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LEVEL OF EDUCATION AND HIV VIRAL LOAD SUPPRESSION IN A POPULATION UNDER UNIVERSAL ANTI-RETROVIRAL THERAPY IN ESWATINI

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Today when I look back and remember Ngugi wa Thion´go´s poem *Dawn of Darkness* especially the words that say, "No night is so dark that, it will not end in Dawn".

The journey continues.

Love,
Dlamini Thembelihle Ntokozo

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ABSTRACT

Introduction: HIV/AIDS continues to be amongst the leading causes of morbidity and mortality in Sub-Saharan Africa. There is no approved cure for HIV, but the disease can be managed using Anti-Retroviral Therapy (ART). If drug adherence of about 95% is achieved, odds for a better clinical outcome increase. The level of education as a marker for many socio-economic status indicators has an impact on an individual´s health. If a country is devasted by the virus, the nation faces both macro and micro economic effects**.** HIV is the leading cause of reduced disability adjusted life years in eSwatini, and the country has the highest HIV prevalence in the world. However, through donor agencies like United States President Emergency Plan for AIDS Relief (PEPFAR) and Global Fund, eSwatini can provide free ART.

Purpose: To determine if the level of education lowers the risk for VLS failure in eSwatini to a population that has universal access to ART.

Material and Methods: The present study included a representative sample of 2025 HIV positive participants with traces of ART in blood-samples who have used ART for at least 6 months aged 15 years or older from the SHIMS 2 study in eSwatini 2016-2017. This cross-sectional survey includes data from blood samples analyses Viral Load Suppression (VLS) and Viral Load Count VLC) and self-administered questionnaires. Multi-variate logistic regression models were used to estimate the un-biased association between level of education and VLS-Failure.

Results: The study included 620 (30.6%) males and 1405 (69.4%) females. The mean age was 40.25 years (range 15 - 80 years). 92.9% of the participants had achieved VLS. In a multivariate regression analysis, increased level of education was associated with lower risk of VLS-failure. After adjusting for confounders (adherence, age, and wealth quintile) people with tertiary education had 76 % less risk of VLS failure compared to people with primary education (OR, 0.24; CI, 0.05-1.03; P, 0.05). For Secondary and High-school levels of education, the ORs were 0.65 (CI, 0.43-0.99; P, 0.05) and 0.55 (CI, 0.33-0.92; P, 0.02) compared to the reference group (Primary education).

Conclusion: This population-based survey is, to the best of our knowledge, the first study to provide data on the association of level of education and VLS-Failure in eSwatini in a

population with blood traces of ART. This study reveals that people who have completed tertiary education have lower risks of VLS-Failure.

Key Words: Human Immunodeficiency Virus, viral load, Viral Load Suppression, Anti-Retroviral Therapy, Adherence, Level of Education, Population-based study

List of Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ART	Anti-Retroviral Therapy
ARV	Anti-Retroviral
CD4	Cluster of Differentiation 4
DALYs	Disability Adjusted Life years
DBS	Dried Blood Spot
EA	Enumeration Area
HAART	Highly Active Anti-Retroviral Therapy
HIV	Human Immunodeficiency Virus
ICAP	US International Centre for AIDS Care Program
INSTI	Integrase Strand Transfer Inhibitor
NICD	South Africa National Institute of Communicable Disease
NRTIs	Nucleoside Reverse-Transcriptase Inhibitors
PEPFAR	US Presidency Emergency Plan for AIDS Relief
PHIA	Population-based HIV Impact Assessment
PLHIV	People Living with HIV
RNA	Ribonucleic Acid
SDGs	Sustainable Developmental Goals
SHIMS	Swaziland HIV Incidence Measurement Survey

SSA	Sub-Saharan Africa
TB	Tuberculosis
UN	United Nations
UNAIDS	The Joint United Nations Programme on HIV and AIDS
UNESCO	United Nations Educational, Scientific and Cultural Organization
US-CDCP	United States Center for Disease Control and Prevention
VL	Viral Load
VLS	Viral Load Suppression
WHO	World Health Organization

1.0 INTRODUCTION

In 2018, the Kingdom of eSwatini (formerly known as Swaziland) had an estimated population of 1.1 million people [1]. This is a landlocked low-middle income country located in the south of Sub-Saharan Africa. The country has the highest adult Human Immunodeficiency Virus (HIV) prevalence not only in the region but in the world [2]. In 2019 the HIV prevalence in 15 to 49 years stands at 27.2 percent, which is slightly higher than the 23.6% in the neighboring Kingdom of Lesotho [2].

HIV is a virus that weakens the human immune system and if not properly managed, it predisposes the host to opportunistic infections which leads to a syndrome called Acquired Immune Deficiency Syndrome (AIDS) [3, 4]. HIV/AIDS is an incurable chronic infection, which reduces life expectancy and is hence a public health concern [5]. HIV/AIDS is the second highest cause of disability-adjusted life years (DALYs) and cause of death in Eswatini [6]. The issue of eradicating HIV by suppressing viral load and halting new infections is central to public health in the country.

1.1 Economic Impacts of HIV/AIDS

Morbidity and mortality from HIV/AIDs have drastic negative effects on the economy both at the individual, household, and societal levels. In the Eswatini economy, many households rely on subsistence farming and remittances from the mining sector in South Africa. HIV/AIDS reduces the labor supply and productivity of both the infected and the rest of the household who become caregivers [5, 7, 8]. In Eswatini, like most African countries, the caregivers are mostly women and girls [7]. In addition, medication and care-related expenses increase, thereby worsening household economy [5, 9]. The macro-level challenges are an aggregate of household-level issue, with a reduced supply of labor that contributes to reduced national output and exports, thereby [10, 11] affecting the country economy at all levels.

