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Factors Associated with Unsuppressed Viral Loads among HIV-Positive Sexually Transmitted Infected Patients Attending STI Services in South Africa, 2019



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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science in Epidemiology (Field Epidemiology)

October 2022

Preface of the Submissable format research report

This study aimed to determine the factors associated with having an unsuppressed viral load (VL) among HIV-positive patients attending sexually transmitted infection (STI) services in South Africa in 2019. The report was written using the School of Public Health guidelines for the submissable format at the University of the Witwatersrand. The structure contains three sections as follows:

Section 1: Contains the Title page, Dedication, Presentation from the study, Abstract, Acknowledgements, Table of Contents, list of figures, list of tables, list of abbreviations, Introduction to the study (Introduction (a paragraph providing an overview of the introduction section), Background, Literature review, Problem statement, Justification, Research question, Aim, Objectives, References

Section 2: Submissable manuscript using the BMC Public Health journal guidelines containing the Abstract, Background, Methods, Results, Discussion, Declaration, References, Figures, tables and additional files.

Section 3: Overall discussion, Conclusions, Recommendations and Appendices

DECLARATION

I, Marceline Mapiye (Student Number 1710465) declare that the research report is my work. I am submitting it in partial fulfilment of the requirements of the Master of Science in Field Epidemiology at the University of the Witwatersrand, School of Public Health, Johannesburg. This report had not been submitted before at any other university for any degree. Acknowledgements and required conventional referencing have been adhered to where I have used the thoughts and ideas of others.

Signed: mmapiye

Date: [4th]day of [October] in the year [2022]

DEDICATION

I dedicate this work to all the people living with HIV and those who fight for better health for all. To my husband and sons thank you for being patient whilst I pursued my studies and the South African Field Epidemiology Training Programme and to my father Willie Dhliwayo you always motivated me.

PRESENTATIONS/PUBLICATIONS FROM THE STUDY

Poster presentation at the International Aids Society – IAS (18-21 July 2021)- Switzerland (virtual conference).

ABSTRACT

Background: South Africa has a high burden of HIV and sexually transmitted infections (STIs). In the absence of viral suppression, STIs may facilitate the onward transmission of HIV to uninfected partners. We determined factors associated with unsuppressed viral loads (VL) among HIV-positive patients attending STI services in South Africa. **Methods:** We conducted a cross-sectional analysis of data on HIV- positive patients attending STI services enrolled at two STI sentinel sites in Western Cape and Gauteng provinces between January–December 2019 in South Africa. Descriptive statistics were performed to describe the patients. A Poisson regression model with robust error variance was used to identify factors associated with having an unsuppressed VL (>50 copies/ml), considering a p-value cut-off of 0.25 for inclusion in the multivariable model. In multivariable analysis, a 95% CI with $P< 0.05$ was considered statistically significant. **Results:** Among the 93 HIV- positive patients attending STI services with VL data, the median age was 32 years (IQR 27–37 years). Overall, 32 (34.41%) patients were on ART and 61 (65.59%) were not on ART; 90.63% of patients on ART were aged ≥25 years and 61 (65.20%) were male. The median HIV VL was 8011 RNA copies/ml (IQR= 78–99171). More than half (56.25%) of patients on ART had an unsuppressed VL and 86.89 % of those not on ART had an unsuppressed VL. After adjusting for age, gender, STI syndrome and ART use, factors associated with having an unsuppressed VL included; age <25 years (adjusted prevalence rate ratio [aPRR]= 1.25, 95% Confidence Interval [95% CI] = 0.99–1.60), being female (aPRR1.12, 95% CI=0.64–1.97). ART use was associated with a 33% lower prevalence of having an unsuppressed VL (aPRR= 0.67, 95% CI=0.49–0.92). Among those on ART, after adjusting for sex partner number, those aged <25 years had a higher likelihood of an unsuppressed VL (aPRR= 1.94: 95 % CI 1.27–2.97) compared to

those ≥ 25 years. **Conclusion:** The proportion of HIV-positive patients attending STI services and reporting ART use was low and had a high prevalence of unsuppressed VLs regardless of ART status. VL suppression is lower than the global target of 95% of HIV-positive persons on ART with viral load suppression. Intensified and targeted ART interventions to support young, HIV-positive females seeking STI services could improve viral suppression outcomes.

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Enormous gratitude to the South African Field Epidemiology Training Programme (SAFETP) for the opportunity to achieve my goals as an epidemiologist and for funding my studies. My gratitude to the Centre for HIV and STIs (CHIV/STI) at the National Institute for Communicable Diseases for my field placement, collecting STI sentinel data and making it available for analysis. I would like to express my sincere appreciation to all my lecturers and staff from the University of Witwatersrand School of Public Health for their assistance during my studies

My appreciation as well goes to all of the support I got from SAFETP staff, Emelda Ramutshila for your constant checks and assistance during conferences and writing of the report, Gila Carter (University of Witwatersrand), Prof Cheryl McCrindle (University of Pretoria) and many of my family and colleagues for their endless support and encouragement throughout the difficult period.

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LIST OF ABBREVIATIONS/ NOMENCLATURE

ART	Anti-Retroviral Therapy
CI	Confidence Interval
GUS	Genital Ulcer Syndrome
HIV	Human Immunodeficiency Virus
IQR	Inter Quartile Range
MUS	Male Urethritis Syndrome
NDoH:	National Department of Health
OR:	Odds Ratio
PRR:	Prevalence Rate Ratio
STI:	Sexual Transmitted Infection
SDG:	Sustainable Development goals
UNAIDS:	United Nations AIDS
U=U	Undetected VL equals Un-transmissible HIV
UTT:	Universal Test and Treat
VDS:	Vaginal Discharge Syndrome
VL:	Viral Load
WHO:	World Health Organization.
<:	Less Than
>:	Greater Than

1. OVERVIEW OF THE STUDY

Globally, viral load (VL) suppression is the main target to reduce Human Immunodeficiency Virus (HIV) transmission to the uninfected and improve the health of HIV-positive people. Despite widespread coverage of antiretroviral therapy (ART) in South Africa, viral outcomes may be compromised by concurrent infections such as other sexually transmitted infections (STIs). There has been a rise in STIs among people living with HIV which is a public health concern due to the effects of the HIV and STI co-infection burden. STIs may result in genital inflammation and higher VLs in HIV-positive patients, which can facilitate the onward transmission of HIV. South Africa is one of the HIV-endemic countries with a syndromic approach to STI treatment. STI services assist in identifying HIV infection and HIV VL outcomes which strengthens HIV STI treatment outcomes. However, there is a need to look more into the effect of STIs on HIV-positive patients beyond the initiation of ART.

This study aimed to determine the factors associated with having an unsuppressed VL among HIV-positive STI service patients in South Africa in 2019. We analysed data from HIV-positive STI service patients to address the aim. We described STI patients with an unsuppressed VL and determined the prevalence and factors associated with an unsuppressed VL using Poisson regression by ART status. Our results showed a higher prevalence of having an unsuppressed VL among young females and a lower likelihood of having an unsuppressed VL among those on ART. Our study results will contribute to existing knowledge and strengthen STI and HIV treatment outcomes. We recommend an integrated and targeted comprehensive approach to HIV and STI treatment.

1.1 INTRODUCTION

This chapter presents the background with an overview of the STI burden worldwide, in Sub-Saharan Africa (SSA), and within South Africa. A background on STI surveillance and the rationale behind HIV and STI co-infection will be described. The chapter will also highlight the burden of STIs in the era of HIV ART and review the literature on the factors associated with having an unsuppressed VL among HIV- positive patients attending STI services.

1.2 BACKGROUND

The incidence of STIs has been increasing globally, mainly among HIV-positive adults who seek health care services, which has been affecting VL suppression outcomes (1). In 2020, the World Health Organization (WHO) estimated about 7.1 million people were newly infected with *Treponema pallidum* and 82.4 million people were newly infected with *Neisseria gonorrhoea* (1). Complications due to STIs affect the health and lives of people accounting for 2.3 million deaths per year (14% of deaths due to all causes) worldwide (1). Sub-Saharan Africa bears about 40% of the global STI burden for morbidity and mortality among key populations such as reproductive women and adults (2).

In SA, the prevalence of curable STIs has been high in 2017 among people aged 15–49 years with about 2.3 million infections of gonorrhoea, 1.9 million new chlamydia cases and 23,175 new syphilis cases (3). Men between 15 and 49 years had an estimated 2.2 million new cases of gonorrhoea, 3.9 million new cases of chlamydia, and 47,500 new cases of syphilis in 2017 (3). SA has a high HIV burden with 8.2 million cases in 2021 (4). High STI volumes among an HIV-burdened population have become a public health concern for the SA National Department of Health (NDoH). The concern is since STIs increase HIV transmission and HIV can prolong STIs this may impact the reproductive health of people and HIV treatment outcomes (5,6). The concerning issue

is that despite STIs being curable, STI incidence keeps on rising, therefore, there is a need to focus on the prevention and treatment of STIs. STI service patients may denote a sub-population with risky sexual behaviours, which in turn may be at higher risk of HIV (7). STIs increase the risk of HIV transmission, while HIV makes some STIs last longer or recur, which may cause morbidities and enhance HIV transmission (8).

The SA government adopted the UNAIDS 95-95-95 targets to end HIV by 2030. The targets are 95% for the following: the proportion of HIV-positive people who know their HIV status by having a test, the proportion of HIV-positive persons who are on ART, and the proportion of HIV-positive persons on ART with a suppressed HIV viral load (9). Studies have shown that VL suppression may be affected by many factors such as the lack of adherence to treatment, treatment failures, drug resistance and socio-economic factors (10–13). Thus, there is a need to assess the burden of HIV and STI co-infection on HIV-positive patients for effective implementation of prevention programs, particularly in high STI-burden settings. This study, therefore, determined the factors that affect VL suppression among HIV-positive patients attending STI services to reduce further HIV transmission.

1.3. LITERATURE REVIEW

1.3.1. STI Surveillance and Prevention

Prevention and surveillance of STIs are important in public health as HIV infections occur more rapidly in the presence of STIs (14). The WHO has outlined strategies to reach STI targets for prevention and control, focusing mainly on sex education and behavioural change (2). In addition, WHO proposes tracking STI incidence through aetiologic surveillance in conjunction with the syndromic approach and routine surveillance in key populations (2). Passive reporting of notifiable

STIs from sentinel surveillance sites, such as STI control programs and laboratories, is used in the United States of America (15). Similarly, Canada uses passive reporting from all health authorities to their national notifiable disease system for STI surveillance (16). Thus, passive surveillance receives STI notifications submitted to the health systems which might not be timely since effective surveillance requires active surveillance for early diagnosis and treatment to prevent further transmission.

