TITLE

The frequency of positive urine multi-drug tests among outpatients with both HIV and psychiatric illnesses at Luthando Clinic, Chris Hani Baragwanath academic hospital, Soweto, South Africa.

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A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, in partial fulfilment of the requirements for the degree of Masters of Science in Medicine in Psychiatry.

DECLARATION

I, Moeketsi Khabisi declare that this thesis is my own work. It is being submitted for the degree of Masters of Medicine (Psychiatry) at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

……..

23rd May 2019

DEDICATION

This is dedicated to Jerminah, Kani, Kamo, Karabo and the whole family for their endless support throughout this Journey.

PLAGIARISM DECLARATION

I, Dr Moeketsi Khabisi, as a postgraduate student registered for a MMed at the University of Witwatersrand declare the following:

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ABSTRACT

Background: There is evidence from both local and international studies on the high levels of substance use in patients with mental illnesses or those diagnosed with HIV (Human Immunodeficiency Virus). However, there is limited data in South Africa (SA) on the level of substance use, particularly cannabis, in patients who have been diagnosed with both HIV and psychiatric illness. The aim of the study is to describe the frequency of positive multi-drug urine tests for a duration of 6 months (1st January-30th June 2014) among outpatients with both psychiatric illness and HIV at the Luthando Neuropsychiatric clinic.

Methods: This was a retrospective record review of all patients who attended Luthando clinic within the 6 month study period. A record sheet with demographics, multi-drug urine test (MDUT) results and clinical variables were completed for each patient and was thereafter subsequently entered into a statistical software programme SAS version 9.4 Windows database. For categorical data, a descriptive analysis was used, while Chi square and Fisher exact tests were used for evaluating associations between MDUT results and clinical variables. Cramer's V and Phi coefficient were employed to measure the association's strengths respectively. A 5% precision and 95% confidence level were used.

Results: A total of 337 file records were reviewed. The prevalence of positive MDUTs was 36.4% (n=118). The most common substance used was cannabis at 94.9%. There was a significant association between positive MDUTs and young, male participants (p=0.030 and p=0.0001, respectively). There was a significant association between a positive MDUT and poor viral suppression (p=0.010), as well as the patient's duration on antiretroviral treatment (ART), with a shorter duration on ART being related to use of substances (p=0.036). There was also a significant association between MDUT outcome and psychiatric diagnoses, specifically bipolar disorder due to HIV and substance use disorder (p=0.0001 and p=0.0006, respectively).

Conclusion: This study demonstrated a high prevalence of substance use with a lower rate of viral suppression among patients attending Luthando Neuropsychiatric clinic. This is of great concern to personal and public health implications, hence such patients must be promptly identified in the course of their illnesses so that they can be effectively managed.

ACKNOWLEDGEMENTS

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Table 1 Abbreviations and Definitions

Abbreviations	Definition
MDUT	Multi-drug urine test
HIV	Human Immunodeficiency Virus
PLWHA	People Living With HIV AIDS
ART	Antiretroviral therapy
CHBAH	Chris Hani Baragwanath Academic Hospital
SACENDU	South African Community Epidemiology Network on Drug Use
WHO	World Health Organization
UNAIDS-SA	The Joint United Nations Programme on HIV/AIDS in South Africa
TB	Tuberculosis
STIs	Sexually Transmitted Illnesses
HLOE	Highest level of Education
THC	Tetrahydrocannabinol
PCP	Phencyclidine
IQR	Inter Quartile Range
SASH	The South African Stress and Health Study

CHAPTER 1 INTRODUCTION

Internationally, approximately half of all people living with HIV/AIDS (PLWHA) have displayed current or past histories of substance use or misuse (Bing et al, 2001; Rabkin et al, 2004). Furthermore, Rabkin (2004) described the relationship between substance use/misuse, some key health behaviours and their implications, such as increased sexual risk patterns, non-adherence to antiretroviral treatment and immunosuppression.

Although there is limited data on HIV and substance use in sub-Saharan Africa, Needle et al, (2006) have documented approximately 35% drug use (both injecting and non-injecting drugs) among PLWHA in Kenya, Tanzania, South Africa, Nigeria and Mauritius. In three South African cities, the prevalence of HIV/AIDS among male and female drug users was 28% (Pithey and Parry, 2006). Despite the limited data in South Africa and sub-Saharan countries as a whole, the study (Pithey and Parry, 2006) shed some light on the alarming rise in substance use among HIV-infected populations. Illicit substances are also globally known either as predisposing or precipitating factors in most primary mental disorders (affective mood disorders, Schizophrenia and anxiety disorders to name a few), and affect the prognoses of these individual disorders (Wiech et al, 2009; Matthew et al, 2009; Sepehmanesh et al, 2014).

In current global studies, medical anthropologists have introduced the term 'syndemic', which looks at the synergistic interaction of two or more illnesses and the exacerbated effects on the disease profiles (Singer et al, 2003). The Centre for Community Health Research, (2003) has shown that in the event of co-occurrence of 2 or more illnesses, the actual biological interactions are heightened with subsequent amplified health consequences.

The South African Community Epidemiology Network on Drug Use (SACENDU), (Dada et al, 2017) has reported a high number of patients with substance use/abuse in the general population (ranging between 9489 and 10047, admitted for treatment in the second half of 2017). Substance abuse is viewed as a common denominator in patients with comorbid mental disorders or HIV/AIDS and the synergistic interaction between these entities can have adverse consequences. However, the limited literature available in sub-Saharan Africa or SA on the extent of substance misuse in patients with co-occurrence of mental disorders and HIV/AIDS is disconcerting. Knowledge on the rates and prevalence of substance use within this vulnerable group of

individuals (i.e. people with the two diagnoses) is very important. This can prompt government and other relevant stakeholders to focus resources in the form of money and adequate health care professionals to alleviate the associated problems and also invest more in relevant research. Hence better evidence-based management strategies can be implemented.