If detected early, HIV can be managed through clinical controls and change in lifestyle or behavior which can help slow or reduce clinical symptomatic progression to AIDS. However, clinical control requires proper diagnosis, treatment, and medical care [4]. Medical care of HIV/AIDS includes the prescription and dispensing of Anti-Retroviral Therapy (ART). ART is a life-long treatment consisting of a dose combination of two nucleoside reverse-transcriptase inhibitors (NRTIs) with an integrase strand transfer inhibitor (INSTI) co-

formulated as one fixed-dose. [12]. This treatment regimen has been observed to suppress the plasma HIV Ribonucleic Acid (RNA) levels to below detectable (viral suppression), which then helps increase the CD4 cell count and increase the chance of people surviving [13-15]. In HIV treatment plan CD4 count indicates robustness of the immune system [16]. Since ART is for life, adherence is the cornerstone for viral load suppression (VLS) [17, 18]. Literature shows that with early diagnosis and initiation to treatment, there is a positive association between drug adherence and VLS in People Living with HIV (PLHIV) [12, 19]. However, matters of public health concern in developing countries is access, availability of ART treatment and to best encourage treatment adherence.

Studies reveal that patients who take Anti-Retroviral (ARV) drugs with a 95% adherence level have 75%-88% chance of achieving VLS [20-22]. A 95% adherence level in this study is defined as taking 95% of medication within the last 30 days. For purpose of this paper, adherence to treatment is understood as the extent to which a person's behavior, taking medication, following a diet, and/or executing lifestyle change, corresponds with agreed recommendations from a health care provider [23]. Most studies on drug adherence, report drug effectiveness when an above 95% threshold of adherence is achieved, although there are studies that show a positive association with adherence above 75% [12, 24]. An HIV RNA of less than 1000 copies has been observed to slow HIV progression to AIDS with low odds for treatment failure [25]. In WHO's recommendations lack of VLS is a trigger to raise "adherence concerns" with the patient [26]. Understanding the factors that affect individual´s adherence to ART regimen is important for achieving VLS and reducing the negative effects of HIV/AIDS in countries like Eswatini.

1.2 Justification

1.2.1 Access to ART

With support from the HIV related global funding programs, public health facilities in Eswatini freely administer the ART treatment to all PLHIV [27, 28]. Since 2002/2003, Eswatini has made significant progress towards the 2020 UN Joint Strategy on HIV presented as 90,90,90. That is, 90% HIV positive people knowing their status, 90% HIV positive people be on Anti-Retroviral Therapy (ART), 90% of the people on ART achieve VLS [26, 29, 30]. The 2017 SHIMS 2 report shows that, among those that are aware of their status, 88.8 percent are on ART with 91.4 percent Viral Load Suppression (VLS). However, even if someone is offered

ART, they might still have barriers to adherence. From other countries, we are aware of loss to follow-up between 10-30% from ART programs [31, 32]. To maintain high percentages of VLS among HIV-positive patients, it is essential to understand the factors that impact ART adherence and VLS among PLHIV in Eswatini.

1.2.2 Adherence

Extensive literature from Africa, including Eswatini shows that adherence and VLS are affected by the complex social and economic environment where individuals live [13, 33]. The challenges are either socio-economic, medication-related or health care system-related [34]. **The socio-economic** where poverty might affect access to transport, quality of diet, out-of-pocket payments, high cost of other health services, and competing household needs that require income [4, 35]. **Medication-related** challenges include drug size, taste, palatability or adverse effects and treatment fatigue [19]. **Health care system-related** factors include clinic accessibility, patient-health professional interactions, and more [4, 13].

Education is a marker for socio-economic status and reflects many of the complex factors described above. Education reflects literacy levels, odds for better jobs, wider social networks and self-awareness in health-related issues, which are important socio-economic factors for the individual's ability and opportunity to manage the barriers mentioned above [36]. It is not surprising that education has been shown to predict both AIDS-related death and events in high-income countries with universal access to health care [27, 37, 38]. These relationship differs in low-income countries due to cultural and historical context [39]. Educational level has been found to interact with ART-adherence levels in LMIC [40, 41]. However, to the best of our knowledge, we have found no papers on the association between educational level and ART adherence for Sub-Saharan Africa, or for LMIC in general. The studies we have found are exploring sociodemographic factors associated with viral load suppression [7, 42]. It is therefore of interest to study this relationship in Eswatini.

1.3 Research question

Does the level of education, decrease the risk for HIV VLS - Failure in a low-middle income country (Eswatini), under universal access to ART treatment?

1.4 Hypothesis

Increased level of education reduces the risk for HIV VLS-Failure in Eswatini, in persons who have traces of ART in their blood.

2.0 MATERIAL AND METHODS

This is an observational study of the adjusted relationship between education and VLS in Eswatini, based on survey data from (SHIMS 2), conducted August 2016 - March 2017. The SHIMS 2 is part of a program called Population-based HIV Impact Assessment (PHIA) led by the International Centre for AIDS Care and Treatment (ICAP) at the Columbia University under the United States Centre for Disease Control and Prevention (US-CDCP) which aims at measuring the reach and impact of HIV programs in PEPFAR-supported countries through national surveys. SHIMS 1 was in 2011 (SHIMS 1) and SHIMS 3 is currently under planning. The survey captures related socio-economic and demographic variables in a representative sample of households and individuals in Eswatini. SHIMS2 used a two-stage, stratified cluster sample design. The sampling frame was comprised of all households in the country based on the 2007 Swaziland Population and Housing Census, which includes 2,064 enumeration areas (EA), containing an estimated 212,195 households. The first stage selected 286 EA (clusters) using a probability proportional to size method. The 286 EAs were stratified by four geographical regions (Hhohho, Manzini, Shiselweni, and Lubombo), with each EA defined by rural and urban status. During the second stage, a national representative sample of 6000 households was randomly selected, within each EA, or cluster, using an equal probability method, where the average number of households selected per cluster was 20 and the actual number of households selected per cluster ranged from 15 to 43. The adults living in these households (approx. 11500), were invited to answer a questionnaire (see below) and to have blood-samples drawn for laboratory analyses (see below). The sample size was calculated to provide a representative national estimate of HIV incidence among adults aged 15-49 years with a relative standard error less than or equal to 20.0% of the general population. Representative regional estimates of VLS prevalence, among HIV-positive adults aged 15-49 years with 95% confidence intervals (CI) with ±10% bounds around the point estimates, were also used. The response rate for those 15 years and older was 86.8% for males and 93.9% for females [43].