However, in Japan and China, sentinel surveillance is done with only syphilis as a reportable condition and in India, STI trends are obtained from cross-sectional surveys (17). In contrast, Australia and New Zealand use laboratories, gonococcal surveillance programs and health clinics (18). In Europe, however, there are established STI surveillance and prevention systems with all STIs as notifiable conditions (18). Due to limited resources in Middle and Northern Africa, much of the STI data is obtained from cross-sectional studies (19). Sub-Saharan Africa uses the syndromic management approach and collects data from cross-sectional surveys and HIV prevention trials (20). STI syndromic management focuses on clinical presentations (symptomatic patients), promotion of condom use, screening for syphilis in antenatal care and promoting inclusive social and behavioural change (21).

South Africa also uses syndromic management guidelines for HIV prevention and treatment together with the surveillance for antimicrobial resistance for *N. gonorrhoeae* (22,23). In addition, STI sentinel etiological surveillance was established in 2005 in SA which identifies male urethritis syndrome (MUS), vaginal discharge syndrome (VDS), and genital ulcer syndrome (GUS) (22,24). Similarly, the SA NDoH implemented clinical sentinel sites that report on STI symptoms through syndromic management to diagnose based on presented symptoms (VDS, MUS & GUS) (25).

Since 2005, the National Institute of Communicable Diseases (NICD) has been doing microbiological sentinel surveillance for STI etiologies associated with MUS, VDS, and GUS (26).

Analysis of STI surveillance data in SA has shown that syphilis and MUS prevalence have been decreasing since 2002 due to ART. However, chlamydia and gonorrhoea prevalence remain relatively unchanged and high (12,27). Although STI surveillance is important to estimate the prevalence of STI, there is a need to look at underlying factors such as sexual behaviours, networks, and STI treatment among people on ART. Counselling and education can enhance health-seeking behaviour and improve the ability to identify STI symptoms. However, due to a lack of awareness, resources, and stigma surrounding STIs, there is still a lot to be done to prevent STIs including HIV (28–30). Despite barriers to primary STI care and education, the main effective method of protection against STIs is the correct and consistent use of condoms (28).

The South African National AIDS Council has established condom distribution programmes that are used to reduce and prevent the transmission of HIV infection (22). Challenges remain in ensuring that condom programmes reach all HIV risk groups and that people use condoms consistently. The voluntary medical male circumcision (VMMC) program is also being promoted to reduce the risk of female-to-male HIV transmission by 60% (31). The National Strategic Plan (NSP) has recommended pre-exposure prophylaxis (PrEP) for the prevention of HIV transmission with about 24,000 people using PrEP in ongoing projects since 2019 (6). Nevertheless, there has been a high incidence of STIs among PrEP users due to the practice of risky sexual behaviours after using PrEP and feeling safe from HIV but remaining susceptible to STIs (32,33). Therefore, there are many prevention efforts focused on the prevention of HIV transmission without considering

exposure to STIs.

1.3.2. HIV and Sexually Transmitted Infections (STIs)

STIs may facilitate the acquisition of HIV due to an established interaction and co-infection epidemiologically through the same transmission route of sexual contact (1,34). High STI prevalence among people living with HIV has been observed worldwide which highlights a critical need for global efforts to improve sexual and reproductive health (35). STI infection indicates risk behaviours that enhance HIV transmission (34–38). Ulcerative or non-ulcerative STIs provide entry for HIV and in the presence of STIs, genital HIV shedding occurs (34–36). STI incidence was 1.5 times higher among HIV-infected people than among HIV-uninfected people (38).

A systematic review on STI co-infection among HIV-positive people from developed and developing countries showed a higher STI prevalence at the time of HIV diagnosis (39). In a cohort study (2013–2020) conducted in Kenya, Nigeria, Tanzania, and Uganda, HIV-positive adults had 63% higher odds of having an STI at cohort enrollment than those without HIV (40). Longitudinal data from Zambia (1994–2012) confirmed an association and contribution of STIs to HIV transmission or acquisition between discordant partners (41). In addition, in a study of 600 STI clinic patients in Zimbabwe, there was a high HIV prevalence of 41.1% and HIV infection was common among those who had a previous STI (42).

Studies in SA have shown that STIs have become a comorbidity among HIV-infected adolescents who were frequently co-infected with STIs compared to HIV-uninfected adolescents (39,43,44). A study estimating STI incidence and acquisition among HIV-positive patients during the first 24 months of ART in Themba Lethu in Johannesburg, SA, found that STIs are common among HIV-infected patients (7.1% of the 1906 patients) (45). The co-existence of HIV and STIs may result in

a higher risk of HIV transmission when one partner has an STI and a higher STI incidence similarly among HIV-positive people (46,47). Therefore, STIs promote HIV transmission epidemiologically and through unprotected sexual encounters while HIV makes some STIs last longer or recur.

South Africa is one of the countries with a high burden of HIV with an estimated 7.8 million people living with HIV in 2020 (48). Despite a high prevalence of HIV, SA has made significant progress towards the 90-90-90 targets to reduce HIV. In 2020, 92% of people living with HIV knew their status, 72% were on treatment and 66% of those on ART were virally suppressed (48). The Universal test and treat (UTT) strategy increased HIV testing rates and new infections of STIs have been declining although the rate of decline is not enough to meet the targets (48). Therefore, a more focused and immediate STI intervention among HIV patients who are at risk of spreading infections to uninfected people is crucial.

Despite these efforts, the burden of STIs continues to worsen the HIV epidemic in South Africa. A study done in Diepsloot informal settlement of Johannesburg found higher odds of STIs among HIV-positive compared to HIV-negative patients (49). The test and treat approach should encourage screening of STIs among the HIV-positive before ART initiation, even in the absence of clinical signs and symptoms, for early detection and treatment of STIs. More patients seek STI treatment before ART initiation, compared to those who are already on ART (37). Integrated health approaches are urgently needed in such risk populations to incorporate HIV education and STI awareness since STI prevalence is high among HIV-infected people.

1.3.3. STI in the era of ART

Research has shown that ART markedly reduces HIV transmission by suppressing viral replication (10,37). WHO has recommended that 95% of people who tested positive for HIV should be on ART (9). An HIV-negative patient with an STI has a higher probability of being infected with HIV per sexual contact (estimated at 6%) than STI-uninfected individuals (0.2%) (46,49). However, since onward HIV transmission is reduced among HIV-infected patients on ART and virally suppressed, studies have identified risky sexual behaviours such as condomless sex (11,30,50,51), which may increase STI transmission.

In a Swiss cohort, high levels of condomless sex among HIV-positive patients on ART and HIV-negative partners were found (50). In the PARTNER study from 14 European countries, among condom-less partners, there was no genetically linked transmission of HIV infection from an HIV VL-suppressed partner to an HIV-negative partner despite incident STIs (54,55). Although patients who reach the VL suppression point have a significantly decreased risk of transmitting HIV, there is still an increased chance of STI acquisition and transmission when practising unprotected sex which could potentially undermine the effectiveness of ART. Therefore, condom use should still be recommended for HIV patients whether on ART or not.

While undetectable levels of HIV while on ART significantly reduce onward HIV transmission, the patient has to be consistent with taking their treatment to achieve VL suppression. Studies have shown that effective management of ART reduces the transmission of HIV as HIV-positive patients not on ART had higher rates of STIs than those on ART (23,52,53). A secondary analysis of patients with STIs who initiated ART in April 2003 and followed up to 2016 in Uganda found a high STI incidence rate of 2.1 per 1000 person-years after follow-up (56). Due to the high HIV

burden, South Africa has established the largest ART program in Africa with about 4.8 million people on ART in 2019 (8). The UTT approach increased ART coverage and capacity in SA as every person who tests HIV positive commence ART (8,57,58). Without ART, there would be higher HIV viral replication, which increases HIV transmission (59). Therefore, effective ART suppresses HIV to a point of no transmission, although there has been an increasing presentation of STIs from patients on ART. STIs may provide additional immune cell targets for infection thereby increasing HIV acquisition risk (44). Consistent ART may be effective in achieving viral load suppression, however, adherence issues among ART patients have led to the rising prevalence of drug-resistant HIV (60). Although adherence to ART is important for viral suppression, some HIV patients on treatment still have unsuppressed VLs. Therefore, despite being on treatment, an unsuppressed VL increases the transmission and infection rate of HIV. Hence, effective administration of treatment and VL monitoring for HIV-positive patients on ART and continued awareness of protected sex may reduce the transmission of HIV.

1.3.4. Factors associated with unsuppressed VL

Antiretroviral therapy (ART) prevents HIV transmission from an infected to an uninfected sexual partner by suppressing viral replication (61,62). VL suppression (VLS) is the most direct measure of ART effectiveness. The 95-95-95 target requires that 95% of patients on ART achieve VL suppression by 2030 (9). Maintaining a suppressed VL needs effective and efficient treatment to reduce the risk of HIV transmission (63,64). However, failure in the treatment of HIV leads to an unsuppressed VL which can be associated with increased transmission of HIV and increased vulnerability to many STIs (12,65,66).

Globally, ART is monitored by measuring CD4 count and if VL suppression for an HIV-positive person reaches optimal suppression (below 75 copies/ml) they cannot transmit HIV to another

(54). In SA, <50 copies/ml is defined as virally suppressed, 50–1000: sub-optimal suppression, >1000 copies/ml is considered a high VL and the patient is then referred to adherence counselling. The VL measure is then repeated after 3 months and if the VL is >1000 copies/ml on two consecutive occasions it is considered virological failure which needs action such as switching regimens or resistance testing (22). With the test and treat policy, there is hope that the WHO's 95% target will be reachedamong HIV-positive people and that those on ART will be virally suppressed. However, not everyone who is living with HIV is on treatment and if those on ART practice unprotected sexual behaviours, there remains a risk of acquiring other STIs. Unprotected sex makes HIV-positive patients susceptible to HIV- reinfection, STIs and infecting the uninfected partner.