Furthermore, the clinical management of these individuals goes beyond the sole management of the illnesses in isolation, but involves the "triple diagnosis" as a whole and the synergistic adverse effects associated (Durvasula and Miller et al, 2014). Singer et al., 2003 have demonstrated a more holistic approach that encompasses interrelationships between the disorders and the influence of the contexts involved.

The World Health Organisation (WHO) policies (2001) have also alluded to the same concept in the form of integration of health care. This is to ensure more efficient and effective holistic management. Dual diagnostic health facilities have emerged both locally and internationally and the results obtained are positive. SA has very few facilities with triple diagnoses integration.

CHAPTER 2 BACKGROUND:

2.1 The HIV Epidemic

Acquired immune deficiency syndrome (AIDS) is currently viewed as a chronic illness (Ettner et al, 2008). According to the Global HIV and AIDS statistics (2016), there are approximately 36.7 million people currently living with HIV in the world and 70% of these individuals are in the sub-Saharan Africa. Globally, new HIV infections and AIDS-related deaths are estimated at 1.8 million and 1.0 million, respectively.

The Joint United Nations Programme on HIV/AIDS in South Africa (UNAIDS -SA, 2017) has demonstrated that SA has the highest number of people living with HIV compared to any other country. There are approximately 7.1 million people living with HIV in SA, constituting about 19% of the South African national population, and SA also has 15% of all new infections and 11% of AIDS-related deaths. This is far beyond the global prevalence of HIV estimated at 0.8%.

Women represented 51% of all adults infected with HIV worldwide (Ettner et al, 2008). According to the HIV and AIDS sub-Saharan Regional overview (2015), there are more females than males infected with HIV across sub-Sahara African countries. They reported that for every 13 women infected with HIV, there are 10 men living with HIV. The reasons contributing to more women contracting HIV include social, but also biological factors. Poor economic conditions precipitated by unemployment and lack of education are among the key social factors reported to contribute to these high rates (Ettner et al, 2008).

Kaiser et al. (2015) demonstrated that young individuals aged between 15-24 years account for 30% of new HIV infections globally. For adults aged 15-49 years in SA, an estimated 20% of the population is HIV-positive and the ratio of female to male prevalence for this age group is estimated at 1.5:1 (Shisana et al, 2012). Within Gauteng, where the current study took place, the prevalence is estimated at 12.4% of the total population (Shisana et al, 2012).

With the largest HIV epidemic in the world, SA has the largest antiretroviral treatment programme, accounting for 20% of the people on antiretroviral therapy (ART) globally. The country itself has the largest domestically funded ART programme, 80% of which is directly from the government (UNAIDS-SA Stats, 2017). Although the burden is still alarmingly high,

there has been a 49% decrease in new infections and a 29% decline in AIDS-related deaths since 2010 (UNAIDS-SA Stats, 2017). The South African National Strategic Plan for HIV, TB and STIs (2017-2022), has been implemented to address these high rates of HIV infections and related complications.

2.2 HIV and Mental illness

The South African Department of Health (2013) stated that mental illnesses are associated with significant distress and impairment in functioning. The lifetime prevalence of any mental disorder in adults in SA is estimated at 30.3%. Anxiety disorders were found to be the most prevalent class of disorders at 15.8%, substance use disorders and mood disorders were at 13.3% and 9.8%, respectively (Herman et al, 2009). A significant number of patients with HIV have a mental illness (Ettner et al, 2008). In the United States, it is estimated that the prevalence of HIV among psychiatric patients is at least seven times higher than in the general population and about 13% of HIV positive patients are reported to have had comorbid psychiatric symptoms (Weiser et al, 2004).

According to the South African DOH report (2013), 25% of the general population develop one or more mental or behavioural disorders in their lifetime. Mental illness and HIV are estimated to co-occur in 43% of patients in this report. Bipolar disorders, major depressive disorders and schizophrenia were psychiatric illnesses that were demonstrated to have strong associations with HIV [South African DOH report (2013)]. From another study, females aged between 18 and 39 years had a higher prevalence of mental illnesses associated with HIV (Jonsson et al, 2011). Jonsson et al. (2011) also described the rapid increase of patients with comorbid HIV and mental illness attending the Luthando Neuropsychiatry clinic in Soweto, Johannesburg, and further highlighted the importance of integrated services for these individuals.

2.3 Substance use disorders

Substance use is on the increase globally despite interventions to eradicate use and abuse (Mitcheson et al, 2012). The Global Drug Survey (2012), showed that globally, alcohol use has the highest prevalence of 90.8%, followed by tobacco and cannabis use at 56.7% and 48.2%, respectively. SA had the second highest prevalence of substance abuse (5.8%) in 2003-2004 among the 14 countries that participated in the World Mental Health Survey (Herman et al, 2009;

Kader et al, 2014). The South African Stress and Health Study (SASH), (Herman et al, 2009) has shown that the highest prevalence of substance use disorders is in young, unemployed individuals who reside in semi-or urban regions. The majority have no source of income and are predominantly unmarried or divorced males.

Substance use disorders are diagnosed clinically according to the criteria from the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM 5). Drugs of abuse can be detected with blood and urine tests. One form is a multi-drug urine test kit that can be used to test for drugs of abuse (Raes et al, 2005).

The drugs tested for in the model used at Luthando include cannabis (THC), cocaine (benzoylecgonine), opiates, phencyclidine (PCP) and amphetamine/methamphetamine. A positive or negative result is based on pre-set values and a positive urine test result shows recent drug use; however it cannot quantitively determine how much of the drug is being used, how often it is being used, or when last the patient used.

2.4 HIV and Substance Abuse

Cannabis is one of the most commonly abused substances globally (Mitcheson et al, 2012). Garin et al. 2015 conducted a study across Europe and described the prevalence of this substance use in HIV positive populations. The prevalence of cannabis use among PLWHA in the United Kingdom was 21.1% and in Germany and France, cannabis use was 19.1% and 11.7%, respectively (Garin et al, 2015). In another study conducted in two Maritime Hospital immunodeficiency clinics (HIV clinics) in Canada in 2014, 38.5% of the study participants were reported as cannabis users (Harris et al, 2014). Ware et al. 2003 found that cannabis use is approximately 2-3 folds more prevalent among individuals living with HIV/AIDS, compared to the general population.