2.1 General study population

Only data collection relevant to our analyses is described here. The household questionnaire was addressed to the household head (male or female) and covered household information like size, relations among individuals, welfare and economic variables including housing, water sources and sanitary issues, among others. All adult (15 years and above) individual members

within each of the identified households (N=11,500 adults) were separately interviewed using an individual questionnaire. Blood sampling: Persons who were included in the survey, and had consented for testing, were HIV tested. Persons who were HIV positive, or had previous confirmed records of being HIV positive, had blood drawn for viral load testing and presence of ART in their blood.

2.2 Inclusion and exclusion criteria for analyses

For this research paper, the study population focuses on adult individuals with laboratory sample results on HIV viral load count: N= 2,988 of 11,500-individuals. We are interested in understanding risk for VLS-failure when ART is available. Our material consists of persons who can expect to achieve VLS, i.e., persons who have detectable levels of ART in their blood sample and report to be on ART treatment for at least 6 months. This reduced the sample to 2038 individuals.

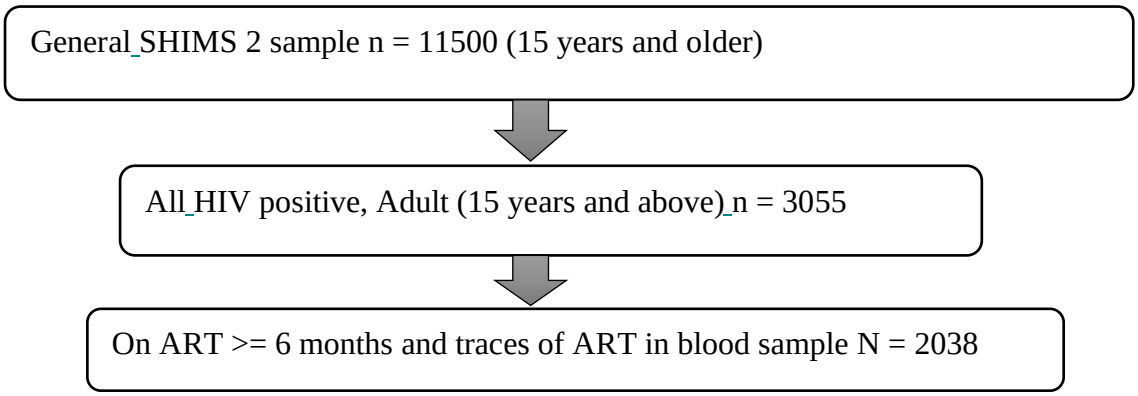

Figure 1: Flow Chart of the Study

2.3 Data and data collection methods

2.3.1 Data Quality

Validity – is a term used to describe a variable's ability to capture the underlying concept and an extent to which the scores from a measure represent the variable they are intended to, which is the best available approximation to the truth of a given proposition [44, 45]. Reliability, also called reproducibility, is more concerned about the consistency of a measure. That is, if we are to do the same test, under the same conditions or circumstances, what is the likelihood of getting an approximately same outcome or result shows the reliability of the measure [44]. Our

evaluation of both validity and reproducibility for the variables included in our analyses are given below. We describe below how different variables contribute to analyses, the data collection method, and provide our assessment of validity and reliability.

2.3.2 Main outcome – Viral Load Suppression (VLS)

These lab analyses are described in detail elsewhere [43]. Briefly, blood samples were first sent to a central laboratory in Eswatini where they were processed and verified for HIV status before assessing the viral load. The central laboratory used the open-mode protocol 28 for the Roche COBAS Ampliprep/TaqMan HIV-1 Assay to prepare the samples for amplification. For the viral load analysis, the samples were sent to the National Institute for Communicable Diseases (NICD) in Johannesburg, South Africa, who used the Gold Standard for testing of Viral Load Count**:** RT-PCR (Reverse Transcriptase - Polymerase Chain Reaction) [46, 47]. More specifically the Abbott m2000 System (Abbott Molecular Inc., Chicago, Illinois, United States) to conduct Dried Blood Spot (DBS) viral load testing. Using both the m2000sp (which carries out automated extraction, purification, and preparation of HIV-1 RNA) and the m2000rt (which amplifies, detects, and measures the HIV-1 RNA load). The laboratory results showed the individual viral load count, which was then aggregated into the VLS variable.

The validity and reliability of the Viral load count assay are described in (figure 2) for standardized specimens (Expected), and the observed mean across 48 test samples, used in approx. 270 tests. The validity of the test is assessed by a comparison of the mean observed VLC compared to the Expected count. The observed VLC differs by up to 30% from the expected VLC, with higher %-deviations in the lower VLC-ranges. The reproducibility here measured by a lognormal %Coefficient of Variation (%CV) is high, reflecting a mediocre reproducibility [48]. Using the WHO-recommendation of a threshold of a VLC of 1000 to classify persons as ART-responders or not, will entail a certain misclassification of the edge cases, i.e., persons with a VLC close to either side of the 1000 threshold due to measurement error. Such a misclassification is likely non-differential, and does not introduce systematic bias, but may bias any associations towards null. Clinically this misclassification is handled by demanding at least 2 tests with VLS. In our epidemiological work, we will handle this uncertainty by sensitivity analyses where we exclude cases that have a VLC within +/- 1SD on each side of the threshold of VLC 1000, and compare to analyses including all persons.

