor: Steven Y. Hong, MD, MPH, MAR

Project Mentor: Alice Tang, PhD, ScM

Statistical Mentor: Jason Nelson, MPH

Abstract

Addressing known and unknown risk factors for non-adherence to antiretroviral therapy (ART) has proved challenging, despite increased access. Work continues to be done to determine how best to optimize adherence, and it remains a priority for HIV/AIDS researchers and implementers. One proposal is to identify sub-groups most at-risk, prior to treatment initiation, and provide resources that they may need to maximize their therapy. Therefore, the purpose of this study was to develop and assess a pre-treatment screening tool to identify individuals most at risk ("high-risk") for sub-optimal ART adherence. The screening tool took the form of a diagnostic predictive model. The outcome of interest was calculated using the medication possession ratio (MPR); an MPR below 75% was defined as sub-optimal adherence. Using the Namibia Defaulter Tracing Study Database, a predictive model was developed and evaluated. Multiple imputation methods were used to address missing data. Prior clinical knowledge and univariable analyses helped inform variables for consideration in the model. Multiple logistic regression techniques were used to build the multivariate model. The final model contained the following variables: age (younger being more vulnerable to sub-optimal adherence), gender (males being more likely to have sub-optimal adherence), travel cost, location, religion and beliefs, and food insecurity. Being younger, being male, having higher travel costs, having greater mobility (location), not being Christian, believing God can heal and food insecurity were associated with a greater likelihood of having sub-optimal adherence. Once the model was built, performance measures were assessed. The overall model had modest performance (Brier score: 0.18, c-statistic: 0.66). The predictors can be used to identify a sub-set of the population that is prone to struggling

with adherence. It will be worth exploring the relevancy, interactions and challenges faced by individuals with any of the following characteristics in Namibia further and comparing the findings to similar populations elsewhere. Next steps will include verifying the findings with providers in practice, externally validating and updating the model and determining ways to present the information in a meaningful manner for use.

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List of Abbreviations

AIC	Akaike Information Criterion
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretrovirals
HAART	Highly Active Antiretroviral Therapy
HFIAS	Household Food Insecurity Access Scale
HIV	Human Immunodeficiency Virus
IRB	Institutional Review Board
LTFU	Loss-to-follow-up
MPR	Medication Possession Ratio
n.d.	No Date
NDTS	Namibia Defaulter Tracing Study
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
PHQ	Patient Health Questionnaire
ROC	Receiver Operating Characteristic
TRIPOD	Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis
VIF	Variance Inflation Factor

Introduction

The Global HIV Epidemic

Great strides have been made in addressing the HIV epidemic [UNAIDS, 2013]. Globally, the incidence of HIV has decreased and more individuals who meet the qualifications to initiate antiretroviral therapy (ART) are receiving antiretroviral (ARVs). Testing is being promoted, as are methods of prevention such as the prevention of mother-to-child transmission, other prophylaxis measures, condoms and male circumcision. Despite these efforts, the brunt of the HIV burden remains in Sub-Saharan Africa [UN, 2004]. Roughly 70% of the estimated 35 million people living with HIV are in Africa, and close to 75% of annual deaths (~1.1 million out of 1.5 million deaths) from HIV are also from the region [WHO, no date (n.d.)]. Some of the reasons behind this disproportionate burden include inadequate health care infrastructure, limited access to quality care, stigma, poor nutrition, poverty, fear and challenges with adherence [AVERT, 2014]. Not all of these challenges are unique to Africa but they are prominent throughout the region.

HIV and ART Adherence in Namibia

Despite increased access to ART globally, optimal adherence to ART remain a challenge. It is conservatively assumed that if a patient does not pick up their medication on time, their treatment has been interrupted. In Namibia, where 13% of the adult population is living with HIV, a recent study found that only 35.8% of those who had initiated therapy picked up their ARVs on-time [CIA, 2014; Tjituka, 2013]. Furthermore, current estimates in Namibia indicate that anywhere from 5-11% of the population of interest have sub-

optimal adherence [Tjituka, 2013; Hong, 2013]. The range is dependent upon the method of measuring adherence and study context.

ART Adherence in the Literature

Considerable amounts of HIV research have been dedicated to adherence. In 2006, Mills et al conducted a meta-analysis on adherence to ART, comparing adherence rates in Sub-Saharan Africa and North America. The finding was that Sub-Saharan Africa had better adherence rates than North America. However, the limitations of the meta-analysis included different medication regimens (with more complex regimens in North America), short-term follow-up, lack of a representative sample (especially in Sub-Saharan Africa where only 12 investigations were represented) and a lack of a standard method for assessing adherence. The article also underlined the importance of identifying risk factors and barriers for non-adherence to optimize treatment and prevention [Mills, 2006 (JAMA)]. Systematic reviews from 2012 and 2014 had similar findings that adherence rates to ART were higher in Sub-Saharan Africa than North America and other resource replete settings; they also identified that further work on improving adherence needed to be done [Reda, 2012; Kim, 2014].

Adherence Challenges

Following that study, some of the same authors focused on the barriers to care [Mills, 2006 (PLoS Med)]. They found some overlap between the two regions but also some context-specific factors. However, they were limited by poor representative sample of studies from Sub-Saharan Africa. The similarities included lack of patient education and/or understanding, treatment complexity and fear of disclosure due to stigma. The authors believed that most of the challenges in developing countries could be addressed

simply through discussion and education [Mills, 2006 (PLoS Med)]. However, recent studies point to more complex drivers and social and environmental issues that influence adherence that subsequently require more intensive resources.

For example, a recent study by Denison et al examined adherence challenges in Tanzania, Uganda and Zambia. The cross-sectional study, which had a large sample size, identified alcohol use and reliance on traditional healers as common barriers to optimal adherence [Denison, 2015]. Prophets or church healings can also serve as barriers [Seeling, 2014]. Depression or depressive symptoms have also been positively correlated with poor adherence, irrespective of socioeconomic status and geography [Uthman, 2014]. Stigma was also identified as a significant barrier to adherence. Fear of disclosure can prevent patients from having adequate social support; it can also lead to patients not taking their medication in order to hide their status [Katz, 2013]. Another study that collected data on self-reported barriers and found that individuals often experienced multiple barriers to adherence, rather than just a single barrier [Genberg, 2015]. It also appeared that the barriers remained relatively consistent over time. This is important to consider when designing interventions to promote adherence. Lastly, the authors note the potential utility of a quick pre-visit assessment tool. The tool could be used to identify patient challenges and inform strategies for providers to work with patients to address the barriers [Genberg, 2015].