Many factors determine virological non-suppression such as higher risks with an increase in age (11,61,65), non-adherence to ART (13,62,66), high levels of initial VL (63,65), co-morbidities such as STIs and TB (54,61,62) and WHO HIV clinical stage (10,60,66) as shown in Table 1. Hence, the efficiency of ART mainly depends on adherence to maintaining sufficient drug concentration to suppress HIV replication and lower plasma VL (56). This study therefore will determine the factors associated with an unsuppressed VL among HIV-positive patients attending STI services whether on treatment or not.

Table 1: Synthesis matrix for factors associated with unsuppressed VL among HIV-positive patients.

Reference(s) and country	Study type	The study sample, population	Unsuppressed VL Cut off	Factors associated	Association with Unsuppressed VL
Hicham et al. 2019, Morocco (67)	Retrospective cohort (January 1, 2007, and January 1, 2017)	181 patients living with HIV-1 on ART	VL >400 copies/ml after 6 months of the first-line ART in HIV-1-positive patients.	Smoking and High initial VL >10,000 copies/ml	Were associated significantly with the risk of unsuppressed VL after 6 months of ART
Davey et al. 2018, South Africa (61)	Cohort: analysis of electronic medical records (January 2004 and April 2016)	244,370 patients from 27 public health facilities with a VL result	VL > 400 copies/ml) on first-line ART for ≥ 6 months	Age, Patients on Tuberculosis (TB) treatment, Men	< 15 years old at ART start had a higher risk of unsuppressed VL than those aged 15-19 Patients on TB treatment and the male gender had increased odds of not achieving viral suppression.

Chhim et al. 2018, Cambodia (65)	Cross-sectional study, August 2016	328 adolescents aged 15-17 who are HIV- positive	VL >1000 copies/ml at latest VL count	Age, High initial VL Receiving HIV care and treatment from a clinic	<17 had a high likelihood of unsuppressed VL Adolescents who had first VL > 628 RNA copies/mL Those who were receiving treatment and care from a clinic had a higher likelihood of VL non-suppression than those who had relatives as home-based caregivers
Bulage et al. 2017, Uganda (62)	A descriptive cross-sectional study of routinely collected data (August 2014-July 2015)	100,678 patients' data on VL across the country	>= 1000 copies/ ml	Poor adherence to ART, Active Tuberculosis (TB) Being on the third-line regimen	Increased the odds of virological non-suppression Third line regimen protected against VL non-suppression

Haas et al. 2020. Eswatini, Lesotho, Malawi, Zambia, and Zimbabwe (2015-2017) (11)	A cross-sectional household survey using home-based HIV testing and treatment	9200 HIV- positive adults aged 15-19	>= 1000 copies/ml	Younger age, males, less education and never married	Associated with higher odd of unsuppressed VLs
Waju et al. 2021, Ethiopia (66)	Facility-based cross-sectional study March 2016 –February 2019	669 patients on first-line ART aged >= 15 years	>= 1000 copies/ml	Duration of ARV therapy (6 months or less), poor adherence to medication, and low immunological failure	decreased the odds of unsuppressed VL
Nabukeera at al. Uganda 2021(68)	Retrospective cohort	300 HIV- positive children (0-14 years)	>= 1000 copies/ml	WHO clinical stage 4, having ART side effects	Significantly associated with non-suppression levels of VL
Zealiyas et al. 2021. Ethiopia (13)	Cross-sectional using the routine Volume licensing program data	8389 adults and children on ART	>= 1000 copies/ml	Advanced WHO clinical stage, poor adherence	Significantly associated with unsuppressed VL

Different factors affect VL suppression in HIV STI patients. Most studies show that treatment adherence improves with age and gives better VL suppression outcomes.

1.4. PROBLEM STATEMENT

The burden of STIs is increasing among HIV-positive patients which increases the risk of HIV transmission to HIV-negative partners (68). South Africa had approximately 7.97 million people living with HIV in 2019 (44). Some HIV-infected patients may present with one or more STI syndromes (45). There is a high infection rate of STIs among people with risky sexual behaviour which can be present as a comorbidity to patients whether they are on HIV treatment or not. The clinical outcomes due to ulcerative STIs may present easy entry points for HIV infection (21). If an STI patient is HIV-positive with an unsuppressed VL (VL>50 copies/ml), there is an increased risk of transmission of HIV and STIs to others and prolonged STIs. Therefore, there is a need to explore the factors associated with having an unsuppressed VL among HIV-positive patients attending STI clinics to further reduce HIV transmission.

1.5. JUSTIFICATION

There is a need to evaluate factors associated with having an unsuppressed VL among HIV-positive patients attending STI services. Literature has looked at the increasing number of HIV-positive patients accessing ART. There is limited information on the factors and burden of VL non-suppression rates among STI and HIV-positive patients by treatment status. There is minimal attention on STI co-infection among HIV-positive persons with an unsuppressed VL, giving rise to an increased incidence of STIs and recent HIV infections. Results from this analysis will bring more attention to STI interventions in HIV management; contribute to existing knowledge and strengthen STI and HIV treatment outcomes.

1.6. RESEARCH QUESTION, AIMS AND OBJECTIVES

Research Question

What are the factors associated with having an unsuppressed VL among HIV-positive patients attending STI services?

AIM

To determine the factors associated with having an unsuppressed VL (>50 copies/ml) among HIV-positive STI patients attending STI services in 2019.

OBJECTIVES

1. To describe clinical and socio-demographic characteristics of HIV-positive patients attending STI services.

2. To determine the prevalence of VL suppression among HIV-positive patients attending STI services by ART status.

3. To determine the factors associated with having an unsuppressed VL among HIV-positive patients attending STI services.

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2. SUBMISSABLE MANUSCRIPT

2.1. TITLE AND DECLARATION

Factors associated with an unsuppressed viral load among HIV-positive sexually transmitted infected patients attending STI services in South Africa, 2019

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Declaration

I, Marceline Mapiye declare that the contents of the manuscript are my work. I am submitting it for publication in BMC Public Health Journal. This manuscript has not been submitted before to any other journal. Acknowledgments and required conventional referencing have been adhered to where I have used the thoughts and ideas of others.

Signed: mmapiye

Date: [4th]day of [October] in the year [2022]

2.1.1. **Abstract**

Background: South Africa has a high burden of HIV and sexually transmitted infections (STIs). In the absence of viral suppression, STIs may facilitate the onward transmission of HIV to uninfected partners. We determined factors associated with having an unsuppressed VL among HIV-positive patients attending STI services in South Africa.

Methods: We conducted a cross-sectional analysis of data on HIV-positive patients attending STI services at STI sentinel sites in Western Cape and Gauteng provinces between January–December 2019 in South Africa. We described the HIV-positive patients attending STI services by demographic and clinical factors. A Poisson regression model was used to identify factors associated with having an unsuppressed VL (>50 copies/ml), considering a p-value cut-off of 0.25 for inclusion in a multivariable model and 95% CI with $P< 0.05$ statistically significant.

Results: Among the 93 HIV-positive patients attending STI services with VL data, the median age was 32 years (IQR 27–37 years). Overall, 32 (34.41%) patients were on ART and 61 (65.59%) were not on ART. The majority of patients (90.63%) on ART were aged ≥25 years and 65.20% (61)were male. The median HIV VL was 8011 RNA copies/ml (IQR= 78–99171). More than half of the patients on ART had an unsuppressed VL (56.25%) and 86.89 % of those not on ART had an unsuppressed VL. After adjusting for age, gender, STI syndrome and ART use; factors associated with having an unsuppressed VL included age <25 years (adjusted prevalence rate ratio [aPRR]=1.25, 95% Confidence Interval [95% CI] = 0.99–1.60) and being female (aPRR=1.12, 95% CI=0.64–1.97). ART use was associated with a 33% lower prevalence of having an unsuppressed VL (aPRR= 0.67, 95% CI=0.49–0.92). In a subgroup of those on ART, after adjusting for sex partner number, patients <25 years old had a higher likelihood of having an unsuppressed VL (aPRR= 1.94: 95 % CI=1.27–2.97) compared to those aged ≥25 years old.

Conclusion: The proportion of HIV-positive patients attending STI services reporting ART use was low and STI service patients had a high prevalence of having an unsuppressed VL regardless of ART status. These results are below the global target of 95%. Intensified ART support interventions targeted at young HIV-positive, females seeking STI services could improve viral suppression outcomes.

Keywords: HIV, Sexually Transmitted Infections, VL, VL suppression, South Africa, antiretroviral therapy, 95-95-95

2.1.2. Background

Sexually transmitted infection (STI) incidence has been increasing globally, mainly among HIV-positive adults (1). In 2020, the World Health Organization (WHO) Global progress report on HIV and STIs estimated about 7.1 million people were newly infected with *Treponema pallidum* and 82.4 million people were newly infected with *Neisseria gonorrhoea* (1). Sub-Saharan Africa bears about 40% of the global STI morbidity and mortality burden (2). Huge progress has been made to access HIV antiretroviral therapy (ART) through the universal test and treat (UTT) programme (3). ART suppresses viral replication to reduce HIV transmission, however, despite ART access, viral outcomes may be compromised by infections such as STIs. STIs increase the infectiousness of HIV-positive persons and the likelihood of viral transmission to HIV-negative persons (4–7).

South Africa (SA) with a high HIV burden has adopted the sustainable development goals (SDGs) targets in which: By 2030, 95% of all HIV-positive patients should know their status by testing, 95% of HIV-positive patients should be on sustained ART and 95% of those on ART should have a suppressed HIV VL (8). SA has a high STI burden with an estimated 2.3 million new cases of gonorrhoea, 1.9 million new chlamydia cases, and 23,175 new syphilis cases among women aged between 15 and 49 years in 2017 (9). In the same year, men aged between 15 and 19 years had approximately 2.2 million new cases of gonorrhoea, 3.9 million new cases of chlamydia, and 47,500 new cases of syphilis (9). There has been an established effect of STIs on HIV VL from a meta-analysis of 14 studies that concluded that co-infection of STIs correlates with a 0.11 log increase in HIV-1 VL (6). Thus, STIs have critical implications for sexual and reproductive health and with the rapid increase, it will affect the spread and control of HIV.

Understanding factors associated with an unsuppressed VL among HIV-positive people seeking STI care can help towards achieving the 95-95-95 targets in HIV/STI prevention programs. Several

studies have identified that VL suppression may be affected by many factors such as lack of adherence to treatment (10–12), high levels of initial VL (13,14), comorbidities such as Tuberculosis (11,15) or STIs (4) and WHO HIV clinical stage (11,12,16). Given the concerns of HIV-STI co-infection, if an STI patient who is HIV-positive has an unsuppressed VL, there is a high risk of transmission of HIV and STIs to others which may prolong STIs.