Expected	Observed	Log normal %CV
50	64	52 %
400	470	24 %
1 000	1 117	21 %
5 000	6 516	19 %
50 003	57 016	16 %
500 035	443 609	25 %
5 000 345	5 333 349	26 %

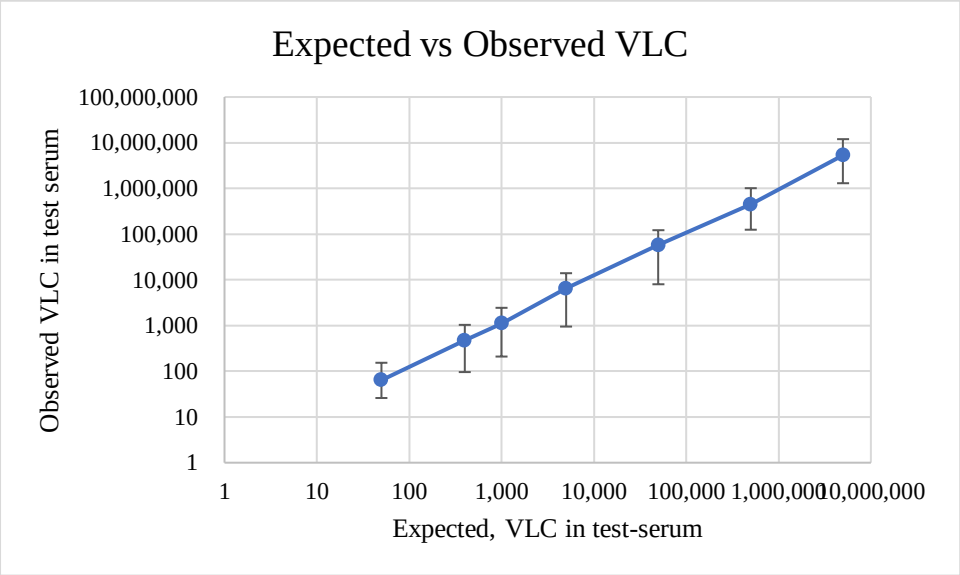

Figure 2: Expected by Observed values of Viral Load Count (VLC). Results of analysis of 48 test samples, representative of the methods used in SHIMSII. The error bars represent the Lognormal Coefficient of Variations

The outcome variable, VLS, is dichotomous, which is why we used logistic regression, using the Odds Ratio as an outcome. Since the VLS-failure is approximately at 7% in our material, in both exposed and unexposed groups, the odds ratio interpretation can be approximated to that of a relative risk [49]. We did consider the Viral load Count (VLC), as an outcome variable, but this is a semi-continuous variable, where approximately 90% of the population have VLC below the detection limit, which would essentially have the same VLC-value. The remainder with detectable VLC had a non-symmetric and skewed distribution. Modelling such a distribution was a challenge, and required either advanced transformations, or regression models such as the negative binomial regression. As VLS is the prognostic golden standard and can be easily modelled in a logistic regression, this was the obvious choice for an outcome variable. The VLC was used for sensitivity analyses, to examine the possible effect of misclassification of persons whose VLC is close to the threshold (+/- 1 SD) for VLS (see above).

2.3.3 Exposure variables from the questionnaire:

The individual adult questionnaires covered personal-related health issues and socio-economic factors, mainly related to HIV/AIDS. In total, the questionnaire captured over 400 individual-related variables. The exact questionnaire and methods used can be found elsewhere [43]. Briefly, the questionnaire variables we have selected for our analyses are:

Primary exposure variable: Level of Education: Education qualification standards in Eswatini follows the UNESCO standards defined as; 0) No education (never attended school or pre-primary education); 1) Primary (spent and completed 7 years, from grade 1-grade 7); 2) Secondary or O-Level (spent and completed 3 years, from form 1- form 3); High School or A-levels (spent and completed 2 years, form 4 and 5); Tertiary (completed college diploma (3 years) or university degree (4 years). Although this is a self-reported variable, international standards were applied during data collection. Individuals have no reason to be untruthful about the qualification since the survey process has no education-related incentives.

Effect modifiers: These are variables that modify the relationship between the exposure and outcome variable. Adherence is part of the causal pathway to the outcome, but it may also be an effect-modifier, in the sense that the impact of education on risk of VLS-failure, may differ by adherence. To assess the impact of education, independently of adherence the study used self-reported responses on adherence question (self-reported adherence) in an interaction term

together with education. We also wished to assess the impact of education, independently of adherence, which is why we included adherence also as an adjustment variable in our analyses. Direct and indirect methods exist for assessing adherence to Anti-Retroviral Drugs, these methods include body fluid assays and biological markers[50]. Most indirect methods include self-reporting in interviews, pill count, pharmacy records, computerized medication caps, and viral load monitoring [50]. However, computerized medication caps need advanced technologies and cannot be afforded by most developing countries, self-reporting is mostly used to monitor drug adherence [12]. Self-reported adherence was therefore by the indirect method. The survey question was formulated as: "People sometimes forget to take all of their ARVs every day. In the past 30 days, how many days have you missed taking any of your ARV pills?". If the response was more than 3 days, the individual was considered not to adhere. Even though there is not a one-to-one correlation of adherence and VLS, VLS is considered a surrogate measure for adherence [20, 22].

Confounders are variables that are associated with both the predictor and outcome and is not part of the causal pathway between predictor and outcome. If adjustment for a variable changes the main effect by > 10%, we considered it a potential confounder [51]. All potential confounders were added to a full model, and we performed a stepwise backwards selection process to create a parsimonious model with as few confounding variables as possible. All the self-reported variables are prone to various forms of reporting bias, especially if the question is sensitive. We had the following assumptions of which variables ought to be relevant confounders:

- Gender: Women have caregiver and family roles that may represent barriers to both education and adherence [4].
- Age: People between the age of 15 and 30 are more mobile, due to high unemployment rates, which affects the opportunity for both education and visits to ART care centers [34]. Detrimental effects of social stigma in HIV-infection might discourage the youth from adherence more than older patients [52].
- Existing comorbidities represent barriers both towards education and access to ART-clinics [15, 19, 53]. A person who is in any of the mentioned categories has less likelihood of stringently taking medication. Thus, the analyses adjusted for variables that capture stress, depression, TB, Malaria, Diabetes, High Blood Pressure, and alcohol consumption.