Adherence Promotion Strategies

Now that HIV care and management is becoming increasingly managed like a chronic disease rather than infectious disease, adherence promotion strategies must include long-term approaches. Such approaches can help prevent treatment interruption, which has

been found to be a better indicator of virologic failure than pill count, alone, when using non-nucleoside reverse transcriptase inhibitors (NNRTIs) (which are in use in Namibia) [Parienti, 2008; Bangsberg, 2013 (Antivir Ther)]. [For the NNRTI drugs, it means that the treatment interruption focus is more on the pattern of adherence rather than average adherence.] Managed problem solving and combining evidence-based interventions are becoming more common in practice [Bangsberg, 2013 (JAMA Intern Med); Yang, 2014]. A review by Chaiyachati and colleagues noted that combined interventions had effects that were similar to (but not necessarily greater than) single interventions. Despite this, combined interventions may more adequately deal with the complex and numerous adherence challenges faced by patients [Chaiyachati, 2014]. Observed combinations typically include education and medication reminders. In their article, Bangsberg and Haberer recommend flexible 'real-time' adherence monitoring for life. They suggest that electronic devices can be used to monitor and provide any necessary support to patients when, where and however they need it [Bangsberg, 2013 (JAMA Intern Med)]. Treatment partners are also recognized as a useful tool [O'Laughlin, 2012]. Not only do partners provide social support, they can also help reinforce patient education, augment counselling and temper stigma-related issues.

The Merits of Early Identification of Adherence Challenges

While there are guidelines to improve adherence and a general consensus on what works well, more information is needed about these strategies [Thompson, 2012; Mathes, 2013; Barnighausen, 2011; Scanlon, 2013]. Addressing known and unknown risk factors for non-adherence has proved challenging. This is for a number of reasons. The risk factors that drive individuals to be adherent or not are dynamic, vary individually and clinical,

environmental, social and other contextual factors are influential, as well [AIDSinfo, 2014]. Work continues to be done to determine how best to optimize adherence and it remains a priority for HIV/AIDS researchers and implementers.

More operational research will help translate evidence and strategies into practice [Scanlon, 2013]. Bangsberg and Deeks provide a framework to think through adherence challenges and potential interventions, keeping resources in mind [Bangsberg, 2010]. The framework encompasses community-level, general patient-level and targeted patient-level interventions. The authors note that resource-intensive interventions may be most appropriate for individuals with significant adherence issues, rather than all patients on ART. Additionally, the authors point out that the earlier adherence issues are identified, the better. All of this aligns with and also provides justification to our study of identifying individuals who are most at-risk for sub-optimal adherence in resource-limited settings. In the future, the findings may be useful for identifying more targeted and cost-effective proactive (rather than reactive) interventions.

Purpose, Aim and Hypothesis

The purpose of this study is to develop and assess a pre-treatment screening tool to identify individuals most at risk ("high-risk") for sub-optimal ART adherence. The screening tool will take the form of a predictive model.

The specific aim and accompanying hypothesis are as follows:

> *Specific Aim:* To develop and validate a predictive model that can be used to identify individuals at high-risk for sub-optimal ART adherence in Namibia.

Hypothesis: The resulting predictive model will be able to identify individuals in Namibia at high-risk for sub-optimal ART adherence.

Materials and Methods

Study Population

The Namibia Defaulter Tracing Study (NDTS) commenced in 2012. The purpose of the study was to identify the factors driving loss-to-follow-up (LTFU) in care for HIV. LTFU contributes to poor ART treatment success. A total of 524 patients were enrolled across seven sites in Namibia. Sites were eligible for inclusion if they started at least 134 patients on ART annually and if their prior LTFU was $\geq$ 15%; the sites were randomly selected from six geographic regions in Namibia. Patients were eligible for inclusion if they were adults (18 years or older) and were eligible to initiate first-line ART and had never initiated treatment before the study period. At baseline, information – including patient characteristics, socioeconomic status, HIV knowledge, motivations and barriers to attending clinic, beliefs about medicines, alternative healing, physical health, depression and mental health screening, social support, household food insecurity access, risks (e.g., alcohol, drugs) and stigma – was collected via surveys. At 12 months and <24 months after baseline, electronic clinic records were used to determine LTFU status. In order to determine adherence to medication, the survey and LTFU data were merged with 12 months of pill count data (starting at baseline) from the national electronic pharmacy management system. It is this merged data – specifically the pill count data – that form the basis for the current research on sub-optimal adherence. Assessments of the study sample size indicated that the data were adequate for the study.

Outcome

Being at risk for sub-optimal adherence was based on how well an individual picked up their pills on time. The findings from a recent adherence study in Namibia determined

that the medication possession ratio (MPR) was the best way to calculate ART adherence in Namibia, in lieu of measuring viral loads (which is invasive and expensive) [Hong, 2013]. The study identified that an MPR <75% was indicative of poor adherence and linked to poor health outcomes. Individuals with an MPR below this cut-off showed evidence of poor virologic outcomes [Hong, 2013]. Using those findings, we defined the outcome of interest (sub-optimal adherence) as an MPR < 75%. The outcome was coded as a binary variable. A minimum of two pill pick-up dates were needed to calculate MPR (and only 3 individuals did not have sufficient data for the MPR to be calculated).

The formula used to calculate MPR is as follows:

$$MPR = \left[1 - \left(\frac{\#\ days\ late\ for\ pill\ pick-up}{\#\ days\ between\ first\ and\ last\ pill\ pick-up}\right)\right] * 100$$

For individuals LTFU, 90 days was added to the number of days late for pill pick-up to account for their LTFU status, as this is the standard definition of LTFU in Namibia. The MPR calculation for those who died during the study period were calculated based on their available follow-up time (similar to the population not LTFU).

Predictors

All variables in the NDTS dataset were reviewed and short-listed for further consideration and subsequent analysis. Variables were selected *a priori* based on knowledge and experience and review of the literature. A requisite for the variables was that they can influence sub-optimal adherence, examples include gender and cost of travel to the clinic.