A lot of focus has been on the access to ART among HIV-positive patients with less attention on STI co-infection in HIV patients with an unsuppressed VL. Focusing on ART independently may have given rise to STI incidences and recent HIV infections. Identifying factors for VL suppression failure from this study will bring more attention to STI interventions in HIV management; contribute to existing knowledge and strengthen STI and HIV treatment outcomes. The aim, therefore, is to determine the prevalence and factors that affect VL suppression among HIV-positive patients attending STI services in South Africa (including those on ART and not on ART) in 2019.

2.2. METHODS

2.2.1. Study design

We conducted a cross-sectional analysis of data collected from NICD STI sentinel surveillance sites between January–December 2019 in South Africa.

2.2.2. Data sources and study sites

The primary study aimed to evaluate and validate self-reported HIV testing, antiretroviral therapy use, and viral suppression measures among sexually transmitted infection (STI) service patients. The primary study enrolled consecutive patients presenting with one or more symptoms of male urethritis (MUS), vaginal discharge syndrome (VDS), and genital ulcer syndrome (GUS)

regardless of HIV status; 18 years and older and willing to consent to ARV adherence questions if HIV-positive. The study was conducted from 1 January to 31 December 2019 at two high-volume STI sentinel surveillance centres in Gauteng and Western Cape. The sentinel sites were located within health facilities that offer HIV treatment. Relative to the 95–95–95 cascade measure, Gauteng had an overall percentage of 86.5% of patients knowing their HIV status and Western recorded 80.9%. Only 60.8% were on ART in Gauteng and 67.2% on ART in Western Cape. Both Gauteng and Western Cape were heading towards the 95% target with 87.7% and 89% with suppressed viral load respectively (3).

Consented participants responded to a questionnaire collecting demographic, behavioural, and clinical data and provided genital specimens, endourethral or endocervical swabs and 10 ml whole blood specimens for laboratory testing. Specimens were tested according to HIV Sero-Molecular reference laboratory procedures. The enrolled participants had confirmatory HIV testing, VL testing, and pooled nucleic acid amplification testing (pNAAT) as well as viral load testing. Data collected from the questionnaire and laboratory were linked through a barcode with a unique identifier which was sent to STI Reference Centre at NHLS and double captured into the Microsoft Access database.

2.2.3. Study population

The study included all adult HIV-positive patients attending STI services (regardless of ART use) with VL clinical information and who had participated in the primary study in 2019. We excluded patients who tested negative on the HIV confirmatory test and those without VL clinical information regardless of being HIV-positive.

The research used all the data available (93 patients) giving an 80% power at a 5% level to detect

the difference in viral load suppression among HIV-positive patients attending STI on ART and those not on ART.

2.2.4. Data management

Data received at the STI Reference Centre (NICD) were captured into an Access database linked through a bar-coded unique identification. Data capturing quality checks in the database were done against the questionnaire. Data were received for analysis in Microsoft Excel password-protected spreadsheets. Consistency checks were done by checking if there were no duplications and errors (for example ensuring that age was not greater than the date of enrolment) if found duplicates were excluded and errors were corrected by using enrolment date and date of birth. Missing values were checked and validated e.g. if age was missing but the date of birth and enrolment date was captured, a new variable with age was created. Data variables were labelled and recorded with the same response or 0 and 1; no, or yes respectively. Variables such as age and age at first sex were categorised.

2.2.5. Description of variables and measurements

The outcome variable was unsuppressed VL analysed as a categorical variable coded with 0 as suppressed VL and 1 as unsuppressed VL and a cut-off of ≥50 copies/ml was used as a threshold for unsuppressed VL. The explanatory variables used were gender (male or female), age in years as continuous, age groups (<25 and ≥25 years), age at first sex (<15 and ≥15 years), type/nature of sexual activity in the past 3 months (none, vaginal (penis in vagina), oral (mouth on penis/ vagina/ anus) or receptive anal (penis in the rectum/anus)), sex partner type in the last three months (casual, regular), number of sex partners in the last 3 months (one partner and > one partner), STI syndrome such as genital ulcer and discharge (VDS, MUS, GUS, none or missing), previous STI in the past

12 months (Yes/No), condom use at last sexual encounter (Yes/No), circumcision among males (Yes, No, and Not applicable (Female)), self-reported knowledge of HIV status (Yes or No), time since recent HIV test (< 3 months and ≥ 3 months) and self-reported ART use in the preceding 3 days (Yes or No).

2.3. DATA ANALYSIS

STATA version 15 (STATA Corporation, College Station, TX, USA) software package was used to analyse data. Descriptive analysis was done to describe the demographic, sexual behaviour, and clinical characteristics to determine frequencies of categorical variables and medians and interquartile ranges (IQR) for continuous variables. We used the Chi-square test and Fisher's exact test for cell counts with fewer than five observations to compare those on ART and those not on ART, a p-value of less than 0.05 was considered statistically significant. The prevalence of having an unsuppressed VL was calculated as the proportion of patients who had a VL result of> 50 copies/ml among the total number of patients with a VL result. For continuous variables, the Wilcoxon rank-sum test was used using a p-value of less than 0.05 was used to be significant.

We used VL ≤50 copies/mL threshold for defining VL suppression set by the National Department of Health (SA) consolidated guidelines (17). To identify factors associated with an unsuppressed VL, a multivariable Poisson regression model with robust error variance was used (18). Explanatory variables with a p-value of ≤0.25 from the univariable analysis were included in the multivariable model. In the multivariable model, variables with a p-value of less than 0.05 were considered statistically significant (19). The Poisson regression estimated the prevalence ratio of having an unsuppressed VL. A prevalence rate ratio greater than one indicates a greater prevalence rate of having an unsuppressed VL while those with less than one shows a smaller prevalence rate of

having an unsuppressed VL after adjusting for covariates. Furthermore, a sub-group multivariable analysis was done to determine factors affecting unsuppressed VL among only patients on ART.

2.4. RESULTS

The primary study enrolled 495 patients. Of these, 353 (71.31%) were HIV-negative and therefore excluded from the analysis, leaving 142 (28.89%) patients who had a positive HIV result. Of the remaining HIV-positive patients, 49 (34.51%) were excluded because their records did not include VL data (the outcome of interest). This left 93 patients eligible for inclusion in the analysis (Figure 1).

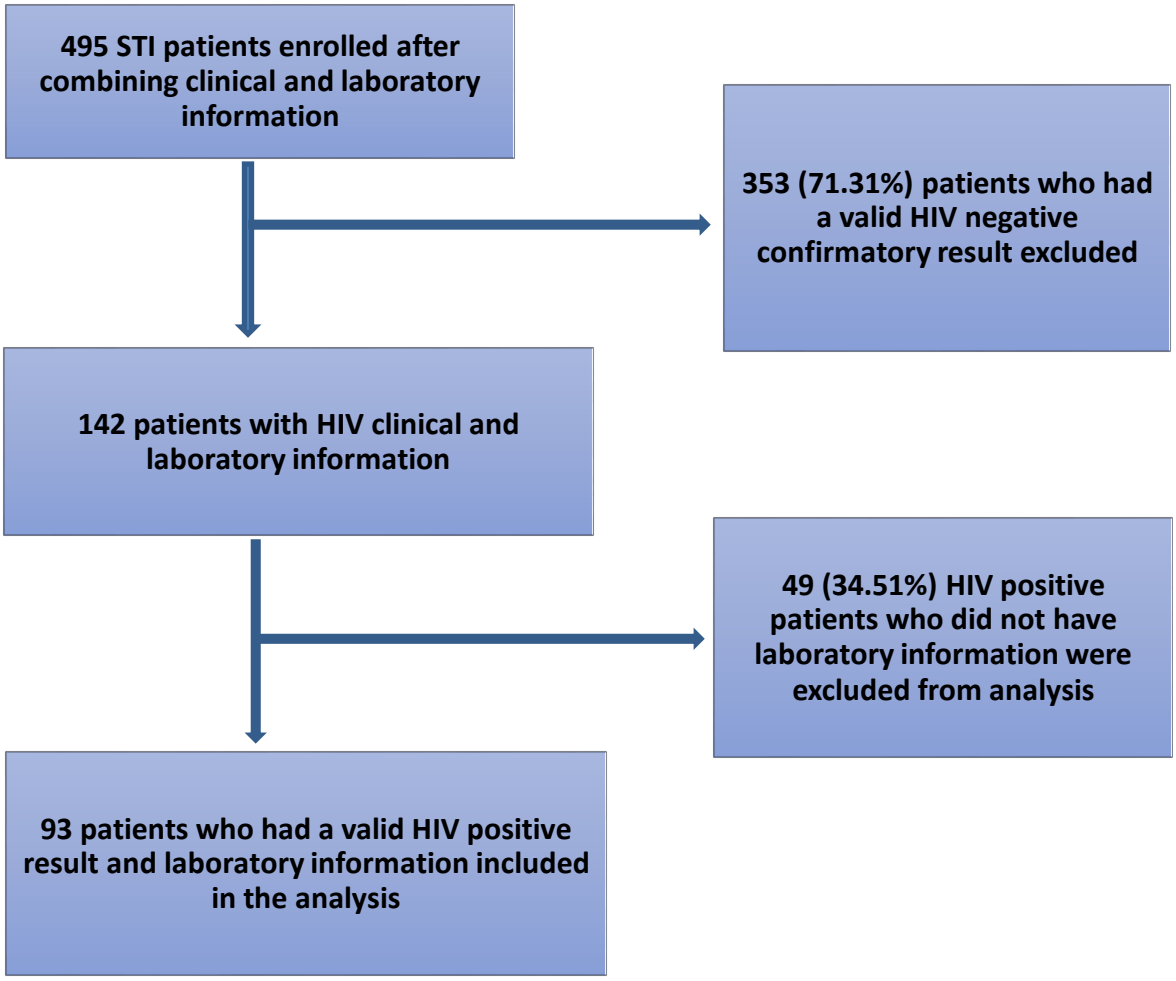


Figure 1: Flowchart showing stages of eligibility and exclusion of patients up to those included for the analysis to investigate factors associated with having an unsuppressed VL, STI service patients, Gauteng and Western Cape, 2019.

We analysed the distribution of socio-demographic characteristics amongst the HIV-positive patients with (93) and without (49) VL data to determine selection bias as a result of missing VL data (Table 1).