A South African study conducted in three urban communities assessed drug use and HIV risk behaviour using a modified version of the Drug Abuse Screening Test, Short Form (DAST-10). The prevalence of illicit substances was 25% for cannabis, 7.3% for methamphetamines, 5.3% for mandrax and any drug injected by needle constituted 1.2% of the study sample (Peltzer et al, 2009). The strongest predictors for HIV risk were cannabis use and needle drug use. HIV has effects on the frontal-striatal brain regions, which are known to promote decision-making

functions (Fujiwara et al, 2015, Peltzer et al, 2009). This may partly explain the high occurrence of comorbid substance use among HIV-positive individuals.

The South African National HIV Prevalence, Incidence and Behavioural Survey, (Shisana et al, 2012), demonstrated that there is an increasing prevalence of substance use in HIV-positive patients. Reviewing South African studies, the prevalence of substance use in HIV individuals is generally high in single, young African males with low socio-economic status (Kader et al, 2012; 2014). Kader et al, 2012 also described the impact of abusing substances among patients attending HIV clinics. It was reported that substance abuse among these individuals contributes to non-compliance to treatment, especially to ART. Substance users had sub-optimal health and were more vulnerable to developing HIV/AIDS-related complications due to high viral loads as opposed to non-substance users. This highlights the significance of screening HIV-positive patients for substance use and dependence within SA clinics.

2.5 Mental illness and Substance abuse

Mental illness is on the increase among people using illicit substances (Sepehmanesh et al, 2014). Weich et al. 2009 reported that there was a high prevalence of substance use disorders among psychiatric in-patients and this resulted in increased aggression compared to the non-substance abusing patients. The patients abusing substances were more likely to be non-compliant to their medication regimens. In the same context, Miller et al. 2009 reported that failure to adhere to treatment regimens resulted in patients relapsing and having multiple admissions, thus adding more strain to health institutions. Cannabis use was specifically identified as a risk factor for patients who were non-compliant to their treatments. Cannabis affects the prefrontal cortex, which lead to these individuals presenting with psychotic features, decline in judgement and disinhibition. Poor insight and impaired judgement were the key factors identified that resulted in non-adherence to treatment (Miller et al, 2009).

Psychotic symptoms increase with the severity of substance use (Matthew et al, 2009). According to Mane et al, 2015, cannabis users had an earlier age of onset of psychosis than non-cannabis users. Continued use of cannabis is associated with poor prognosis and its use is a predictor of increased illness severity and may contribute substantially to disability associated with psychosis (Myles et al, 2015). The reasons stated by patients with mental illness for using

cannabis were described by Mane et al, 2015 “to arrange their thoughts and deal with the hallucinations and suspiciousness”, for “ treatment of negative symptoms” and “ for treatment of side effects associated with antipsychotic medication”.

Studies in SA also showed strong associations between substance use disorders and mental illnesses. A prospective, descriptive study on prevalence of substance use disorders among psychiatric in-patients at Stikland Hospital in Western Cape (Weich et al, 2009), showed that schizoaffective disorder had the greatest link with substance use, followed by bipolar disorder and schizophrenia. Major depressive disorder and adjustment disorders had the least association. Cannabis use was specifically linked to schizophrenia and schizoaffective disorders.

2.6 Triple diagnosis

There is a proportion of triply diagnosed patients, namely those with HIV/AIDS, substance use disorders and other mental health disorders. Whetten et al, 2005 reported that in South America, patients with more advanced HIV disease were those with multiple comorbidities, including mental illnesses and substance use disorders. From the same study, 23% of individuals with HIV had mental illness and substance abuse symptoms.

Ettener et al. 2008 demonstrated that triply diagnosed populations showed less use of professional health care than those with a single diagnosis of HIV. A possible explanation for this could be a lack of facilities that provide integrated services addressing these three diagnoses. Another explanation could be that a triple diagnosis could worsen patient symptoms due to the neurocognitive strain the nervous system is burdened with, i.e. by experiencing HIV, mental illness as well as substance abuse. All three of these conditions are known to possibly cause neurocognitive decline and thus when combined, could be more likely to lead to a more severe neurocognitive disorder. This leads to less ability to seek out health care, fear of seeking healthcare due to the illegality of substances of abuse, missed appointments, loss of work opportunities, poor impulse control, and many other sequelae.

For those who are able to follow up, the individual clinics could also be putting strain on the patients with multiple appointments. The overall outcome is likely to be less use of these resources. However, dual diagnosis clinics (mental illnesses and substance misuse or mental

illnesses and HIV/AIDS) are developing and have proven to be effective thus far in the South African health systems (Jonsson et al, 2011).

The World Health Organization's (WHO) (2001) fundamental health care recommendations include integration of health services, with mental health included. Mental disorders and other chronic illnesses can be highly comorbid and occur over long durations of time, hence they require ongoing care and monitoring. Therefore, integrating care for these chronic illnesses improves their management and reduces disability. The presence of comorbidities results in significant decline in socioeconomic opportunities (WHO, 2001).

According to WHO (2001), integrated care is cost-effective and improves accessibility to high quality health services. These three inter-dependent disorders could therefore be more effectively managed through integrated services, which are currently uncommon in our health system in South Africa.

2.7 Summary

Research has demonstrated a high prevalence of mental illnesses, substance use disorders and HIV/AIDS individually, their co-occurrence as dual diagnoses and the impact of each disorder on the health system. There is however, limited data available on the three diagnoses occurring simultaneously in our setting. WHO'S Department of Mental Health and Substance Abuse (2001) stated that 'from both a policy and clinical point of view', patients with a triple diagnosis are an important population. Therefore, one can only extrapolate the burden imposed on the health system due to high prevalence of HIV/AIDS with co-occurring mental illnesses and substance use disorders. The use of substances results in multiple relapses due to non-adherence and treatment dropouts, as well as resistance to treatment and high rates of opportunistic infections specifically in PLWHA (Mane et al, 2015).