- Employment, residential area, distance to Care facility: These have an impact on access and adherence to treatment [18, 37] mostly among individuals living in rural areas. This is mainly because the public health system in most developing countries, including Eswatini, is not decentralized, hence forcing individuals to travel long distances. Studies in Africa mostly show that lack of adequate transportation and transport money is a key factor that results in non-adherence among individual on ART treatment [4, 35, 53]. Rural/ urban area is captured through Central statistics office according to Enumeration Area code.
- Wealth quintile and Household size: Income is a socio-economic variable which is a surrogate marker for a host of underlying enablers/ barriers to adherence A home can both be a place of social support while on the contrary, more household members could imply competing needs with regards to income or wealth [36].

2.4 Data Analysis

The PHIA project shared the raw SHIMS 2 data in excel and SPSS files including the codebook. For this study, the data was analyzed in SPSS analytical software.

The results section includes the following tables with both crude unadjusted and adjusted regression analytical results.

1) Crude summary statistics of all predictors, modifier, and confounding variables by VLS. Table shows means/ median (for continuous variables), and % for count variables. For each predictor variable, there is a uni-variate test of the significance of the association between the crude predictor and the outcome (VLS).
2) Crude summary statistics of VLS by education level, stratified by ART adherence levels. Table shows the distribution of population in a cross-tabulation figure and Chi-Square statistics.
3) Table showing crude, and fully adjusted estimates of Odds Ratios (OR), from a logistic regression model for the effect of education on VLS, which will be stratified by ART adherence levels if an interaction is detected. Table shows both OR, Confidence intervals and exact p-values.

2.5 Ethical considerations and consent

The SHIMS survey and data management processes were approved by both the Ministry of Health in Eswatini, and the Columbia University in the United States. The Population-based HIV Impact Assessment (PHIA) project that manages the data, shares the raw data on the condition that is it is for academic purposes. By using this data, this study acknowledged the research and ethical considerations that facilitated the survey processes.

However, since the study was done in partial fulfilment for a Master of Science in Public Health at the Arctic University of Norway, the data use and storage fall under the research and ethical consideration of Norway. Thus, the proposal to use this data was submitted to the Regional Ethics Committee (REK) in Norway which adjudicated it as not requiring approval from their office. The reason indicated was that the use of SHIMS data was not under REK jurisdiction, therefore, the use of this data in this study was based on the clearance from the PHIA project and feedback from ethics committee North of Norway.

Since the data in question contained sensitive health data, we have on our own initiative made the data anonymous, so that no single individual can be identified in the material. All variables that might be used for backwards identification, (age, gender, geographical region etc), were cross-tabulated, and the cross-tabulation contained no cells with less than 5 individuals. In addition, we have abided by the storage rules as guided by the University data management guidelines.

3. RESULTS

3.1 Basic characteristics of study population

Table 1 shows the basic characteristics of the study population along with the prevalence of VLS. The results are from a sample of N = 2025 participants where a high proportion 1881 (92.9%) achieved VLS while only 144 (7.1%) had VLS Failure. All the participants had been on ART for at least 6 months and had the anti-retroviral drugs traces in their blood. The mean age of participants was 40.25 years. The minimum age was 15 years and maximum age was 80 years.

Most of the participants had been through primary education level however only 80 (4%) had graduated from a tertiary institution. A high proportion of the participants came from rural areas 1587 (78.4%) compared to only 438 (21.6%) coming from urban areas. The study population had more females 1405 (69.4%) than males 620 (30.6%). More than half of the participants were employed 1126 (55.6%). The participants in the youngest age group (15-24) had the highest VLS-failure (23.5%) compared to other age groups. Study participants who had indicated not adhering to ART had 8% VLS-failure compared to 6.9% for participants who had indicated to have been adhering to ART.

Table 1 Crude analysis of individual factors (N) Column % and VLS (N Row %) and P Value (T- test/ Chi Square) in the study sample of 2016/2017 SHIMS2

Factors	**Category**	**Total SAMPLE (COL *% OF N*)**	**VLS (NO) (ROW *% OF N*)**	**VLS (YES) (ROW *% OF N*)**	**P-value (T-test/ Chi square)**
Education Level	**1. NEVER**	185 (9.1)	8 (4.3)	177 (*95.7*)	0.043
	2. PRIMARY	751 (37.1)	68 (*9.1*)	683 (*91.0*)	
	3. SECONDARY	576 (28.4)	41 (*7.1*)	535 (*92.9*)	
	4. HIGH	420 (20.7)	25 (6.0)	395 (*94.1*)	
	5. TERTIARY	80 (4.0)	2 (*2.5*)	78 (*97.5*)	
	Missing	13 (0.6)	0 (0.0)	13 (100.0)	
	Total	2025			
Adherence	1. Yes	1925 (*96.1*)	132 (*6.9*)	1793 (*93.1*)	0.004
	2. No	44 (*2.2*)	8 (*8.0*)	36 (81.8)	