2.4.1. Demographic and sexual behaviour patterns of HIV- positive STI patients on ART and not on ART

Table 2 compares the demographics and sexual behaviour patterns of participants (on ART and

those not on ART) based on self-reported ART use. Among the 93 HIV-positive patients attending STI services, the median age was 32 years (IQR 27–37 years). Overall, less than half of the patients were on ART (32, 34.4%) and 61 (65.6%) were not on ART. Most of the patients on ART were aged ≥25 years (90.6%) and male (65%). A higher proportion of those practising receptive anal sex was not on ART (11%) compared to those who practiced receptive anal sex and on ART, and half the number of patients having casual sex partner type were on ART (50%) but the number of cases was too small to be significant. About 75% of the patients did not use condoms whether on ART or not.

Table 2: Demographic and sexual behaviors of HIV-positive STI patients by ART use, Gauteng and Western Cape provinces, 2019

Characteristic	All patients (N=93)		On ART (N=32)		Not on ART (N=61)		p-value
	n	%	n	%	n	%	
Age (years) (median, IQR)	32	(27–37)	33	(27–38)	32	(27–37)	0.464
Age (years)							
< 25	11	(11.83)	3	(9.38)	8	(13.11)	
>=25	82	(88.17)	29	(90.63)	53	(86.89)	0.596
Age at first sex:							
<15 years	10	(10.75)	3	(9.38)	7	(11.48)	
>=15 years	83	(89.25)	29	(90.63)	54	(88.52)	0.756
Gender							
Male	61	(65.59)	20	(62.50)	41	(67.21)	
Female	32	(34.41)	12	(37.50)	20	(32.79)	0.649
Oral sex in the past 3 months							
No	85	(91.40)	29	(90.63)	56	(91.80)	
Yes	8	(8.60)	3	(9.38)	5	(8.20)	0.847
Receptive anal sex in the past 3 months**							
No	85	(91.40)	31	(96.88)	54	(88.52)	
Yes	8	(8.60)	1	(3.13)	7	(11.48)	0.256
Sex partner type:							
Casual	18	(19.35)	9	(28.12)	9	(14.75)	
Regular	75	(80.65)	23	(71.88)	52	(85.25)	0.167
Number of sex partners (last 3 months)							
One partner	59	(63.44)	21	(65.63)	38	(62.30)	
Two or more partners	34	(36.56)	11	(34.38)	23	(37.70)	0.751
Had sex with someone living in another province in the past 3 months							
No	69	(74.19)	25	(78.13)	44	(72.13)	
Yes	24	(25.81)	7	(21.88)	17	(27.87)	0.530
Condom use at last sexual encounter							
Yes	23	(24.73)	11	(34.38)	12	(19.67)	
No	70	(75.25)	21	(65.63)	49	(80.33)	0.118

****Wilcoxon rank-sum test**
IQR-Interquartile range

2.4.2. Clinical characteristics

There was a higher frequency/occurrence of patients with MUS who were not on ART (51%) than those with VDS (26%) and GUS (23%). The median HIV VL among all HIV-positive STI patients was 8011 copies/ml (IQR= 78–99171) with a statistically significant association with ART use as well as the duration since the last HIV test. Among male patients, less than half (38%) were circumcised. Among those who were circumcised, 26% were circumcised using the traditional circumcision method. Regardless of being on ART or not, the prevalence of having an unsuppressed VL was high at 76.34% using a threshold of >50 copies/ml and 65.6% had an unsuppressed VL using a threshold of >1000 copies/ml threshold (Table 3).

Table 3: Clinical characteristics of HIV-positive STI patients on ART and not on ART (initiated on ART before attending STI services).

Characteristic	All patients (N=93)		ON ART (N=32)		Not on ART (N=61)		p-value
	n	%	n	%	n	%	
STI Syndromic symptoms (genital ulcer and discharge), n (%)							
GUS	26	(27.96)	12	(37.50)	14	(22.95)	
MUS	42	(45.16)	11	(34.38)	31	(50.82)	
VDS	25	(26.88)	9	(28.13)	16	(26.23)	0.238
Treatment without success for the same STI in the past 3 months, n (%)							
No	86	(92.47)	28	(87.50)	58	(95.08)	

Yes	7	(7.53)	4	(12.50)	3	(4.92)	0.188
Previous STI in the last 12 months, n (%)							
No	77	(82.80)	27	(84.38)	50	(81.97)	
Yes	16	(17.20)	5	(81.97)	11	(18.03)	0.770
Ever circumcised *, n (%)							
No	26	(27.96)	9	(28.13)	17	(27.87)	
Yes	35	(37.63)	11	(34.38)	24	(39.34)	
N/A (Female)	32	(34.41)	12	(37.50)	20	(32.79)	0.872
Circumcision method *							
Medical	11	(11.83)	3	(9.38)	8	(13.11)	
Traditional	24	(25.81)	8	(25.00)	16	(26.23)	
Not circumcised	26	(27.96)	9	(28.13)	17	(27.87)	
N/A (Female)	32	(34.41)	12	(37.50)	9	(28.13)	0.941
Duration since last HIV test (months)							
<3months	35	(37.63)	3	(9.38)	32	(52.46)	
≥ 3months	58	(62.37)	29	(90.63)	29	(47.54)	<0.001**
VL (copies/ml), median (IQR)	8011 (78-99171)		142.5 (20-7724)		32983 (3415-192677)		<0.001**
Unsuppressed VL (>1000 copies/ml)							
Unsuppressed (≥ 1000 copies/ml)	61	(65.59)	12	(37.50)	49	(80.33)	
Suppressed (<1000 copies/ml)	32	(34.41)	23	(62.50)	12	(19.67)	<0.001**
Unsuppressed VL (>50 copies/ml)							
Unsuppressed (>= 50 copies/ml)	71	(76.34)	18	(56.25)	53	(86.89)	
Suppressed (<50 copies/ml)	22	(23.66)	14	(43.75)	8	(13.11)	<0.001**

***Denominator for circumcision was total males only**
***Variables with a p-value <0.25 were selected for multivariable analysis**
****p <0.05 in the adjusted model**

2.4.3. Prevalence of an unsuppressed VL

Of the 93 patients, more than half (71, 76.43%) had an unsuppressed VL (>50 RNA copies/ml) (Table 3). The prevalence of having an unsuppressed VL was higher in females (80.33%) than males (68.75%), patients aged <25 years (90.90%) compared to those ≥25 years (74.39%), those who had first sex at age <15 years (90.00%) compared to those who had first sex aged ≥15 years (74.70%), or those who did not use a condom during their last sexual encounter (81.43%) compared to those who used a condom (73.91%) and among patients who were not on ART (86.89%) compared to those on ART (56.25%). There was a higher proportion of patients with GUS and an unsuppressed VL (19/26) than those with either VDS or MUS (52/67) (Table 4).

2.4.4. Factors associated with unsuppressed VL

To identify the factors associated with having an unsuppressed VL, a univariable Poisson regression with robust error variance was run (Table 4). Patients aged <25 years had a 22% higher likelihood of having an unsuppressed VL (PRR=1.22, 95%, CI 0.97–1.53) than those aged ≥25 years. Furthermore, those who had first sex aged <15 years had a 20% higher likelihood of having an unsuppressed VL (PRR=1.20, 95% CI 0.94–1.53) than those who had first sex aged ≥15 years. Women were 17% more likely to have an unsuppressed VL than their male counterparts (PRR= 1.17, 95% CI 0.89–1.52) and those on ART were 35% less likely to have an unsuppressed VL (PRR= 0.65, 95% CI 0.47–0.89) than those not on ART. These were identified to be included in the multivariate analysis ($p<0.25$).

To determine the effects of explanatory variables on having an unsuppressed VL, a multivariable Poisson regression analysis was done where we adjusted for age, gender, age at first sex, and ART use (Table 3). ART use was associated with a 33% lower prevalence of having an unsuppressed

VL (adjusted prevalence rate ratio [aPRR]= 0.67, 95% confidence interval [95% CI] =0.49–0.92). The prevalence of having an unsuppressed VL was higher among those aged <25 years (aPRR=1.25, 95% CI= 0.99–1.60) compared to those aged ≥25 years, among females (aPRR=1.12, 95% CI 0.64–1.97) compared to males and among those who had first sex aged <15 years (aPRR=1.11, CI=0.88–1.40) compared to those who had first sex aged ≥15 years, although the associations did not reach statistical significance (Table 4).

Table 4: Prevalence and factors associated with virological non-suppression (VL >50 copies/ml) among HIV- positive STI patients by ART use, Gauteng and Western Cape, 2019.

Characteristic	VL>50 (n/N)	% with VL>50	Univariable PRR (95% CI)	p-value	Multivariable PRR (95% CI)	p-value
Age category						
>=25 years	61/82	74.39	Ref			
<25 years	10/11	90.90	1.22 (0.97-1.53)	0.08*	1.30 (0.98-1.71)	0.069
Age at first sex						
>=15 years	62/83	74.70	Ref			
<15 years	09/10	90.00	1.20 (0.94-1.53)	0.13*	1.14 (0.92-1.41)	0.221
Gender						
Male	49/61	68.75	Ref			
Female	22/32	80.33	1.17 (0.89-1.52)	0.25*	1.20 (0.90-1.59)	0.209
Number of sex partners (last 3 months)						
One partner	45/59	76.27	Ref			
Two or more	26/34	76.47	1.00 (0.79-1.26)	0.98		
Oral sex						
No	64/85	75.29	Ref	64/85		
Yes	7/8	87.50	1.16 (0.87-1.55)	7/8		
Anal sex						
No	65/85	76.47	Ref	0.31		
Yes	6/8	75.00	0.98 (0.64-1.49)	0.92		

Sex partner type						
Regular	58/75	77.33	Ref			
Casual	13/18	72.22	0.93 (0.68-1.28)	0.67		
Condom use						
No	54/70	81.43	Ref			
Yes	17/23	73.91	0.96 (0.73-1.26)	0.75		
STI Syndrome						
VDS/MUS	52/67	77.61	Ref			
GUS	19/26	73.07	0.94 (0.72-1.23)	0.66		
Treatment of STI no success (3 months)						
No	66/86	76.74	Ref			
Yes	5/7	71.43	0.93 (0.57-1.51)	0.77		
Previous STI in the last 12 months						
No	59/77	76.62	Ref			
Yes	12/16	75.00	0.97 (0.72-1.33)	0.89		
on ART						
No	53/61	86.89	Ref		Ref	
Yes	18/32	56.25	0.65 (0.47-0.89)	0.008*	0.67 (0.48-0.91)	0.012**

***Variables with a p-value <0.25 were selected for multivariable analysis**
***p <0.05 in the adjusted model**

2.4.5. Sub-group analysis for those on ART only

The study also looked at reported adherence to ART among HIV-positive STI patients taking ART. The findings showed that among those on ART, 21/32 (67.74 %) reported excellent self-adherence and reported not missing any day of taking their treatment. The majority of the patients on ART (68.75%) sometimes took their treatment correctly between 4 and 10 days a month (Table 5).