This study aimed to estimate the frequency of positive urine drug tests among patients with HIV/AIDS and a mental disorder, and includes description of their socio-demographic profiles.

We postulated that there is a high rate of substance use, particularly cannabis, in patients with a dual diagnosis (HIV/AIDS and psychiatric illness) at Luthando Neuropsychiatric clinic. The study objectives were as follows:

1) To determine the number of HIV positive, psychiatric outpatients who screen positive on a urine multi-drug screen at one or more Luthando clinic visits during the six-month period of study;

2) To determine which substance is the most common substance of abuse recorded on a urine multi-drug test;

3) To describe and compare socio-demographic profiles and clinical characteristics of patients who screen positive and who screen negative on a urine multi-drug test.

CHAPTER 3 METHODS AND MATERIALS

3.1 Study design and Study Environment

A retrospective, descriptive study was conducted at the Luthando Neuropsychiatric Clinic (Luthando), Chris Hani Baragwanath Academic Hospital (CHBAH). This is an outpatient's clinic that caters for the population of Soweto, Johannesburg, South Africa, which is estimated at 1.3 million (Jonsson et al, 2011). It is a specialized, dual diagnosis clinic, treating patients with HIV and a psychiatric illness. The Luthando clinic is run by psychiatrists and HIV specialists. There are also trainee psychiatrists who rotate through the clinic as part of their training. The clinic has a complementary team of psychologists, occupational therapists, nurses and social workers.

3.2 Study Population

Adult psychiatric patients who are HIV positive are referred to Luthando clinic after a confirmatory positive HIV test (HIV ELISA). A urine multi-drug test (One step Rapid test-Future) is done routinely at every clinic visit on all patients. A total of 350 patient files were reviewed. This was the number of patients that attended the clinic during the six-month study period.

3.2.1 Inclusion Criteria

- Outpatients treated at the Luthando Clinic from 1st January 2014 to 30th June 2014.
- Patients with a dual diagnosis (any psychiatric disorder and HIV/AIDS confirmed by HIV ELISA).

Patients aged 18 to 65 years.

3.2.2 Exclusion criteria

- Patients aged less than 18 years and above 65 years**.** Although there were no patients found above the age of 65 years, these were excluded as we did not want a confounder of neurocognitive disorder.
- Patients with incomplete records**.**

3.3 Data source

Data was collected from the clinical records of all out-patients who attended the Luthando clinic between 1st January 2014 and 30th June 2014. A record sheet with demographics and clinical variables was completed for each patient and entered into a database (Tables 3.1 and 3.2) [See Appendix 1. Data Collection Sheet].

Table 3.1 Demographic variables

Demographics	Age in years
	Gender
	Highest level of education (HLOE)
	Employment Status
	Marital Status

Table 3.2 Clinical variables

Psychiatry diagnosis
Outcome of multi-drug urine test (MDUT)
o If positive, type and number of substances identified
Number of MDUT tests conducted over study period
CD4 count (a 1-year time period from appointment date with positive urine MDUT was included)
Viral load at time of MDUT
If not available, Viral load within 1-year period from time of appointment with positive MDUT results
Antiretroviral Treatment prescribed.
If on ART, duration of current regimen and whether regimen has been changed in the past

3.4 Data analysis

A statistical software programme SAS version 9.4 for Windows was used to carry out analysis of data.

Quantitative descriptive analyses were compiled according to the two categories of socio-demographic and clinical variables. Variables were summarised using frequencies, percentages, means, medians and interquartile ranges.

For the prevalence of patients with a positive MDUT, based on a worst-case (for sample size) estimate of 50%, 5% precision and the 95% confidence level, a sample size of 385 would be required. However, only 350 participants attended the clinic during the study period. The actual sample size of 337 due to files being excluded corresponded to a precision of 5.3% (rather than 5.0%), which was adequate.

Sample size for prevalence was determined using the formula:

$$n = \frac{Z^2 P(1-P)}{d^2}$$

Where
n = sample size,
Z = Z-statistic for the chosen level of confidence,
P = expected prevalence or proportion
d = precision

For association between the positive/negative MDUT outcome and the other study categorical variables, we used mostly chi-square (X^2) tests, predominantly with two categories (MDUT outcome) x two categories (other study variable). For the determination of small, medium and large effect sizes with 80% power at the 5% significance level, sample sizes of 785, 87 and 31 were required; we however typically aimed for at least the detection of medium effect size. The actual sample size of 337 patients was thus adequate for this objective. Fisher's exact test was used for 2 x 2 tables or where the requirements for the X^2 test could not be met. The strength of the associations was measured by Cramer's V and the phi coefficient respectively.

The relationship between age, CD4 count, duration on ART and a positive/negative MDUT outcome was assessed by the independent samples t-test. The strength of the association was measured by the Cohen's d.

3.5 ETHICAL CONSIDERATIONS

Permission to conduct the study was granted by Chris Hani Baragwanath Hospital's CEO, as well as the psychiatric department. Clinical records were the exclusive source of information for the study. Patients' hospital numbers were assigned reference numbers on a sheet and these were used to unlock patient's clinical records. No patient's names or any other additional information was used to identify patients, hence confidentiality was maintained. Ethical clearance was obtained from the Human Research Ethics Committee of the University of Witwatersrand Ethics (Protocol number: M160606.) [See Appendix 2 for Ethics Clearance Certificate].