A short-list of variables of interest was developed *a priori* (see Table 1). The short-list represents variables that were of highest interest for analysis and potential inclusion in the model; the short-listed variables were analyzed.

Table 1. *A Priori* Risk Factors of Interest and How They Were Measured

Variable	**Measurement**
Age (in years)	Continuous
Alcohol use	Categorical
Baseline CD4 count	Ordinal categories
Beliefs about medicine*	Continuous scale
Clinic experience	Categorical
Difficulty leaving work to go to the clinic	Categorical
Difficulty traveling to/from the clinic	Categorical
Drug use	Categorical
Education	Categorical
Food insecurity score	Continuous
Food insecurity status	Categorical
Gender	Binary
Home amenities (as a proxy for socio-economic status)	Categorical
Income (in Namibian Dollars (N$))	Ordinal categories
Influence of religion on taking ART as prescribed	Categorical
Marital status	Categorical
Mental health (PHQ-9 score)	Continuous scale
Mode of transportation [to/from clinic]	Categorical
Physical health	Categorical
Receive support when sick from family or friends (social support)	Categorical
Religious affiliation	Categorical
Stigma Score*	Continuous scale
Travel cost to/from the clinic	Continuous
Travel time to the clinic (in minutes)	Continuous
Use of alternative healing (i.e., traditional healers)	Categorical
World Health Organization HIV clinical stage	Ordinal categories

*PHQ-9 = Patient Health Questionnaire #9 (on mental health, screening for depression), * = Developed a scale and scores using the literature and exploratory factor analysis techniques*

Missing Data

To maximize use of the data, increase power and reduce bias due to missing information, multiple imputation methods were used. The *mice* package in R was used to explore and impute missing data [van Buuren, 2015]. Prior to imputation, the three cases that did not have pill count data were dropped from the dataset. Based on the proportion of missing data to not missing data, it was determined that a minimum of five imputations would be needed. The imputation model was developed on the dataset with the binary MPR outcome variable and plausible covariates for the predictive model. The plausible covariates included those in Table 1. Using the *mice* package we applied predictive mean matching and regression techniques to impute the missing data, generate five imputed datasets and pool results across imputations [van Buuren, 2015]. Multiple imputation permitted full analysis for all 521 patients with pill count data in the dataset.

Summary statistics (e.g., median, interquartile range (IQR)) of the pre-imputation dataset, variables with missing data and imputed dataset were generated and compared. After imputation, visualizations of the imputed data were created and assessed. To generate the visualizations, *mice* and its complementary packages (*VIM, lattice and ggplot2*) were used.

Model Building Approach

Prior clinical knowledge and univariable analyses helped inform the selection of variables for consideration in the model. Differences in *a priori* risk factors between

outcome groups were analyzed using t-tests (for normal continuous variables), Mann-Whitney-Wilcoxon test (for nonparametric continuous data), fisher's exact test (for categorical variables where the expected cell count for at least one cell had fewer than 5 datum) or chi-square test (for categorical variables).

Variables with statistically significant associations ($p<0.05$) with the outcome were selected for inclusion in the final model. Based on power and sample size estimates, no more than 13 variables were considered for inclusion in the model building analysis. Interaction terms were considered and investigated for age, gender, site and marital status. Multiple logistic regression techniques, with backward and forward variable selection, were used to build the multivariable model. Site was forced into the model. Using *mice*, the regression and selection techniques, as well as the model performance measures, are automatically computed in each individual imputed dataset and then pooled to account for the between imputation variability.

To build and assess the performance of the parsimonious model, a similar approach was used as above. However, site was not forced into the model.

Statistical Analyses

The Akaike Information Criterion (AIC) was generated and compared across the full and parsimonious models. Likelihood ratio tests were conducted to assess if the full and parsimonious models differed from one another. If the likelihood ratio test was significant, it would indicate that the predictors in the full model provide important information not present in the parsimonious model, and if the test is not significant, there is no additional predictive information provided by the full model as compared to the

parsimonious model. The Hosmer-Lemeshow p-values were used to determine the goodness of fit for the final model in relation to the imputed data. A significant p-value indicates that the model is a poor fit for the data. Variance inflation factors (VIF) were reviewed to ensure that no collinear variables were unnecessarily included in the model. VIF values above 5 indicate collinearity between two or more variables and would require review of whether or not it is appropriate to retain all of the collinear variables in the model. Overall model performance was assessed using the Brier score; the lower the Brier score, the better the indication that the model is accurately predicting the outcome. Coefficients and standard errors were transformed into odds ratios and 95% confidence intervals (using the pooled imputed data).

Visualizations of the model were generated to aid in assessing model discrimination and calibration. The visualizations included a calibration plot, receiver operating characteristic (ROC) curve. The c-statistic was obtained, as well. The c-statistic is a measure of discrimination and tests how well the model is able to discern between patients with and without the outcome of interest.

Supplementary code identified in online forums for the *mice* and *rms* packages were used to set-up the dataset for internal validation and run the necessary model performance assessments [tormodb, 2016]. As a part of the validation, the Brier score, calibration plots and ROC curve were generated and assessed and compared to the original findings.

All analyses were carried out using R versions 3.2.2, 3.2.3 and 3.3.0 with packages *ROCR, rms, visreg, psych, car, survival* and *mice* [The R Foundation, 2016].

Results

Study Population Characteristics

Of the 524 patients in the NDTS database, 521 had sufficient data to calculate the MPR; the data on the 521 patients were used to build the diagnostic predictive model. Roughly 25.5% (n=133) of individuals had sub-optimal adherence (<75% MPR), according to their pill pick-up data. At baseline, the majority of the study population was female (61.2%, n=319) and young (median age = 35 years old). Most (90.4%, n=471) of the population had some education (primary school and above), and both alcohol and drug use were not common (22.8%, n=119; 6.3%, n=33; respectively). A large proportion of individuals were in the first clinical stage for HIV (49%, n=257) but a substantial proportion of the population had low CD4 counts (CD4 count <200; 42.5%, n=221). The clinical stages are used as a means to prioritize the distribution of ART based on severity of the disease [Ministry of Health and Social Services, 2010].