Table 5: Self-reported adherence to ARTs among HIV-positive STI patients taking ARTs

Characteristics	**Patients on ART, N=32**	
	n	**%**
Days missed ART doses, n(%)		
0 days	21	(67.74)
Between 1 and 5 days	9	(29.03)
5 or more days	1	(3.23)
Self-rate adherence of ARVs, n (%)		
Good	1	(3.23)
Very good	3	(9.68)
Excellent	6	(19.35)
Often take doses correctly		
Always (every day)	1	(3.13)
Almost always (21-29 days)	1	(3.13)
Sometimes (4-10 days)	22	(68.75)
Rarely (1-3 days)	4	(12.50)
Never (0 days)	4	(12.50)

2.4.6. Prevalence and factors associated with having an unsuppressed VL among HIV- positive STI patients only on ART.

In a subgroup analysis including only those on ART, all patients < 25 years (100%, 3/3) had an unsuppressed VL compared to 51.72% (15/29) of patients aged ≥25 years. More women using ART (58.33%, 7/12) had an unsuppressed VL compared to men using ART, where 55% (11/20) had an unsuppressed VL. More patients who had regular sexual partners (56.52 %) had an unsuppressed VL compared to those who reported having casual sexual partners. Patients with GUS syndrome had a higher prevalence of having an unsuppressed VL (58.33%) compared to patients who had either MUS or VDS (Table 6).

The univariate analysis limited to patients on ART showed that there was a higher likelihood of having an unsuppressed VL among patients aged <25 years compared to those aged ≥25 years (PRR= 1.93, 95% CI= 1.35–2.76), among those who first had sex at age <15 years (PRR= 1.21, 95% CI= 0.50–2.91) compared to those who first had sex at ≥15 years of age, among those who had ≥2 sexual partners (PRR=1.53, CI= 0.85–2.74) compared to those who had <2 sexual partners, among patients who practice oral sex (PRR= 1.94, 95% CI= 1.35–2.76) compared to anal sex and higher among those with GUS (PRR=1.06, 95% CI= 0.56–1.99) compared to VDS/MUS and among those who had an STI in the past 12 months (PRR=1.08, CI=0.48–2.41) compared to those who reported no STI in the past 12 months. In a multivariable subgroup analysis limited to patients on ART, patients aged <25 years had a higher likelihood of having an unsuppressed VL (aPRR=1.94; 95% CI= 1.27–2.97) compared to those aged ≥25 years in a model adjusting for sex partner number and oral sex (Table 6).

Table 6: Factors associated with having an unsuppressed viraL LOAD (VL >50 copies/ml) among HIV-positive STI patients on ART in South Africa (N=32).

Characteristic	VL>50 (n/N)	% with VL>50	Univariable (PRR; 95% CI)	p-value	Multivariable (PRR; 95% CI)	p-value
Age						
Age <25	3/3	100.00	1.93 (1.35-2.76)	<0.001*	1.78 (1.11-2.87)	0.02
Age>=25	15/29	51.72	Ref			
Age at first sex						
<15 years	2/3	66.67	1.21 (0.50-2.91)	0.67		
>=15 years	16/29	55.17	Ref			
Gender						
Male	11/20	55.00	0.94 (0.50-1.77)	0.86		
Female	7/12	58.33	Ref			
Anal sex						
Yes	1/1	100.00	1.83 (1.32-2.52)	<0.001*		
No	17/31	54.84	Ref			
Oral sex						
No	3/3	100.00	1.92 (1.35-2.76)	<0.001*		
Yes	15/29	51.72	Ref			
Sex partner type						
Casual	5/9	55.56	0.98 (0.49-1.97)	0.96		
Regular	13/23	56.52	Ref			
Number of sex partners (last 3 months)						
One partner	8/11	72.73	1.53 (0.85-2.74)	0.16*	1.41 (0.68-2.92)	0.35
two or more partners	10/21	47.62	Ref			
Condom use						
Yes	12/21	57.14	0.95 (0.49-1.86)	0.89		
No	6/11	54.55	Ref			
STI Syndromic symptoms (genital ulcer and discharge)						
GUS	11/20	55.00	1.06 (0.56-1.99)	0.855		
VDS/MUS	7/12	58.33	Ref			
Treatment no success in 3 months						

Yes	2/4	50.00	0.88 (0.31-2.49)	0.80
No	16/18	57.14	Ref	
Previous STI in the last 12 months				
Yes	3/5	60.00	1.08 (0.48-2.41)	0.85
No	15/27	55.56	Ref	

***Variables with a p-value <0.25 were selected for multivariable analysis**
***p <0.05 in the adjusted model**

2.5. DISCUSSION

This study looked at factors associated with having an unsuppressed VL among HIV-positive patients attending STI services in SA. The prevalence of having an unsuppressed VL was high regardless of ART status (76.0%). We found a low proportion of HIV-positive STI patients on ART (34.4%), and low condom use (25.0%). Our analysis demonstrated that factors associated with having an unsuppressed VL were age (<25 years), female gender, having first sex before the age of 15 years and not currently using ARTs. After adjusting for these factors, being on ART was associated with a lower likelihood of having an unsuppressed VL. A subgroup analysis among only those on ART showed that younger age and a higher sex partner number were associated with having an unsuppressed VL.

Significantly, ART was protective against having an unsuppressed VL since ART use results in direct suppression of HIV VL. Correspondingly, it is consistent with studies that found that being on ART increases VL suppression (11,20). Additionally, the results highlighted that younger patients aged <25 years had a higher risk of having an unsuppressed VL. Studies that looked at age as a factor for unsuppressed VL similarly concluded that younger ages had a higher likelihood of VL non-suppression (13,15,21). The prevalence of having an unsuppressed VL was higher in females (80.30 %) than males (68.80%). This contrasts with many studies where men had a higher likelihood of having an unsuppressed VL than women due to differences in health-seeking behaviour and ART adherence (14,15,22).

We found a low proportion of HIV-positive STI patients on ART (34.40%) and high levels of having an unsuppressed VL defined as a VL >50 copies/ml (76.00%). Also, considering the 1000 copies/ml threshold, the rate of having an unsuppressed VL was 65.60% which did not reach the 95-95-95 HIV prevention cascade benchmark and prevention goals. In addition, the study found that the proportion

of HIV-positive patients attending STI services on ART was less than the 95% target. Among those on ART, the proportion of VL suppression was well below the 95% target as well. The low rates of ART and viral suppression are concerning since patients may be seeking STI services based on symptoms and the presence of an STI which increases the risk of HIV transmission. High levels of having an unsuppressed VL may indicate gaps in the monitoring of ART adherence and/or clinical management of HIV-positive patients seeking STI services. Antiretroviral therapy has been the key intervention to reduce HIV transmission and improve the health of HIV-infected persons (15,23,24).

In addition, we found low levels of reported condom use, which is concerning since there is an increased risk of transmission to uninfected partners among HIV-positive people. Similar findings studies such as the PARTNER study from 14 European countries also found a high prevalence of condom-less sexual practices among HIV-positive patients on ART seeking STI treatment (25). Many studies likewise found low condom use among HIV-positive patients on ART (11,26–28). HIV guidelines recommend consistent and correct use of condoms to reduce HIV transmission in hand with ART treatment (29). ART can suppress VL to an undetectable level making HIV untransmissable (Undetected=Untransmissable). Condom use can be low if partners are virally suppressed, however, in the era of U=U, our findings suggest that this was not the case in our study population given the high prevalence of having an unsuppressed VL (76%). Consequently, more education and promotion of condom use among HIV-positive patients, regardless of whether they are on ART, is needed to reduce STI rates and HIV acquisition. STIs are a marker of risky sexual behaviours which can range from having many sexual partners to no or inconsistent condom use, starting sex at a young age (14,30,31) which increases the transmission of the virus.

In a subgroup analysis among only those on ART, the prevalence of having an unsuppressed VL was high among females aged <25 years which may be due to non-adherence or no direct

monitoring of treatment. Poor adherence amongst young adults to ART has been found in other studies with a higher likelihood of having an unsuppressed VL (26,32,33). Having multiple sex partners was associated with low VL suppression among HIV-positive STI patients on ART. Literature has equally highlighted an association between the failure to achieve VL suppression among patients on treatment and increased risky sexual behaviours, including having multiple sexual partners (24,32,34). Despite low levels of ART coverage, being on ART showed a marked decrease in the prevalence of having unsuppressed VL.

2.6. Limitations

The study contributes to existing data on factors associated with having an unsuppressed VL among HIV-positive STI patients by ART use. However, our findings must be considered with some limitations. Firstly, the main outcome of having unsuppressed VL is laboratory-based which provided VL data for only HIV-positive patients who had samples collected for laboratory examination. We might have missed HIV-positive patients who did not consent to sample collection and those who were waiting for results from the laboratory. Secondly, we analysed self-reported data on the use of ART, previous STI symptoms, sex type, sex act type, sex partner number, age at first sex as well as being on ART among many others. Self-reporting may be biased due to recall and underreporting since sexual behaviour is confidential and thereby not easy to disclose. Thirdly, secondary data used had HIV-positive patients attending STI services enrolled from two provinces which limits the generalizability of our findings to the rest of South Africa. We used secondary data where the primary study collected data appropriate for sentinel surveillance on STI patients. An example is a question on condom use which was limited to the last sexual encounter and therefore did not capture whether earlier sexual encounters were condom-protected. The data did not have information on the duration of the current STI infection, only data on males circumcised was

collected without considering female genital mutilation as well. Lastly, the study ended up with a small sample size, since we had to limit our analysis to patients with a recorded VL as the main outcome which limited statistical power.