CHAPTER 4 RESULTS

4.1 Demographic characteristics

There were 350 patients seen at the clinic within the study period and therefore 350 files were available for review. Thirteen files had incomplete data (i.e. most information required on clinical variables and demographics was missing) and hence these files were rendered unusable, which reduced the sample size to 337 files (Figure 1). Of these 337 individuals, 228 were females (67.7%) and male participants accounted for 109 (32.3%). The median age (range 18 to 65 years) was 47 years with IQR=12 (IQR=46-34). The majority of participants were single (62.6%), followed by those married, estimated at 18.7%. Over three quarters of the participants were unemployed (79.2%) and most participants had a secondary school level of education (43.6%).

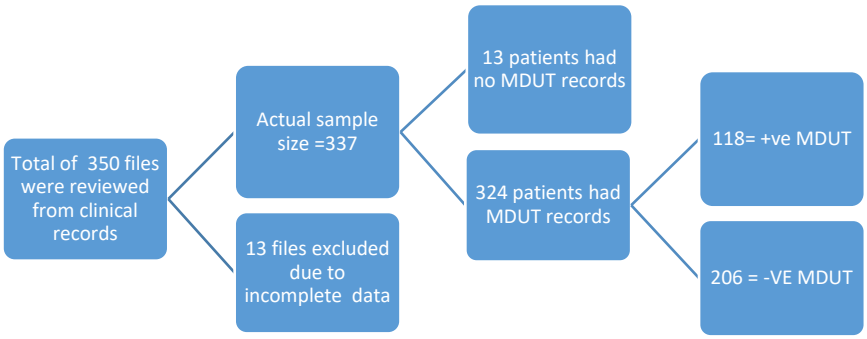

Figure 1 Breakdown of sample demographics

Table 4.1 Socio-demographic characteristics of patients (n=337)

Variable	
Age, median (IQR)	47 (12)
Gender, n (%)	
Female	228 (67.7%)
Male	109 (32.2%)
Marital Status, n (%)	
Single	211 (62.6%)
Married	63 (18.7%)
Divorced	25 (7.4%)
Widowed	18 (5.3%)
Unknown	20 (5.9%)
Education, n (%)	
Primary	128 (40.0%)
Secondary	147 (43.6%)
Tertiary	18 (5.3%)
None	8 (2.4%)
Unknown	36 (10.7%)
Employment, n (%)	
Unemployed	267 (79.2%)
Employed	48 (14.2%)
Unknown	22 (6.5%)

4.2 Prevalence of positive MDUT

The total number of patients with MDUT results was 324 because 13 patients did not have recorded MDUT results. From those with records, 118 participants had a positive MDUT at least once during the study period. The prevalence of a positive MDUT during the study period was 36.4% (Figure 1).

4.3 Clinical Characteristics

Clinical variables recorded included the type of substance of abuse, number of MDUT's performed on each patient, CD4 counts, VL at time of MDUT, VL (1-year time period from clinic visit with positive urine MDUT), ART use and psychiatric diagnoses.

4.3.1 Substance of abuse

The most common substance of abuse, as recorded from the 118 patients with positive MDUTs, was cannabis at 94.9%, followed by opiates at 21.2%. (Figure 2).

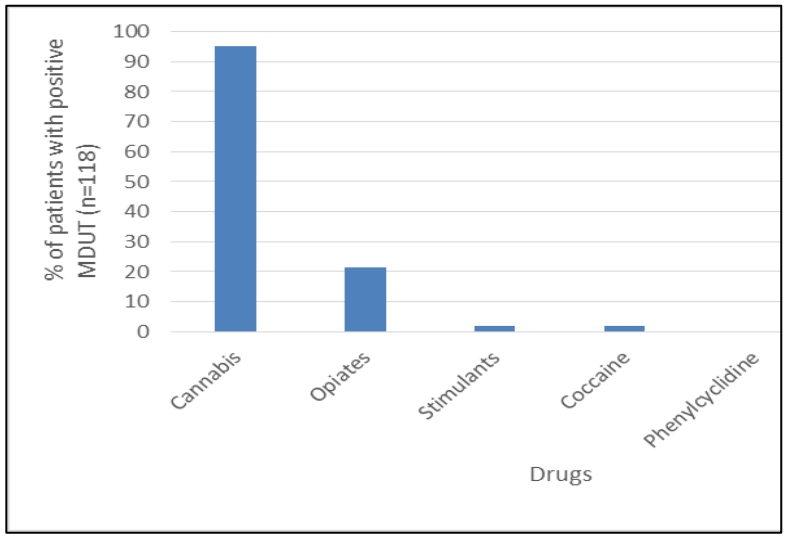

Figure 2: Prevalence of Drugs of Abuse detected by MDUT

4.3.2 Multi-Drug Urine Tests

The maximum number of multi-drug urine tests which could be conducted per individual within the study period was approximately six (one test per visit occurring once a month within a six-month period). There were 324 positive MDUTs in total throughout the entire six-month period. The graph below (Figure 3) depicts the range of urine drug tests conducted on each participant during the study period.

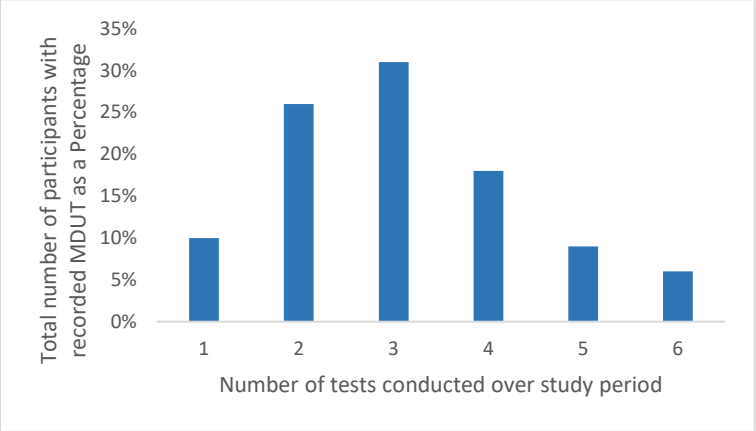

Figure 3: Number of MDUT's conducted on each patient over study period

4.3.3 CD4 counts

Amongst the 337 participants, only five (1.5%) had CD4 counts below 50 cells/mm^3, 53 (15.7%) patients had CD4 counts between 51-200 cells/mm^3 and majority of CD4 counts were above 200 cells/mm^3, accounting for 279 (82.8%) patients.