When examining the population with sub-optimal adherence (n=133) as compared to optimal adherence (n=388), the two populations were similar in age (mean age: 34.8 years old, 36.2 years old; respectively; p-value 0.18), education (p-value 0.61), income levels (p-value 0.06), mental health status (p-value 0.13), alcohol use (p-value 0.61) and drug use (p-value 0.09). However, individuals with sub-optimal adherence were more likely to be male (48.5% versus 35.6%; p-value 0.01), find it challenging to travel to the clinic for follow-up appointments (35.3% versus 25.5%; p-value 0.04), be food insecure (38.3% versus 27.1%; p-value 0.02); have little to no physical energy (47% versus 35.8%; p-value 0.03) and believe that God can heal their HIV (24.2% versus 14.1%; p-value 0.01) as compared to their counterparts with optimal adherence. The adherence

differences across the seven study sites were also statistically significant (p-value 0.005). (See Table 2)

Table 2. Baseline Characteristics by Adherence Status (Prior to Imputation)

Variable	**Optimal Adherence, MPR ≥ 75 (n=388)**	**Sub-Optimal Adherence, MPR < 75 (n=133)**	**Number of missing datum**	**P-value**
Age (in years), mean (SD)	36.2 (10.5)	34.8 (10.4)	2	0.18
Gender				
Female, n (%)	248 (64.4)	67 (51.5)	6	0.01
Male, n (%)	137 (35.6)	63 (48.5)		
Education				
Primary and Below, n (%)	153 (39.4)	57 (42.9)	0	0.78
Secondary and Above, n (%)	235 (60.6)	76 (57.1)		
Site				
Site 1, n (%)	44 (11.3)	13 (9.8)	0	0.005
Site 2, n (%)	60 (15.5)	29 (21.8)		
Site 3, n (%)	35 (9.0)	21 (15.8)		
Site 4, n (%)	56 (14.4)	23 (17.3)		
Site 5, n (%)	48 (12.4)	20 (15.0)		
Site 6, n (%)	12 (3.1)	5 (3.8)		
Site 7, n (%)	133 (34.3)	22 (16.5)		
Income (in Namibian Dollars (N$))				
N$ 0-500, n (%)	205 (52.8)	57 (42.9)	82	0.06
N$ 501 and Above, n (%)	183 (47.2)	76 (57.1)		
Have a Stove in the Home				
Yes, n (%)	191 (49.4)	44 (33.1)	1	0.001
No, n (%)	196 (50.6)	89 (66.9)		
Months Spent in Town/at Location				0.036
12 Months in Town, n(%)	341 (88.1)	106 (80.3)	1	
WHO HIV Stage				0.19
1, n(%)	197 (51.9)	58 (45.7)	17	

Variable	Optimal Adherence, MPR ≥ 75 (n=388)	Sub-Optimal Adherence, MPR < 75 (n=133)	Number of missing datum	P-value
2, n(%)	123 (32.5)	39 (30.7)		
3, n(%)	52 (13.7)	25 (19.7)		
4, n(%)	7 (1.8)	5 (3.9)		
Baseline CD4 Count				
<200, n (%)	155 (41.3)	56 (44.8)		0.23
200-349, n (%)	176 (46.9)	61 (48.8)	21	
> 350, n (%)	44 (11.7)	8 (6.4)		
ART Regimen				
Efavirenz-based, n (%)	47 (12.2)	24 (18.2)	4	0.12
Nevirapine-based, n (%)	338 (87.8)	108 (81.8)		
BMQ-HAART Score, median (1st, 3rd Quartiles)	42 (40,45)	41 (39,44)	21	0.02
Religion				
Non-Pentecostal Christian, n (%)	302 (77.8)	98 (73.7)		0.09
Pentecostal Christian, n (%)	74 (19.1)	25 (18.8)	0	
Traditional and All Others, n (%)	12 (3.1)	10 (7.5)		
Religious Leader Encouraging Not Taking ARVs as Prescribed				
Yes, n (%)	14 (3.6)	8 (6.1)	6	0.34
No, n (%)	370 (96.4)	123 (93.9)		
Taking ARVs Shows Lack of Faith in God				
Yes, n (%)	18 (4.6)	10 (7.5)	0	0.29
No or Don't Know, n (%)	370 (95.4)	123 (92.5)		
Believe God Can Heal HIV				
Yes, n (%)	54 (14.1)	32 (24.2)	6	0.01
No or Don't Know, n (%)	329 (85.9)	100 (75.8)		
Method of Confirming Healing (If respond 'yes' for "Believe God Can Heal HIV")*				
Religious Leader Tells Me, n (%)	2 (10.5)	0 (0)		0.03
Get Retested, n (%)	11 (57.9)	1 (10.0)		
Stop ARVs and See if Sick, n (%)	1 (5.3)	1 (10.0)	57	
Don't Know, n (%)	3 (15.8)	6 (60.0)		
Other, n (%)	2 (10.5)	2 (20.0)		

Variable	Optimal Adherence, MPR ≥ 75 (n=388)	Sub-Optimal Adherence, MPR < 75 (n=133)	Number of missing datum	P-value
Marital Status				
Divorced or separated, n (%)	25 (6.4)	10 (7.6)	1	0.95
Married or living together, n (%)	148 (38.1)	52 (39.4)		
Never married and never lived together, n (%)	199 (51.3)	65 (49.2)		
Widowed, n (%)	16 (4.1)	5 (3.8)		
Physical Energy				
Minimal: None to Little, n (%)	138 (35.8)	62 (47.0)	3	0.03
Moderate: Normal Amount to Quite a Lot, n (%)	248 (64.2)	70 (53.0)		
Difficulty Leaving Work to Get to Clinic				
Easy, n (%)	290 (74.7)	89 (66.9)	0	0.10
Not Easy: Little Difficulty to Very Difficult, n (%)	98 (25.3)	44 (33.1)		
Difficulty Traveling to Clinic				
Easy, n (%)	289 (74.5)	86 (64.7)	0	0.04
Not Easy: Little Difficult to Very Difficult, n (%)	99 (25.5)	47 (35.3)		
Travel Time (in minutes), median (1^{st}, 3^{rd} Quartiles)	30 (20,60)	30 (20,82.50)	4	0.18
Travel Cost to Clinic (in N$), median ($1^{st}$, 3^{rd} Quartiles)	15 (9,20)	10 (9,25)	85	0.21
Clinic Experience				
Fair or Poor, n (%)	14 (3.6)	6 (4.5)	2	0.61
Good to Excellent, n (%)	373 (96.4)	126 (95.5)		
Food Security Category (Food Insecurity)				
Food Secure, n (%)	283 (72.9)	82 (61.7)	0	0.02
Food Insecure: Mildly, Moderately and Severely, n (%)	105 (27.1)	51 (38.3)		
Food Insecurity Score, median (1^{st}, 3^{rd} Quartiles)	0 (0,2)	0(0,8)	10	0.01
Alcohol Use				
None, n (%)	302 (77.8)	100 (75.2)	0	0.61
Some, n (%)	86 (22.2)	33 (24.8)		
Drug Use				
None, n (%)	368 (94.8)	120 (90.2)	0	0.09
Some, n (%)	20 (5.2)	13 (9.8)		