2.7. Conclusion

It is concluded in this study that factors associated with having an unsuppressed VL among HIV-positive STI patients are being young (<25 years old), female, and ART use. The study found that VL suppression among HIV-positive STI patients was low (24.00%) compared to the UNAIDS target of 95%. For those on ART, VL suppression was higher (43.80%) but still did not reach the 95% target. The study has furthermore demonstrated that despite the national achievement of expanded HIV testing there is still a need to improve ART initiation and adherence to achieve VL suppression. Therefore, more interventions should be targeted to those at higher risk of having an unsuppressed VL such as the young females to start and continue ART. Improved implementation of integrated HIV-STI prevention, testing, and treatment will efficiently and effectively reach high-risk populations and help reduce transmission.

2.8. Recommendations

The findings show that there should be intensified ART support for young and female STI-HIV-positive adult to start and continue ART to improve viral suppression outcomes and expansion of VL monitoring interventions. There is a need for policymakers to ensure the effective implementation of consolidated screening, prevention, and treatment approaches for HIV and STIs in clinical settings as recommended by the national guidelines. To achieve effective results, all STI patients must be tested for HIV (with consent), initiated for treatment if positive, and counselled about the importance of ART continuation and adherence. There is a need to keep

patients on treatment despite improved regimens and services providing ART.

We recommend researchers and scientists move to a more effective approach to improving adherence to achieve VL suppression, to look at the effect of co-infections such as STIs on HIV-positive patients. The next step can be to evaluate the use of HIV self-testing in STI services as a more comfortable dual approach for patients. A longer-lasting ART regimen such as a durable injectable regimen to enhance adherence and effective treatment outcomes might improve treatment and close the gaps. From the findings, efforts targeted to young females who are HIV-positive will improve the treatment response among the population at risk. The use of virological failure to indicate the risk of HIV transmission will allow early adherence interventions. It becomes crucial during policy-making and reviewing of guidelines on HIV management for HIV programme managers to design targeted age-specific treatment and care policies. The recommendations will help to reinvent existing programs and interventions informed by recent studies/ findings to achieve the 95-95-95 UNAIDS targets by 2030.

2.9. LIST OF ABBREVIATIONS

ART: Antiretroviral therapy; CI: Confidence Interval; GUS: Genital ulcer syndrome; Human HIV: Immunodeficiency Virus; IQR: Interquartile range; MUS: Male urethritis syndrome, NDoH: National Department of Health; OR: Odds ratio; PRR: Prevalence rate ratio; STI: Sexual Transmitted Infection; SDG: Sustainable development goals; UNAIDS: United Nations AIDS; U=U; Undetected=Un-transmissible; UTT: Universal test and treat; VDS: Vaginal discharge syndrome; VL: Viral Load; WHO: World Health Organization; <: less than; >: Greater than.

2.10. DECLARATIONS

Ethics approval and consent to participate

The primary study received ethical clearance from the University of Witwatersrand Human Research Ethics Committee **(HREC NUM: M181071)** into which this study is embedded. Participants enrolled in the STI surveillance study consented before answering the questionnaire and provide blood samples using anonymous and barcoded samples for privacy and confidentiality. An ethical declaration for this secondary analysis was obtained from the Assessor group during protocol assessment on 22 April 2020 at the University of the Witwatersrand which is attached in the annexures. To analyse the data, permission from the primary study Principal Investigator was obtained. Patient personal identifiers were de-identified to maintain confidentiality.

Consent for publication

Not applicable

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Availability of data and materials

Data from this study are available from the Centre for HIV/ STI at the National Institute for Communicable diseases (NICD), South Africa, but restrictions apply to the availability of these data. However, data is available from the authors upon reasonable request and with permission of the Centre for HIV/ STI.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MM wrote the concept note, protocol for the secondary analysis, analyzed data and wrote the manuscript. TK supervised the study from conceptualization, analysis, interpretation and writing up. ADV and KR assisted with supervision and writing. All authors contributed with critical inputs in the writing of the manuscript. All authors read the final manuscript and approved it.

Acknowledgements

The authors would like to thank the Centre for HIV and STIs at NICD for collecting STI sentinel data and making it available for analysis. We are also thankful to Professor Cheryl McCrindle from the School of Health Systems and Public Health, University of Pretoria and Ms. Emelda Ramutshila from the SAFETP for the assistance.

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3. FIGURES, TABLES AND ADDITIONAL FILES

Table 1: Comparison of characteristics between HIV-positive STI patients with and without viral load data

Characteristic	All Patients (N=142)	Patients with VL data (N=93)	Patients without VL data (N=49)	p-value
	n %	n %	n %	
Age median (IQR)**	31 (26-36)	32 (27-37)	29 (25-33)	0.0013
Age categories (years)				
< 25	23 (16.20)	11 (47.83)	12 (52.17)	0.052
≥25	119 (83.80)	82 (68.91)	37 (31.09)	
Age at first sex				
<15 years	17 (11.97)	10 (58.82)	7 (41.18)	0.538
≥15 years	125 (88.03)	83 (66.40)	42 (33.60)	
Gender				
Male	95 (66.90)	61 (64.21)	34 (35.79)	0.648
Female	47 (33.10)	32 (68.09)	15 (31.91)	
Oral sex in the past 3 months				
No	131 (92.25)	85 (64.89)	46 (35.11)	0.599
Yes	11 (7.75)	8 (72.73)	3 (27.27)	
Receptive Anal sex in the past 3 months				
No	132 (92.96)	85 (64.39)	47 (35.61)	0.317
Yes	10 (7.04)	8 (80.00)	2 (20.00)	
Sex partner type				
Casual	25 (17.61)	18 (72.00)	7 (28.00)	0.451
Regular	117 (82.39)	75 (64.10)	42 (35.90)	
Sex partner number (last 3 months)				
One partner	85 (61.15)	59 (69.41)	26 (30.59)	0.431
≥two partners	54 (38.85)	34 (62.96)	20 (37.04)	

Previous STI syndrome in the past 12 months						
No	117	(82.39)	77	(65.81)	40	(34.19)	0.137
Yes	23	(16.20)	16	(69.57)	7	(30.43)	
Missing data *	2	(1.41)	0	(0.00)	2	(100.00)	
STI syndrome was diagnosed on the day of attending							
GUS	36	(25.35)	26	(72.22)	10	(27.78)	0.126
MUS	69	(48.59)	42	(60.87)	27	(39.13)	
VDS	35	(24.65)	25	(71.43)	10	(28.57)	
None/ missing*	2	(1.41)	0	(0.00)	2	(100.00)	
Condom use							
No	115	(80.99)	70	(60.87)	45	(39.13)	0.017
Yes	27	(19.01)	23	(85.19)	4	(14.81)	
Antiretroviral use in past 3 days							
No	108	(76.06)	61	(56.48)	47	(43.52)	<0.001
Yes	34	(23.94)	32	(94.12)	2	(5.88)	

4. OVERALL DISCUSSION, CONCLUSION AND RECOMMENDATIONS

Introduction

This chapter will summarise the findings of the study, give an overall discussion, conclusion of the study and provide recommendations.

Findings and discussion

The findings showed a high prevalence of having an unsuppressed VL among HIV-positive patients attending STI services regardless of ART status. There was a low proportion of HIV STI services patients on ART and low condom use reported at the last sex. The factors associated with having an unsuppressed VL were age (<25 years), female gender, having first sex before the age of 15 years and ART use. The subgroup analysis of only those on ART showed that age (<25 years) and sex partner number were associated with having an unsuppressed VL. ART use was protective against having an unsuppressed VL despite low ART use in this study population. These findings reflected more on high un-suppression rates among young women with low ART use.

Low condom use and multiple sex partners were associated with having an unsuppressed VL which is concerning risky behaviour in the prevention of HIV. As the young population of STI patients who are HIV-positive continues to grow, comprehensive strategies will effectively assist in the prevention of HIV and STI transmission to achieve viral load suppression. The government and policymakers need to consider regular testing of HIV and STI among the young population and early initiation to treatment for the positive with proper support and knowledge.

Conclusion

It is concluded in this study that factors associated with unsuppressed VL among HIV-positive STI patients are being young, female and ART use. Therefore, more effort should be put on targeted interventions for those at risk of having an unsuppressed VL such as the young females to start and continue ART. The study has demonstrated that despite national achievement in HIV testing, there is still a need to improve ART initiation and adherence to achieve the VL suppression level. Strengthened implementation of HIV-STI education, prevention, testing, and treatment will efficiently and effectively reach the high-risk population and help reduce transmission. As the fight to end the HIV pandemic continues, an integrated target approach across all age groups and populations on HIV and the effects of other infections such as STIs are needed to reach the 95-95-95 targets by 2030.

Recommendations

The findings show that there should be intensified targeted ART support for the young and female STI-HIV-positive adults to start and continue ART to improve viral suppression outcomes. Multifaceted support such as sex education to the young from school, behavioural strategies and implementation of age-appropriate HIV programs may be effective. Enhancing access to HIV information, and treatment and addressing the barriers will help to adapt HIV services to the needs of young people.

Efforts should be made to regularly monitor of HIV viral loads of STI patients by administering routine testing, awareness of STI symptoms and knowledge on adherence to treatment. Such knowledge will help in identifying STIs early, frequent health-seeking behaviours, and early testing and treatment. Once risky populations are informed of the benefits of testing and treatment

adherence, the fight against HIV/ STI will be reduced by achieving the targets.

Policymakers need to ensure effective screening, prevention and treatment approach to HIV/STI in clinical settings to increase coverage and adherence for better viral load suppression rates. Services must be friendly such as self -HIV testing tools introduced at STI services which should have less disclosure to improve HIV testing for STI patients without any stigma.

There is a need to strengthen STI prevention among HIV- positive and negative people, ensure that positive is initiated for treatment, continue being on ART and remain virally suppressed as well as to facilitating access to STI services for those who are HIV- positive patients.

Researchers and scientists should lead in moving towards a more effective approach to adherence to achieve VL suppression. A more focused approach on moving towards ending the effect of STI-HIV co-infection such as a longer ART injectable regimen. This will help program managers to reinvent the existing approaches and interventions to achieve the 95-95-95 UNAIDS targets by 2030 of ending the HIV epidemic.