4.3.4 Concurrent Viral load

There were 241 patients who had a viral load done at the same time as a multi-drug urine test during the six-month study period. Just over half (51.0%) of these patients were virally suppressed.

4.3.5 Viral load (within 1-year time period)

Not all participants had a viral load done at the same time as the urine MDUT. Thus, a time period was chosen in which a viral load could have been done. This period was at any point during the study period and at any time point up to six months prior to the study period, ie June

2013 - June 2014. This was chosen because a viral load is supposed to be drawn once a year according to the South African DOH guidelines. The group included all viral loads collected during this time, even if it was at the same time as the MDUT. A total of 324 patients had a viral load present at any time within this one-year period. 183 (56.5%) of these patients were virally suppressed and 141 (43.5%) were not virally suppressed, where viral suppression is defined as VL<50 copies/ml and/or Lower than Detectable (LTD), depending on the machine used.

4.3.6 Patients on Anti-retroviral treatment

There were only two patients out of 337 participants who were not on Anti-Retroviral treatment within the study period and the reasons were not documented in these patients' files. Among patients on ART, 41 (12.2%) were on 2nd line regimen ART. Reasons for this included a previous history of immunological and /or virological failure or changing regimen due to adverse effects of prescribed drugs.

4.3.7 Psychiatry Diagnoses

The most commonly recorded psychiatric diagnosis among the 337 participants was Bipolar Disorder due to Another Medical Condition (AMC), specifically HIV, with 249 (73.9%) patients having this diagnosis. This was followed by Bipolar Disorder, with 18.4% patients receiving this diagnosis. Psychiatry patients can have differential diagnoses i.e. more than one diagnoses, while clinicians are still determining a primary disorder or where the ultimate diagnosis is not clear, hence the total will not add up to the total number of participants. The graph below (Figure 4) depicts the range of psychiatric diagnoses.

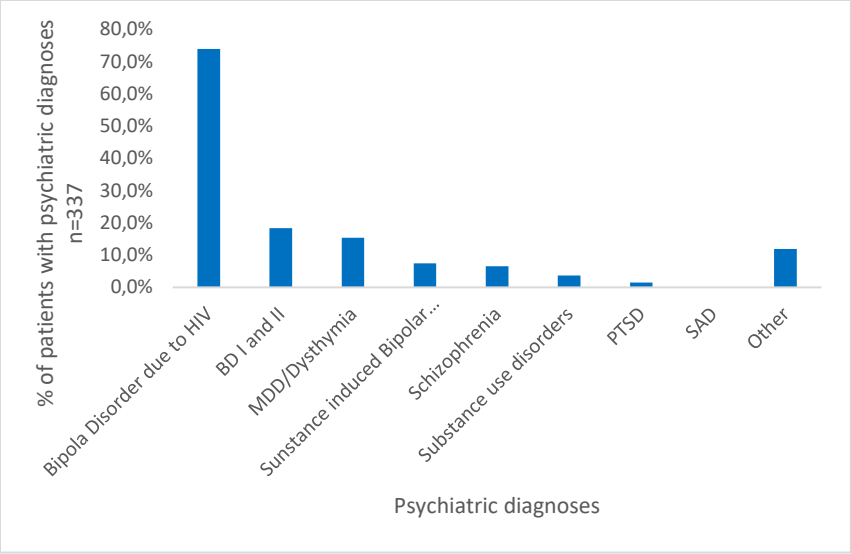

Figure 4: Psychiatric Disorders diagnoses at Luthando Clinic during study period

4.4 Associations between positive/negative MDUT outcome and other study variables

Due to the small group sizes, the following groups were combined or created:

- HLOE: None and primary were combined.
- Some psychiatric diagnoses: bipolar I and II disorders were combined.

4.4.1 Association between MDUT outcome and Age

The mean age of the patients with a positive MDUT (38.7y; sd=9.2y) was lower than the mean age of patients with a negative MDUT (41.1y; sd=9.6y) (t-test; n=324; p=0.030). The effect size was small (Cohen's d=0.25).

4.4.2 Association between MDUT outcome and gender

There was a significant association between MDUT outcome and gender (Fisher's exact test; n=324; p=0.0001; phi coefficient=0.22). The proportion of positive tests was greater amongst males (51.4%) than females (29.2%). The graph below (Figure 5) describes this relationship.

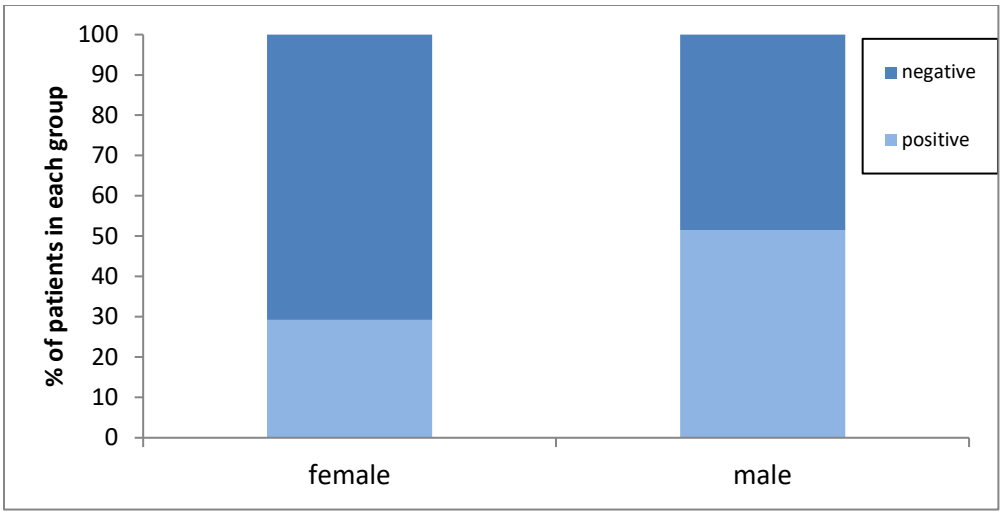

Figure 5: Distribution of positive and negative MDUT tests by gender

4.4.3 Association between MDUT outcome and current viral load (VL)

There was a significant association between MDUT outcome and current VL (VL done at the same time as the MDUT) (Fisher's exact test; n=237; p=0.010; phi coefficient=0.17). The proportion of positive tests was greater amongst those with an unsuppressed VL (44.8%) than amongst those with a suppressed VL (28.1%) (Figure 6).