Variable	Optimal Adherence, MPR ≥ 75 (n=388)	Sub-Optimal Adherence, MPR < 75 (n=133)	Number of missing datum	P-value
PHQ-9 Score				
No Depression (0-4), n (%)	178 (45.9)	41 (30.8)	0	0.13
Depression: Mild to Moderately Severe (5-27), n (%)	210 (54.1)	92 (69.2)		
Stigma Score, median (1st, 3rd Quartiles)	1 (0,2)	1 (0,3)	11	0.05

ART = Antiretroviral Therapy; BMQ = Beliefs About Medicine Score, specific to ART with higher scores indicating healthier beliefs; N$ = Namibian Dollar (2012-2014 Average Exchange Rate for N$ to USD: 10.4N$ to 1 USD); PHQ-9 = Patient Health Questionnaire #9 (on mental health, screening for depression); WHO = World Health Organization

**Skip pattern question*

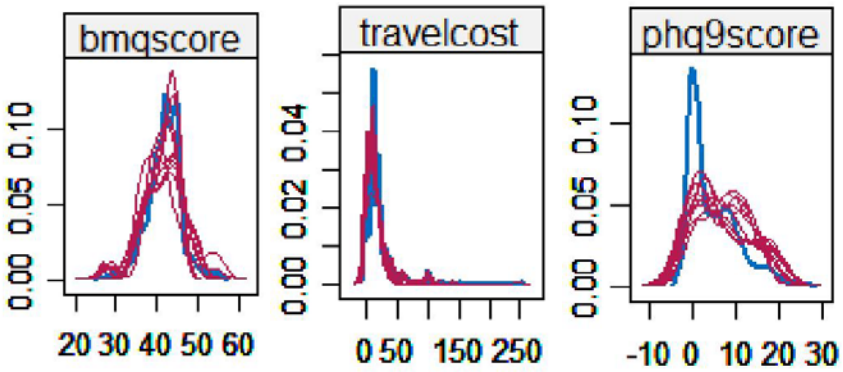
Missingness and Multiple Imputation

Only ten variables (not counting some clinic variables) had more than 20 missing data points; they were BMQ-HAART score, CD4 Count, LTFU, income, travel cost (to clinic), travel cost source, concern of missing ARVs if drink alcohol, specific reasons why leaving work to go to clinic is difficult, God healed HIV (subset of "believe God can heal") and the PHQ-9 score. Of those 10 variables, three reflected variables that had skip patterns (travel cost source, concern of missing ARVs if drink alcohol; God healed HIV), meaning that the response was linked to and depended upon how another item was answered; these variables were not used to impute the dataset by not including them in the imputation. Clinical variables (e.g., height (n=502 missing variables), weight (n=208

missing variables), viral load (n=456 missing variables)) had the most missing data; they were not included in the imputation.

Density plots of the imputed data indicated similar distributions of the imputations with the observed data (see examples, Figures 1a-e). Investigations comparing the original data and the imputed data indicated that the two were comparable (data not shown).

Figures 1a-c. Density Map of Select Imputed Data Distributions as Compared to Observed Data for Variables with Missing Data



a. BMQ Score *b. Travel Cost (in N$)* *c. PHQ9 Score*

Blue = observed data; magenta = imputed data

BMQ Score = Beliefs About Medicine (for ART) Score, Travel Cost = Cost of transport to the clinic in Namibian Dollars (N$); PHQ 9 Score = Patient Health Questionnaire-9 Score for mental health

Full Model

The univariate analyses corroborated clinical insights on candidate risk factors. Variables found to be significant included the following: gender, site, stove in the home (as a proxy for socioeconomic status), months spent in town, beliefs about medicine, belief that God can heal HIV, physical energy, difficulty traveling to the clinic and clinic experience. Further review and consideration of all candidate variables ultimately resulted in the inclusion of age, gender, difficulty traveling to the clinic, cost of travel to the clinic, religion, stove in the home, drug use, site, months in town, food insecurity score, beliefs about medicine score, believe that God can heal HIV (yes – which may imply an individual will seek alternatives to ART/no – which may imply an individual will comply

with ART) and physical energy, being included in the multivariable logistic regression model prior to running the regression and variable selection. The full model consisted of age, gender, site, cost of travel to the clinic, religion, stove in the home, months in town, food insecurity score and believe that God can heal HIV (Table 3). None of the variables were collinear with each other (VIFs ranged from 1-3).