	Missing	56 (2.8)	4 (7.1)	52 (92.9)	
TB Comorbidity	1. Yes	489 (24.2)	41 (*8.4*)	448 (*91.6*)	0.191
	2. No	1535 (75.*8*)	102 (*6.6*)	1433 (*93.4*)	
	Missing	1 (0.1)	1 (100.0)	0 (0.0)	
	Total	2025			
Place of Residence	1. Urban	438 (*21.6*)	29 (*6.6*)	409 (*93.4*)	0.652
	2. Rural	1587 (*78.4*)	115 (*7.3*)	1471 (*92.8*)	
	Total	2025			
Age Categories	1. 15-24	160 (*8.0*)	36 (*22.5*)	124 (*77.5*)	0.000
	2. 25-34	578 (*28.5*)	46 (8.0)	532 (*92.0*)	
	3. 35-44	616 (*30.4*)	35 (*5.7*)	581 (*94.3*)	
	4. 45-59	522 (*25.8*)	21 (*4.0*)	501 (*96.0*)	
	5. 60 and above	149 (*7.4*)	6 (*4.0*)	143 (*96.0*)	
	Total	2025			
Wealth Quintile	1. Lowest	546 (*27.0*)	44 (*8.1*)	502 (*91.9*)	0.530
	2. Second	457 (*22.6*)	27 (*5.9*)	430 (*94.1*)	
	3. Middle	435 (*21.5*)	33 (*7.6*)	402 (*92.4*)	
	4. Fourth	328 (*16.2*)	19 (*5.8*)	309 (*94.2*)	
	5. Highest	258 (*12.7*)	21 (*8.1*)	237 (*91.9*)	
	Missing	1 (0.1)	0 (0.0)	1 (100.0)	
	Total	2025			
Gender	1. Male	620 (*30.6*)	42 (*6.8*)	578 (*93.2*)	0.695
	2. Female	1405 (*69.4*)	102 (*7.3*)	1303 (*92.7*)	
Distance to HIV Facility	1. Less than one hour	1192 (*58.9*)	78 (*6.5*)	1114 (*93.5*)	0.496
	2. One to two hours	573 (*28.3*)	39 (*6.8*)	534 (*93.2*)	
	3. Two or more hours	230 (*11.4*)	20 (*8.7*)	210 (*91.3*)	
	Missing	30 (1.5)	7 (23.3)	23 (76.7)	
	Total	2025			
Gender of Household Head	1. Male	859 (*42.4*)	55 (*6.4*)	804 (*93.6*)	0.287
	2. Female	1166 (*57.6*)	89 (*7.6*)	1077 (*92.4*)	
	Total	2025			
Employed	1. Yes	1126 (*55.6*)	89 (*7.9*)	1037 (*92.1*)	0.120

	2. No	899 (*44.4*)	55 (*6.1*)	844 (*93.9*)	
	Total	2025			
Alcohol Consumption	1. Never	1693 (*83.6*)	124 (*7.3*)	1569 (*92.7*)	0.583
	2. Monthly or less	171 (*8.4*)	9 (*5.3*)	162 (*94.7*)	
	3. Two-Four times a month	102 (*5.0*)	7 (*6.9*)	95 (*93.1*)	
	4. Two-Three times a week	38 (*1.9*)	2 (*5.3*)	36 (*94.7*)	
	5. Four-More times a week	12 (*0.6*)	2 (*16.7*)	10 (*83.3*)	
	Missing	9 (0.4)	0 (0.0)	9 (100.0)	
	Total	2025			
Household Size	Mean value ± SD	3.21 ± 2.05	3.43 ± 2.43	3.19 ± 2.02	0. 180

3.2 Univariate and Bivariate Regression Analysis

A univariate regression analysis was performed to get a crude odd ratio (OR) and 95% confidence interval (CI) for the relationship between the level of education and VLS failure. Participants in the tertiary education group had approximately 74% lower risks of VLS compared to participants in primary education group.

A bivariate regression analysis was then performed on the effect of education and VLS failure adjusting for the following variables in each of the bivariate analyses: age category, wealth quintile, adherence, gender, gender of household, household size, employment, alcohol use and place of residence. This was done to find potential confounders that changed the main effect OR 10% or more, compared to the crude relationship between Education and VLS. Age category and wealth quintile are the only variables that produced a 10% or more OR change in one or more of the education levels and these were potential confounders.

Table 2: Odds Ratio (OR) with 95% confidence interval (CI) and Odds Ratio Change (%) of VLS failure results by level of education, adjusted for age categories, adherence, and wealth quintile of 2016/2017 SHIMS2.

Variables	Crude OR (95% CI)	Bivariable OR (95% CI)	OR Change
Level of Education vs VLS Failure			
0. None	0.45 (0.21-0.96)		
1. Primary (reference)	1		
2. Secondary	0.77 (0.51-1.15)		
3. High school	0.64 (0.4-1.02)		
4. Tertiary	0.26 (0.06-1.07)		
Age			
0. None		0.58 (0.27 -1.26)	29%
Primary (reference)		1	0%
2. Secondary		0.67 (0.44 - 1.01)	-13%
3. High school		0.61 (0.38 - 1)	-5%
4. Tertiary		0.29 (0.07 - 1.22)	12%
Adherence			
0. None		0.41 (0.18 - 0.91)	-9%
1. Primary (reference)		1	0%
2. Secondary		0.76 (0.5 – 1.15)	-1%
3. High school		0.64 (0.4 – 1.04)	0
4. Tertiary		0.27 (0.06 – 1.11)	4%
Wealth Quintile			
0. None		0.45 (0.21 - 0.95)	0%
1. Primary (reference)		1	0%
2. Secondary		0.78 (0.51 - 1.17)	1%
3. High school		0.62 (0.37 - 1.01)	-3%
4. Tertiary		0.23 (0.05 – 0.97)	-12%

In this context adherence could be both a mediator and interacting variable. In the apriori plan for analysis, we included adherence, independent of the 10%-rule mentioned above, we wished to assess the effect of education irrespective of adherence level. By including adherence as an adjustment variable, the analysis answers the question of: "what is the contribution of education, irrespective of adherence level", to VLS-failure.

3.3 Interaction

A check of interaction between adherence and level of education on the effect of VLS failure, was performed to check if adherence should be considered a stratifying variable. Table 3 shows the interaction term between adherence and level of education was not significant at 5% level, and we therefore did not stratify by adherence in further analyses [54].