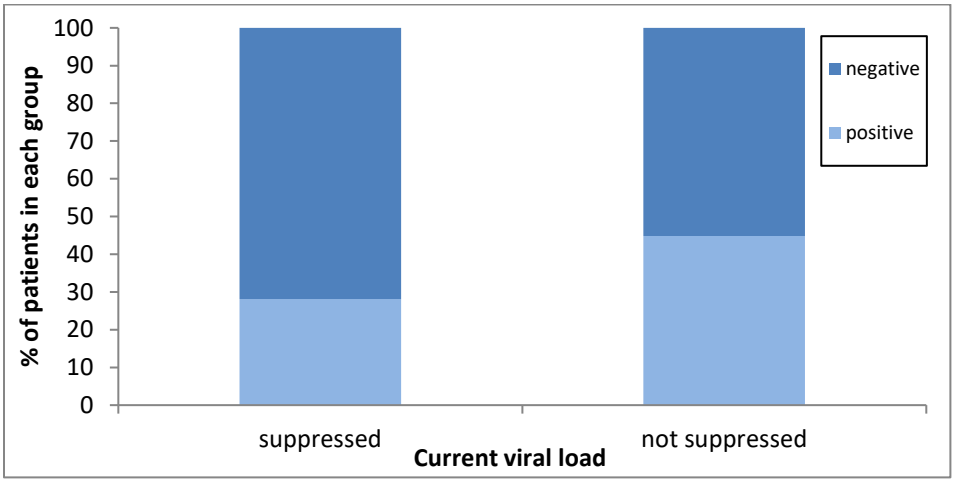

Figure 6: Results of MDUTs outcome among patients with either suppressed or unsuppressed viral load (current).

4.4.4 Association between MDUT outcome and Viral Load within 1-year time period

There was also a significant association between MDUT outcome and 1-year VL (Fisher's exact test; n=324; p=0.0017; phi coefficient=0.18). The proportion of positive tests was greater amongst those with an unsuppressed VL (46.1%) than amongst those with a suppressed VL (29.0%) (Figure 7).

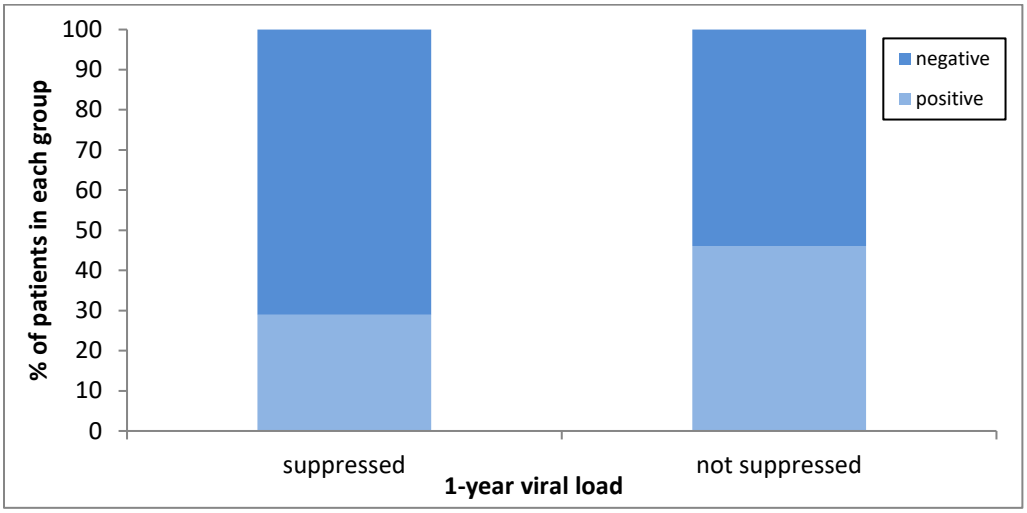

Figure 7: Results of MDUTs outcome among patients with either suppressed or unsuppressed viral load within 1-year time period

4.4.5 Association between MDUT outcome and duration on antiretroviral treatment (ART)

The median duration for the entire population on treatment was 50 months. The median duration on treatment for patients with a positive MDUT (34 months; IQR =10-57months) was lower than the median duration on treatment of patients with a negative MDUT (46 months; IQR 21-68 months) (Wilcoxon rank sum test; n=322; p=0.036). The effect size was small (r=0.12).

4.4.6 Association between MDUT outcome and psychiatric diagnoses

There were significant associations between MDUT outcome and diagnoses of major depressive/dysthymic disorder, bipolar disorder due to substances, and substance use disorder (Fisher's exact test; n=324; p=0.0038, p<0.0001, p=0.0006 respectively; phi coefficient=0.12, 0.23, 0.20, respectively). The proportion of positive tests was greater amongst those with these diagnoses (50.0%, 80.0%, and 90.0%, respectively) than amongst those who did not have the diagnoses (33.9%, 33.6%, and 34.7%, respectively).