Table 3. Model Coefficients and Odds Ratios for the Full (Site-Inclusive) and Parsimonious Multiple Logistic Regressions Modeled on Sub-Optimal Adherence

	FULL MODEL	**PARSIMONIOUS MODEL**
Model Coefficients	**Odds Ratio (95% Confidence Interval)**	**Odds Ratio (95% Confidence Interval)**
Age*5 Years	0.89 (0.84, 0.95)	0.9 (0.86, 0.95)
Gender		
Female (reference)	--	--
Male	1.94 (1.26, 3.01)	1.9 (1.24, 2.9)
Months in Town		
12 months (reference)	--	--
<12 months	1.44 (0.77, 2.69)	1.66 (0.93, 2.9)
Site		
Site1 (reference)	--	--
Site 2	1.91 (0.84, 4.54)	--
Site 3	2.93 (1.19, 7.41)	--
Site 4	1.24 (0.51, 3.06)	--
Site 5	1.82 (0.73, 4.61)	--
Site 6	1.68 (0.42, 6.24)	--
Site 7	0.97 (0.41, 2.35)	--
Travel Cost*100 N$	3.63 (3.49, 3.78)	2.83 (1.87, 4.28)
Food Insecurity Score	1.05 (1.01, 1.09)	1.05 (1.02,1.09)
Religion		
Christian (Non-Pentecostal) (reference)	--	--
Christian (Pentecostal)	1.10 (0.55, 2.17)	0.92 (0.53, 1.55)
Traditional, Others and None	2.89 (1.10, 7.31)	2.62 (1.03, 6.51)
Believe that God Can Heal HIV		
No (reference)	--	--
Yes	1.59 (0.92, 2.70)	1.9 (1.12, 3.18)

For every 5-year increase in age, there was an 11% decreased odds of having sub-optimal adherence and this is significant. Men had 1.94 times increased odds in having sub-optimal adherence, as compared to females and this is significant. Individuals who were mobile (i.e., spent <12 months in town) had a 1.44 times increased odds of having sub-optimal adherence (and this was not significant). For every 100 N$ increase in travel cost, there is a significant 3.6 times increased odds of having sub-optimal adherence, and for every one-point increase on the food insecurity scale, there is a 1.05 increased odds of having sub-optimal adherence, and this is significant. There had been an attempt to use the food insecurity categories, but the variable did not end up being statistically significant in the final model, whereas the score was borderline significant due to its ability to pick up smaller incremental changes and differences in food insecurity. For the score, the higher the value, the greater the risk of being food insecure. In terms of beliefs, there is significant 2.9 times increased odds in having sub-optimal adherence for those who hold traditional, none or other non-Christian beliefs as compared to Non-Pentecostal Christian (controlling for all other factors); and for those that believe that God can heal their HIV, there is a 1.6 times increased odds in having sub-optimal adherence (but this is not significant).

Parsimonious Model

An attempt was made to develop a more parsimonious model. The parsimonious model did not include site (see Table 3 *above*). In the parsimonious model, the directionality of the effects remained the same as the effects observed in the site-inclusive model. For every 5-year increase in age, there was a 10% decreased odds of having sub-optimal adherence and this was significant. Men had 1.9 times increased odds in having sub-

optimal adherence, as compared to females and this was significant. Individuals who were mobile (i.e., spent <12 months in town) had a 1.7 times increased odds of having sub-optimal adherence. For every 100 N$ increase in travel cost, there is a significant 2.8 times increased odds of having sub-optimal adherence, and for every one-point increase on the food insecurity scale, there is a 1.05 times increased odds of having sub-optimal adherence, and this is significant. The food insecurity categories were not statistically significant in the final model; however, the food insecurity score was borderline significant likely due to its ability to pick up smaller incremental changes and differences in food insecurity. For the score, the higher the value, the greater the risk of being food insecure. In terms of beliefs, there was a significant 2.6 times increased odds in having sub-optimal adherence for those who hold traditional, none or other non-Christian beliefs as compared to Non-Pentecostal Christian (controlling for all other factors); and for those that believe that God can heal their HIV, there was a 1.9 times increased odds in having sub-optimal adherence. All of the VIFs were below 1.1.

Evaluating Model Performance

The parsimonious model had decent performance as compared to the full (site-inclusive) model; it was designated as the final model. The final model developed had moderate to strong discriminatory ability (see Figure 2). The pooled c-statistic, which was an average calculated by hand across the individually imputed datasets, was 0.66 (see Table 5). The p-value of the likelihood ratio test for the parsimonious model and full model was not significant (0.09). Therefore, the full model is not significantly different than the parsimonious model, and it is possible that site may not add predictive information. The AIC was smallest for the final model, which could be expected given its inclusion of the

additional variable (site). Further investigations identified that the final model did not have significant lack of fit for the dataset (Hosmer-Lemeshow p-value was not significant). The pooled Nagelkerke R^2 was 0.09, which is low. This was expected due to the fact that the model is attempting to predict human behavior. In addition, the pooled Brier score was low (0.18), indicating decent calibration of the predictions made using the model. Unsurprisingly, the internal validation had similar findings, with the model performing moderately well.

Figure 2. Model Performance Calibration Chart of the First Imputed Dataset

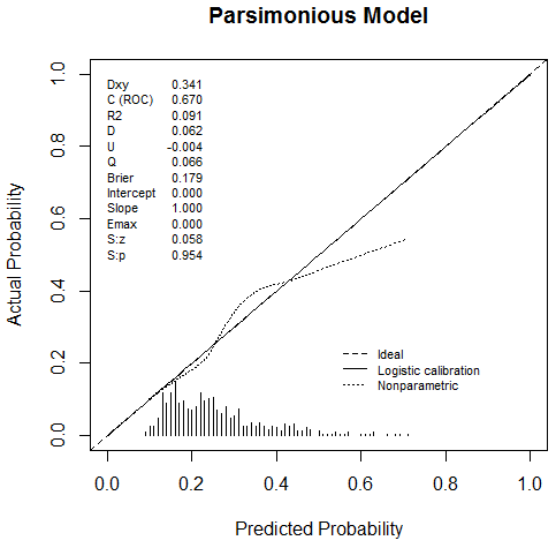


Table 4. Model Performance Across the Imputed Datasets Including Pooled Values

	Imputation #1	Imputation #2	Imputation #3	Imputation #4	Imputation #5	**Averaged Value**	Bootstrap Validation (Corrected)
C-statistic	0.67	0.66	0.66	0.67	0.66	**0.66**	0.65
Pseudo-R^2	0.09	0.08	0.08	0.09	0.08	**0.09**	0.06
Brier Score	0.18	0.18	0.18	0.18	0.18	**0.18**	--

Discussion and Future Directions

While the effects of age, gender, socioeconomic status, location, religious beliefs and food insecurity on sub-optimal adherence are not large, their presence and collective influence on adherence is notable. The predictors can be used to identify a sub-set of the population that is prone to struggling with adherence. It will be worth exploring the relevancy, interactions and challenges faced by individuals with any of the following characteristics in Namibia further and comparing the findings to similar populations elsewhere:

- Younger individuals (i.e., young adults)
- Males
- Mobile or itinerant individuals
- Lower socioeconomic status
- Non-Christians
- Food insecure

Risk in the Literature

The findings corroborate with adherence risk factors identified throughout Sub-Saharan Africa [Reda, 2012; Gourlay, 2013; Hodgson, 2014; Adejumo, 2015]. In the literature, most ‘models’ were linear regressions exploring risk factors to adherence. The explorations were not designed as prediction models and often ended prior to assessing performance. However, age has been increasing in focus with youth and adolescent adherence being prioritized [Muller, 2011; Adejumo, 2015], as has food insecurity (especially in Namibia) [Hong, 2014]. While not identified as significant in the model but

still of note, the importance of social support has led to numerous innovations seeking to address gaps in social support [Cummings, 2014; Lifson, 2015].