Table 3: P value and 95% confidence interval (CI) of the viral load suppression (VLS) results between the interaction between ARV adherence and level of education of 2016/2017 SHIMS2.

VLS	Coef.	P>z	[95% Conf.Interval]	
Level of Education and Adherence				
0. None#0. NO	0			
0. None#1. YES	5.21	0.10	-0.97	11.39
1. Primary#0. NO	0			
1. Primary#1. YES	2.92	0.17	-1.22	7.06
2. Secondary#0. NO	0			
2. Secondary#1. YES	1.49	0.18	-0.67	3.64
3. High school#0. NO	0			
3. High school#1. YES	0			
4. Tertiary#0. NO	0			
4. Tertiary#1. YES	0			

 # Indicates interaction between level of education and VLS Yes/No

3.4 Multivariate Regression Analysis

A multivariate regression analysis was performed, variables that had a 10% odds ratio change were put in the final model as confounders. Table 4 shows the multivariate analysis of VLS failure between level of education, age category, wealth quintile and adherence, which are discussed separately below.

3.4.1 Level of education

After adjusting for covariates, the results of the multivariable regression analysis of VLS failure showed a significant association. Participants in the none-education level group were not statistically different at 5% from the primary group and had a p value of 0.17. The relationship between VLS-failure and level of education seems to be peak shaped between those having only primary school are at highest risk and all other groups having lower risks for VLS failure. Participants in the secondary, high, and tertiary education level showed a statistically significant difference from participants in the primary group, whereas participants in the "no education" group did not differ significantly from the primary-education group.

In the adjusted analysis, the risk of VLS failure in tertiary education was 76% lower in the tertiary education group, compared to those who had primary education only.

Table 4: Odds Ratio (OR) with 95% confidence interval (CI), P value and VLS failure results by level of education, adjusted for age categories, wealth quintile and adherence of 2016/2017 SHIMS2.

Variables	**Odds Ratio (OR)**	**[95% Conf. Interval]**		**P>|z|**
Highest education qualification level				
0. None	0.58	0.27	1.27	0.17
1. Primary (reference)	1			
2. Secondary	0.65	0.43	0.99	0.05
3. High school	0.55	0.33	0.92	0.02
4. Tertiary	0.24	0.05	1.03	0.05
Number of observations		1968		

Adjusted for Age categories, wealth quintile and adherence

3.5 Sensitivity Analysis

Due to a high Coefficient of variation on the Viral load measurements (See method section) there is a risk that persons whose Viral load is close to the threshold for VLS-failure (VLoad=1000/ ml), may be misclassified. A sensitivity analysis was done where we excluded edge cases that had a VLC within +/- 1SD on each side of the threshold (see method section).

This analysis reduced N from 1968 to 1956. It did not change our results materially as presented in Table 5.

Table 5: Odds Ratio (OR) with 95% confidence interval (CI) and the results of VLS failure between the five education level groups, adjusted for age categories, wealth quintile and adherence of 2016/2017 SHIMS2 without excluded edge cases.

Variables	**Odds Ratio**	**P>|z|**	**[95% Conf. Interval]**	
Highest education qualification level (1: Primary)	1			
0. None	0.53	0.13	1.45	0.19
2. Secondary	0.66	0.05	0.85	0.01
3. High School	0.56	0.03	1.09	0.07
4. Tertiary	0.24	0.06	2.89	0.04
Number of observations	1,956			

Another sensitivity analysis was performed to address the smaller (n) in the extremes of the education distribution, i.e., the No primary-category and the Tertiary education level, to have more robust analysis. For this analysis, we collapsed the education level variable from five categories to three.

After the sensitivity analysis the only collapsed education level group that came out significantly different from the none + primary group was the high school + tertiary education level. Participants who had been completed high school and or tertiary had 55% (95%CI 0.33-0.90) of VLS failure compared to those who never completed any and or completed primary education level. There is now a more linear dose response relationship between education and VLS failure.

Table 6: Odds Ratio (OR) with 95% confidence interval (CI) and the results of VLS failure between the collapsed education level groups, adjusted for age categories, wealth quintile and adherence of 2016/2017 SHIMS2.

Variables	Odds Ratio (OR)	[95% Conf. Interval]		P>|z|
1 None + Primary (reference)	1			
2. Secondary	0.69	0.45	1.05	0.08
3. High and Tertiary	0.54	0.33	0.88	0.01
Number of observations	1968			

Adjusted for Age Categories, Wealth Quintile and Adherence

4. DISCUSSION

4.1 Summary of results

The present study was conducted to determine if the level of education increases the risk of VLS failure amongst persons aged 15 years and above who were under universal ART access in eSwatini. In our multivariate analyses (adjusted for: age, wealth quintile and adherence) we found that the highest risk of VLS-Failure is experienced by persons with primary education. The lowest risk of VLS-Failure was found in persons with tertiary education. Surprisingly, persons with no formal education had a better outcome than those with a primary education., although this difference was not statistically significant. When the two smallest education groups at both extremes of the education scale (no-education and Tertiary education) were added to their larger neighbouring groups, the pattern of increasing risk of VLS-failure with lower education level was clearer. Both analyses show that higher education is associated with a lower risk of VLS-failure, in persons who enjoy access to ART, even after adjustment for self-reported adherence. Surprisingly, adjustment for adherence did not weaken the main effect materially, nor was adherence an effect modifier. The variables gender, distance to care, TB comorbidity, alcohol use, employment, household size and place of residence were not confounders in our study.

4.2 Discussion of the main results

To our knowledge, this is the first cross sectional study based on SHIMS 2 database to determine if the level of education increases the odds for VLS amongst participants aged15 years or above who were under universal ART access in eSwatini.