5. APPENDICES

APPENDIX 1: Plagiarism declarations

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

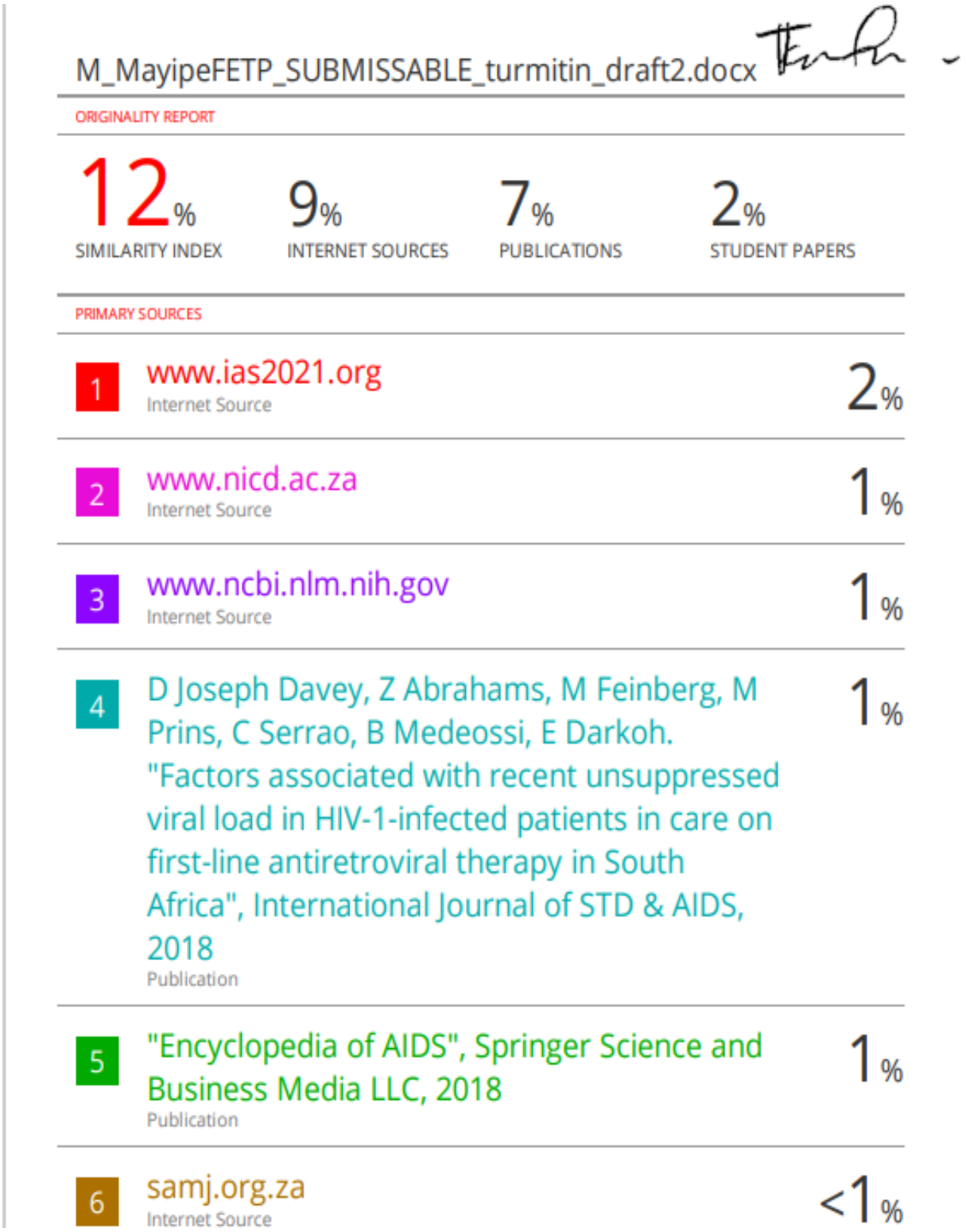
I Marceline Mapiye (Student number: 1710465) am a student registered for the degree of MSc EPIDEMIOLOGY in the academic year 2019.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: mmapiye Date: 25/01/2022

APPENDIX 2: Turnitin report



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ORIGINALITY REPORT

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2	www.nicd.ac.za Internet Source	1%
3	www.ncbi.nlm.nih.gov Internet Source	1%
4	D Joseph Davey, Z Abrahams, M Feinberg, M Prins, C Serrao, B Medeossi, E Darkoh. "Factors associated with recent unsuppressed viral load in HIV-1-infected patients in care on first-line antiretroviral therapy in South Africa", International Journal of STD & AIDS, 2018 Publication	1%
5	"Encyclopedia of AIDS", Springer Science and Business Media LLC, 2018 Publication	1%
6	samj.org.za Internet Source	<1%

APPENDIX 3. Primary Study Ethics

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Dr T Kufa-Chakezha, et al
School of Public Health
Medical School
University

E-mail: tendesayikc@nicd.ac.za

CC: Supervisor: Not applicable <>
and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 06/12/2018

REF: *R14/49*

PROTOCOL NO: **M181071** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *Evaluation and validation of self-reported HIV testing, antiretroviral therapy use and viral suppression measures among sexually transmitted infection (STI) service attendees*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr T Kufa-Chakezha, et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M181071

NAME: (Principal Investigator)	Dr T Kufa-Chakezha, et al
DEPARTMENT:	School of Public Health Medical School University
PROJECT TITLE:	Evaluation and validation of self-reported HIV testing, antiretroviral therapy use and viral suppression measures among sexually transmitted infection (STI) service attendees
DATE CONSIDERED:	26/10/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Not applicable
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	06/12/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date of the meeting when the study was initially reviewed. In this case, the study was initially reviewed in **October** and will therefore reports and re-certification will be due early in the month of **October** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 4: Ethics declaration for secondary analysis

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

University of the Witwatersrand Student Ethics Declaration Form

(To be completed during the protocol assessor meeting)

Background

All Research conducted by a University of the Witwatersrand student, with human subjects or animals, requires approval by the Wits Human Research Ethics Committee or Animal Research Ethics Committee, respectively.

If research has been undertaken without the necessary ethics approvals, this is considered an ethics violation. This will be reported to the relevant structures, the data will have to be discarded, and in the case of students, they cannot use the data towards their degree.

To prevent any ethics violations, the ethics requirements for the proposed project will be discussed with you at the protocol assessment.

Declaration

Based on the current protocol assessment (and any proposed changes suggested by the assessor committee), we, the undersigned, understand that the proposed research requires:

1. Human Research Ethics clearance certificate	Yes	No
a. Covered under existing supervisor ethics	Yes	No
b. Requires a new HREC application	Yes	No
2. Animal Research Ethics clearance certificate	Yes	No
3. No Human or Animal Ethics Clearance	Yes	No
4. Unclear, will seek appropriate guidance from the HREC/AREC committees (whichever relevant)	Yes	No

Signatures

Supervisor/s: _____ Student: _____

Date: 27/05/2020.

11 March 2019/MP

APPENDIX 5: Author guidelines (BMC Public Health)

BMC Public Health

Research article

Criteria

Research articles should report on original primary research or new experimental or computational methods, tests or procedures. Manuscripts reporting results of a clinical trial must conform to CONSORT 2010 guidelines. Authors of randomized controlled trials should submit a complete CONSORT checklist alongside their manuscript, available at : www.consort-statement.org.

Research articles may also report on systematic reviews of published research provided they adhere to the appropriate reporting guidelines which are detailed in our editorial policies. Please note that non-commissioned pooled analyses of selected published research and bibliometric analyses will not be considered.

Studies reporting descriptive results from a single institution will only be considered if analogous data have not been previously published in a peer reviewed journal and the conclusions provide distinct insights that are of relevance to a regional or international audience.

Authors can receive free advice on how and where to share their research data, according to their the specific research community, from a team of research data editors by contacting our Research Data Helpdesk.

Preparing your manuscript

The information below details the section headings that you should include in your manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

Title page

The title page should:

• present a title that includes, if appropriate, the study design e.g.:

o "A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"

o or for non-clinical or non-research studies a description of what the article reports

- list the full names and institutional addresses for all authors

o if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the "Acknowledgements" section in accordance with the instructions below

- indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

- **Background:** the context and purpose of the study
- **Methods:** how the study was performed and statistical tests used
- **Results:** the main findings
- **Conclusions:** brief summary and potential implications
- **Trial registration:** If your article reports the results of a health care intervention on human participants, it must be registered in an appropriate registry and the registration number and The date of registration should be in stated in this section. If it was not registered prospectively (before enrollment of the first participant), you should include the words 'retrospectively registered'. See our editorial policies for more information on trial registration

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

Methods

The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in

parentheses

- the type of statistical analysis used, including a power calculation if appropriate

Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
- Consent for publication
- Availability of data and materials
- Competing interests
- Funding
- Authors' contributions
- Acknowledgements
- Authors' information (optional)

Please see below for details on the information to be included in these sections.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Ethics approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue must:

- include a statement on ethics approval and consent (even where the need for approval was

waived)

• include the name of the ethics committee that approved the study and the committee's reference number if appropriate Studies involving animals must include a statement on ethics approval and for experimental studies involving client-owned animals, authors must also include a statement on informed consent from the client or owner. See our editorial policies for more information. If your manuscript does not report on or involve the use of any animal or human data or tissue, please state "Not applicable" in this section.

Consent for publication

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Availability of data and materials

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Slifka MK, Whitton JL. Clinical implications of dysregulated cytokine production. Dig J Mol Med. 2000;doi:10.1007/s801090000086.

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Book chapter, or an article within a book

Wyllie AH, Kerr JFR, Currie AR. Cell death: the significance of apoptosis. In: Bourne GH, Danielli JF, Jeon KW, editors. International review of cytology. London: Academic; 1980. p. 251-306.

OnlineFirst chapter in a series (without a volume designation but with a DOI)

Saito Y, Hyuga H. Rate equation approaches to amplification of enantiomeric excess and chiral symmetry breaking. Top Curr Chem. 2007. doi:10.1007/128_2006_108.

Complete book, authored

Blenkinsopp A, Paxton P. Symptoms in the pharmacy: a guide to the management of common illness. 3rd ed. Oxford: Blackwell Science; 1998.

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Doe J. Title of subordinate document. In: The dictionary of substances and their effects. Royal Society of Chemistry. 1999. http://www.rsc.org/dose/title of subordinate document. Accessed 15 Jan 1999.

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University site

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Doe, J: Trivial HTTP, RFC2169. ftp://ftp.isi.edu/in-notes/rfc2169.txt (1999). Accessed 12 Nov 1999. *Organization site*

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Zheng L-Y, Guo X-S, He B, Sun L-J, Peng Y, Dong S-S, et al. Genome data from sweet and grain sorghum (Sorghum bicolor). GigaScience Database. 2011. http://dx.doi.org/10.5524/100012.

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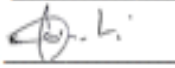
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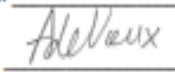
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