Strengths and Limitation

Despite developing a diagnostic predictive model that is able to identify individuals at risk for sub-optimal adherence in a limited resource setting, there are limitations to the approach and the model. The overarching limitation is generalizability.

The NDTS database is a rich database – made stronger through its links to an electronic database with adherence information – that includes numerous variables not routinely collected in clinical care. As was evidenced in the findings, many of the variables assessed were unique to the database, and in the final model. All but two of the variables in the model are not clinical variables. However, the case can be made that the information captured by the variables in the final model could be quickly obtained and monitored during routine care.

Since context can influence adherence, the database may include patients receiving differential care. However, this is unlikely. What may be possible is unnoticed information bias stemming from social desirability bias (individuals misrepresenting their true thoughts and conditions in an effort to look good). There are some redundancies built in to the survey to mitigate such biases, but they are not applicable to all variables.

Using the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) Checklist, the study adequately addressed all of the applicable checklist items for the development and internal validation of a diagnostic prediction model [Collins, n.d.]. Imputation techniques used to address missingness in

the database were successful and could have addressed some of the sample size concerns. Future research, including external validation of the model as an immediate next step, could strengthen the model and verify its relevancy with providers in limited resource settings.

Implications and Future Research

Overall, the study demonstrates that there are sub-groups of persons living with HIV who have sub-optimal adherence and that they could be identified relatively easily during clinical visits. Age, gender and food insecurity are increasingly receiving more attention. However, they are often not looked at in conjunction with each other. This research will hopefully be an additional step in generating the evidence needed to bring about social and systemic changes that can ultimately improve ART adherence. In particular, it will be worth exploring if and how the model is relevant in other settings in Sub-Saharan Africa and elsewhere. Immediate next steps should include external validation; providers can also be engaged to corroborate the findings with current trends in practice, and patients can also provide qualitative validation of the findings.

References

1. Adejumo, O.A., Malee, K.M., Ryscavage, P., Hunter, S.J., Taiwo, B.O. Contemporary issues on the epidemiology and antiretroviral adherence of HIV-infected adolescents in sub-Saharan Africa: a narrative review. Journal of the International AIDS Society. 2015. 18(1): 20049.
2. AIDSinfo. HIV Medication Adherence. HIV Treatment 2014 [cited 2015 10 February]; Available from: http://aidsinfo.nih.gov/education-materials/fact-sheets/21/54/hiv-medication-adherence.
3. AVERT. HIV and AIDS in sub-Saharan Africa. 2014 [cited 2015 10 February]; Available from: http://www.avert.org/hiv-aids-sub-saharan-africa.htm.
4. Bangsberg, D.R. and S.G. Deeks, Spending more to save more: interventions to promote adherence. Ann Intern Med. 2010. 152(1): 54-6.
5. Bangsberg, D.R. and E.J. Mills, Long-term adherence to antiretroviral therapy in resource-limited settings: a bitter pill to swallow. Antivir Ther. 2013. 18(1): 25-8.
6. Bangsberg, D.R. and J.E. Haberer, Lifetime HIV antiretroviral therapy adherence intervention: timing is everything: comment on "Managed problem solving for antiretroviral therapy adherence". JAMA Intern Med. 2013. 173(4): 306-7.
7. Barnighausen, T., et al., Interventions to increase antiretroviral adherence in sub-Saharan Africa: a systematic review of evaluation studies. Lancet Infect Dis. 2011. 11(12): 942-51.
8. Chaiyachati, K.H., et al., Interventions to improve adherence to antiretroviral therapy: a rapid systematic review. AIDS. 2014. 28 Suppl 2: S187-204.
9. CIA. Namibia. The World Factbook 2014 [cited 2015 10 February]; Available from: https://www.cia.gov/library/publications/the-world-factbook/geos/wa.html.
10. Coates, J., Swindale, A., Bilinksy, P. Household Food Insecurity Access Scale (HFIAS) for Measurement of Food Access: Indicator Guide (v. 3). Washington, D.C.: FHI 360/FANTA.
11. Collins, G.S., Reitsma, J.B., Altman, D.G., Moons, K.G. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement. n.d. Available from: http://www.tripod-statement.org/Downloads.
12. Cummings, B., Gutin, S.A., Jaiantilal Prafulta, Correia, D., Malimane, I., Dawson, R.C. The Role of Social Support Among People Living with HIV in Rural Mozambique. AIDS Patient Care and STDs. 2014. 28(11): 602-612.
13. Denison, J.A., et al. Incomplete adherence among treatment-experienced adults on antiretroviral therapy in Tanzania, Uganda and Zambia. AIDS. 2015. 29(3): 361-71.
14. Genberg, B.L., et al., Four Types of Barriers to Adherence of Antiretroviral Therapy are Associated with Decreased Adherence Over Time. AIDS Behav. 2015. 19(1): 85-92.
15. Gourlay, A., Birdthistle, I., Mburu, G., Iorpenda, K., Wringe, A. Barriers and facilitating factors to the uptake of antiretroviral drugs for prevention of mother-