We know from other studies, that education and adherence are closely linked, through complex socio-economic mechanisms that may prevent the patient from 1) accessing ART, and 2) understand the significance of ART-continuity and effects on VLS and disease development [24]. However, the Education-VLS-failure association was surprisingly not weakened, nor was it modified by adherence in our study. In a study that was done in Ethiopia, in a group of patients who despite being enrolled in an ART program, were experiencing VLS-failure, higher education was associated with higher VLS after adherence counselling [55]. However, in the Ethiopian study, ART-adherence was not assessed by blood-sampling, so VLS-failure might to a greater degree be linked to challenges in accessing the ART-program itself. As we included only participants who had traces of ART in their blood samples, we know that our

patients both had access to, and were ingesting the drugs, even when they reported less than ideal adherence. This might explain why adherence had less impact on the education-VLS-failure relationship in our study.

4.2.1 Education and VLS-failure in other LMIC countries:

Our study´s findings are consistent with findings from a multi-national (Botswana, Kenya, Malawi, South Africa, Zimbabwe, India, Thailand, Brazil, and USA) retrospective cohort, HIV Prevention Trials Network (HPTN) 052 trial which had 1566 participants (serodiscordant couples) who were on ART and followed up for 6662 person-years. The aim of the trial was to evaluate factors associated with time to viral suppression and virologic failure in participants who initiated ART in HPTN 052. Participants in this trial had access to ART and had traces of the drugs in their system however drug adherence was not measured. Low level of education was associated with virological failure, in persons using ART with 22.8 % of VLS-failure in no education group, compared to the reference group [56].

A clinical cohort study done in Nigeria between April 2008 and February 2009 randomly selected 628 HIV positive patients and were followed up for 12 months. These patients had access to ART and had the blood samples taken for a detailed laboratory virologic and immunologic testing. Participants in this study had traces of ART in their blood [57].The results from this prospective cohort showed that the level of more than secondary education lowers the risk for VLS-failure by 60%. The result is consistent with the result of our study. These findings could be associated with the fact that PEPFAR funds ART access in eSwatini and Nigeria which helps lower the barrier to drug access.

4.2.2 High income countries:

A cross sectional analysis done in the UK which aimed at investigating the association of socio-economic factors with ART non-adherence, VLS-Failure, and virological rebound in HIV positive people on ART. The study found that each of the 4 measures of lower socio-economic status were strongly associated with non-adherence, and VLS failure. The study had used data of 2983 patients from Antiretrovirals, Sexual Transmission Risk and Attitudes (ASTRA) from 8 HIV outpatient clinics between Feb 1, 2011, and Dec 31, 2012. Participants in this study had traces of ART in their blood [36]. The study found that non-university education was associated with increased risk for VLS-Failure by 52% compared to reference group. Findings from the

ASTRA study is consistent with the results of our study and shows the link between socio-economic status and VLS failure. A similar result was found in 15 cohorts conducted in 8 European countries (Austria, Germany, France, Greece, Italy, Spain, Switzerland and Denmark) between 1996 -2013, which investigated differences by educational level in clinical, virological and immunological responses to combined ART in HIV positive men and women [58].

All these studies confirm our findings, showing that even in patients who have access to ART, as shown by ART blood traces, there is still a link between education and risk of VLS. This was surprisingly not mediated by self-reported adherence in our study, as adjustment for this variable did not change the relationship between education and VLS-failure. This might indicate that the self-reported adherence variable did not capture true adherence. We also speculate that positive lifestyles linked to education, such as quality of diet, control of life-context, better understanding of all sides of HIV-treatment and risks have an impact on VLS, in addition to the importance of adherence.

4.3 Implications for research and practice

The high risks of VLS-failure in participants who had none or primary education in LMIC and in High Income Europe could be explained by socio-economic inequalities but also health literacy that comes with higher levels of education [59]. The mechanisms by which education protects from VLS failure, even after physical access to ART has been secured are probably mediated through both through adherence itself, better nutrition, and other lifestyle changes which are highly associated with health literacy. Another challenge which adds to VLS failure is ART resistance, which develops either through non-adherence or acquired in previous treatments. The ART resistance is significantly higher in low- and middle- income countries than in high income countries. There are many factors that lead to ART resistance newborns can get a resistant HIV variant from their parents furthermore poor absorption of the drugs because of the person´s body response and pre-treatment exposure either through prevention of mother to child transmission or pre-exposure prophylaxis. However, good knowledge about this phenomenon can help one avoid developing drug resistance [60]. More research is needed on the association between ART resistance and socio-economic status.

The results from this thesis could have important implications for recommended ART in HIV positive patients in eSwatini. It sheds a light on the factors that need to be considered when managing HIV beyond physical ART administration, such as the awareness and understanding of strict adherence and general health literacy. The study provides an insight on the importance of education as a marker for associated socio-economic variables that help determine clinical outcome.

Age and wealth quintile are variables that need to be considered when planning the management of HIV in eSwatini. Part of this could include the patient-health worker interaction, which could be negative attitudes of health care workers towards 15-30 years old ART enrolled patients. There should also be more research on the drug burden, adverse effects, and drug size in relation to ART administration to try improving ART adherence.

4.4 Strengths and Limitations

The strengths of this present study are the proper sampling that was done to ensure representativity at the population level, strong measurement methods on the main outcome and sensitivity analyses to ensure that measurement error does not bias our result.

However, there are limitations. First, as this study used questionnaire data for some variables, there could be self-report inaccuracies for the education variable and some of the confounders. The lack of association between adherence and VLS might indicate weak data quality. Second, the wide coefficient of variation on the measurement of viral load count is a weakness. However, we showed in our sensitivity analyses that this challenge did not change results materially.

Our study did not investigate the mechanisms of how education might impact VLS, which would be essential to understand which protective life-skills or life contexts that are associated with higher education, which all PLHIV should be aware of. Lastly, the lack of information on other socioeconomic variables than education such as income, meant that we were unable to assess the effect of other socio-economic factors on VLS.

5 Conclusion

The main conclusion is that an increase in level of education is associated with a lower risk of VLS failure. People who have been to and completed tertiary education have higher odds for a better clinical outcome.

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