to-child transmission of HIV in sub-Saharan Africa: a systematic review. Journal of the International AIDS Society. 2013. 16(1): 18588.
16. Hodgson, I., Plummer, M.L., Konopka, S.N., et al. A Systematic Review of Individual and Contextual Factors Affecting ART Initiation, Adherence, and Retention for HIV-Infected Pregnant and Postpartum Women. PLoS ONE. 2014. 9(11): e111421.
17. Hong, S.Y., et al. Medication possession ratio associated with short-term virologic response in individuals initiating antiretroviral therapy in Namibia. PLoS One. 2013. 8(2): e56307.
18. Hong, S.Y., et al., Household food insecurity associated with antiretroviral therapy adherence among HIV-infected patients in Windhoek, Namibia. J Acquir Immune Defic Syndr. 2014. 67(4): e115-22.
19. Horne, R., et al. Patients' Perceptions of Highly Active Antiretroviral Therapy in Relation to Treatment Uptake and Adherence: The Utility of the Necessity-Concerns Framework. Epidemiology and Social Science 45(3): 334-341.
20. HyLown Consulting. Power and Sample Size Calculators. Available from: http://powerandsamplesize.com/Calculators/Compare-2-Proportions/2-Sample-Equality.
21. Kalichman, S.C., et al. Development of a Brief Scale to Measure AIDS-Related Stigma in South Africa. 2005. 9(2): 135-143.
22. Katz, I.T., et al. Impact of HIV-related stigma on treatment adherence: systematic review and meta-synthesis. J Int AIDS Soc. 2013. 16(3 Suppl 2): 18640.
23. Kim, S., Gerver, S.M., Fidler, S., Ward, H. Adherence to antiretroviral therapy in adolescents living with HIV: systematic review and meta-analysis. AIDS. 2014. 28(13): 1945-56.
24. Lifson, A.R., Workneh, S., Hailemichael, A., Demissie, W., Slater, L., Shenie, T. Perceived social support among HIV patients newly enrolled in care in rural Ethiopia. AIDS Care. 2015. 27(11): 1382-6.
25. Mathes, T., et al. Cost-effectiveness of adherence interventions for highly active antiretroviral therapy: a systematic review. Int J Technol Assess Health Care. 2013. 29(3): 227-33.
26. Mills, E.J., et al., Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. JAMA. 2006. 296(6): 679-90.
27. Mills, E.J., et al. Adherence to HAART: A systematic review of developed and developing nation patient-reported barriers and facilitators. PLoS Med. 2006. 3(11): e438.
28. Ministry of Health and Social Services: Directorate of Special Programmes. National Guidelines for Antiretroviral Therapy, Third Edition. 2010. Available from: http://www.who.int/hiv/pub/guidelines/namibia_art.pdf.
29. Muller, A.D., Bode, S., Myer, L., Stahl, J., von Steinbuchel, N. Predictors of adherence to antiretroviral treatment and therapeutic success among children in South Africa. AIDS Care. 2011. 23(2): 129-38.

30. O'Laughlin, K.N., et al., How treatment partners help: social analysis of an African adherence support intervention. AIDS Behav. 2012. 16(5): 1308-15.
31. Parienti, J.J., et al. Not all missed doses are the same: sustained NNRTI treatment interruptions predict HIV rebound at low-to-moderate adherence levels. PLoS One. 2008. 3(7): e2783.
32. Petrillo, J., et al. Using Classical Test Theory, Item Response Theory, and Rasch Measurement Theory to Evaluate Patient-Reported Outcome Measures: A Comparison of Worked Examples. Value in Health. 2015. 18(2015): 25-34.
33. Reda, A. A., and S. Biadgilign, Determinants of Adherence to Antiretroviral Therapy among HIV-Infected Patients in Africa. AIDS Research and Treatment. 2012. 574656.
34. Scanlon, M.L. and R.C. Vreeman, Current strategies for improving access and adherence to antiretroviral therapies in resource-limited settings. HIV AIDS (Auckl). 2013. 5: 1-17.
35. Seeling, S., et al., Barriers to access to antiretroviral treatment for HIV-positive tuberculosis patients in Windhoek, Namibia. International Journal of Mycobacteriology. 2014. 3(4): 268-275.
36. Sjolander, M., Eriksson, M., Glader, E. The association between patients' beliefs about medicines and adherence to drug treatment after stroke: a cross-sectional questionnaire survey. BMJ Open. 2013. 3: e003551.
37. Slavec, A., and M. Drnovsek. A Perspective on Scale Development in Entrepreneurship Research. Economic and Business Review. 2012. 14(1): 39-62.
38. The R Foundation. The R Project for Statistical Computing. [Cited 2016]; Available from: https://www.r-project.org/.
39. Thompson, M.A., et al. Guidelines for improving entry into and retention in care and antiretroviral adherence for persons with HIV: evidence-based recommendations from an International Association of Physicians in AIDS Care panel. Ann Intern Med. 2012. 156(11): 817-33, W-284, W-285, W-286, W-287, W-288, W-289, W-290, W-291, W-292, W-293, W-294.
40. Tormodb. "fit.mult.impute no longer accepts "fitter = lrm" #17." Harrelfe/rms chatroom. [Cited 2016]; Available from: https://github.com/harrelfe/rms/issues/17.
41. Tjituka, F., et al., Namibia Antiretroviral Therapy Adherence Baseline Survey Report, in USAID Systems for Improved Access to Pharmaceuticals and Services (SIAPS). 2013, Management Sciences for Health: Arlington, VA.
42. UN, New UN Report Cites Devastating Effects of HIV/AIDS, UN, Editor. 2004, UN.
43. UNAIDS, Global Report: UNAIDS report on the global AIDS epidemic 2013. 2013, UNAIDS.
44. U.S. Preventive Services Task Force. Patient Health Questionnaire (PHQ-9). [Cited 2016]; Available from: www.uspreventiveservicestaskforce.org/Home/GetFileByID/218.

45. Uthman, O.A., et al. Depression and adherence to antiretroviral therapy in low-, middle- and high-income countries: a systematic review and meta-analysis. Curr HIV/AIDS Rep. 2014. 11(3): 291-307.
46. van Buuren, S., et al. Multivariate Imputation by Chained Equations. [Cited 2016]; Available from: https://cran.r-project.org/web/packages/mice/mice.pdf.
47. WHO. Global Health Observatory (GHO) data. n.d. [Cited 2015 10 February]; Available from: http://www.who.int/gho/hiv/en/.
48. Yang, Y., State of the science: The efficacy of a multicomponent intervention for ART adherence among people living with HIV. J Assoc Nurses AIDS Care. 2014. 25(4): 297-308.