4.4.7 Association between MDUT outcome and number of psychiatric diagnoses

There was a trend towards an association between MDUT outcome and number of psychiatric diagnoses (Fisher's exact test; n=324; p=0.014; phi coefficient=0.14). The proportion of positive tests was greater amongst those with 2-3 diagnoses (46.2%) than amongst those with only one diagnosis (31.7%) (Figure 8).

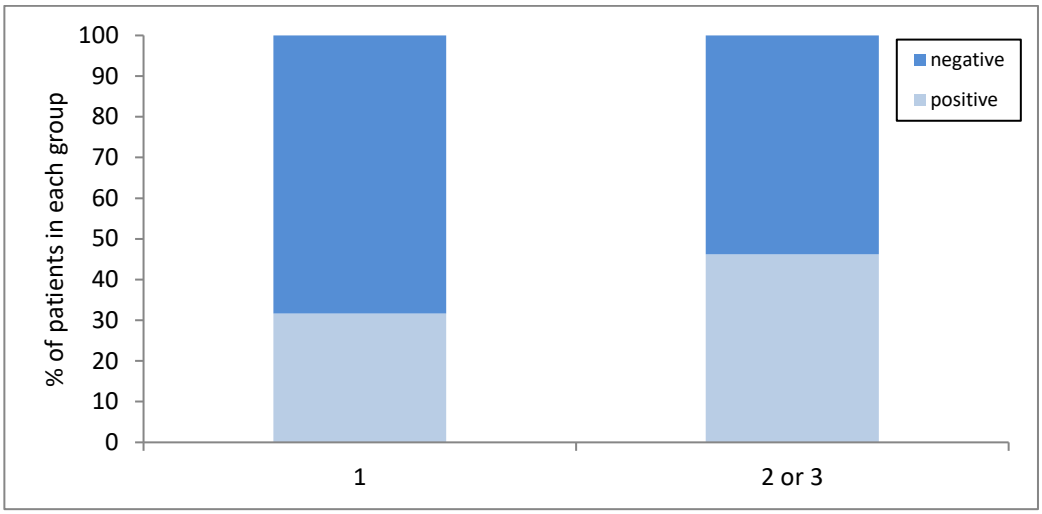

Figure 8: Comparison of MDUT outcomes among patients with one or more psychiatric diagnoses

There was no significant association between a positive/negative MDUT outcome and the following categories:

- Relationship status
- HLOE
- Employment status
- Number of MDUTs within the study period
- Median CD4 count
- Previous change of ART regimen (among those on treatment)

CHAPTER 5 DISCUSSION

The current study demonstrated a high prevalence of positive MDUTs among outpatients attending Luthando clinic. Cannabis use was the most common drug of abuse [94.9% (n=118)]. There were significant associations found between younger participants of male gender and positive MDUTs. Unsuppressed viral loads were mostly found among participants with current substance use/misuse, as evidenced by a positive MDUT. There were some specific psychiatric disorders which were significantly associated with positive MDUT results. Shorter duration on ART post initiation was associated with a greater likelihood of positive MDUT results, which may have indicated inadequate health education due to short time in contact with the health system. In some individuals, this may have meant insufficient time to have processed their HIV status and possibly self-medicating the stress of the diagnosis with substances. Another important factor may have been a compounding effect of each disorder on cognition which may have made it difficult for patients to make good decisions and instead use substances.

5.1 Demographic profile

The majority of patients were females (67.7%) compared to males (32.3%). Luthando is a specialized dual diagnostic clinic, with HIV as one of the comorbidities. Females have a higher HIV infection rate than males. Beyond known biological factors contributing to females being more likely to be infected, poorer economic backgrounds of these patients may also play a role in their risk of acquiring HIV, with the known South African odds ratio of female to male of 1.5:1 (Shisana et al, 2012). Epidemiological data have further shown that women are more health-seeking than men. Thus, this finding was unsurprising in the setting of the study.

The majority of participants (both males and female) were in the age range of 35 to 55 years. This is different to the expected profile of relatively younger generations with substance use/misuse. Younger age is also associated with the onset of primary psychiatric illnesses and promiscuous behaviours that are likely to expose youth to sexually transmitted illnesses e.g. HIV (Shisana et al. 2012). The Luthando clinic is not set up for substance abuse specifically, hence the age group may be in keeping with its primary goal of treating HIV and mental illnesses. The older age profile might also be partially explained by the fact that secondary psychiatry illnesses (e.g. bipolar disorder due to HIV) can be a later manifestation of the HIV disease in this type of population (Bing et al. 2001). The State of Mental health and mental health services (2013) have

also indicated that late presentations may be attributed to the stigma and discrimination that people with mental illnesses are often subjected to within their communities.

The majority of participants within the study population were single (62.6%) and unemployed (79.2%). This is in keeping with similar studies conducted among people with comorbid HIV and substance use disorders. Kader et al. (2012, 2014) demonstrated that the majority of people with both HIV and substance use disorders are young Africans who are single and living in low socio-economic environments. The catchment area of the hospital is predominantly a low socioeconomic location, which may address the low level of education as a huge number of patients had only a primary school education and also explains the high rates of unemployment (Jonsson et al, 2011). The Department of Health in 2013, also reported on significant distress and impairment in function linked to mental illnesses. Thus, such individuals are unable to function effectively in open labour markets, contributing to the high percentages of unemployment in these vulnerable groups of individuals.

5.2 Common substance(s) of use and testing

Substances of abuse were identified by use of a MDUT kit. The kit could only test for the presence of five groups of drugs; namely: cocaine, cannabis, opiates, phencyclidine and methamphetamines. The pick-up rates differ according to the different half-lives of each drug. For example, cannabis has a longer half-life than cocaine, hence it had a higher detection rate in urine and blood samples, than the other aforementioned drugs and therefore accounts for the high rates of cannabis use found in this study. Most individuals had at least three tests done within the study period; however, the reason behind this was not ascertained. The reasons for these frequent visits are not known, but these may range from serious psychopathology requiring frequent monitoring to reviewing of patient treatments, including positive MDUT tests found during the visits.

The most common drug of use/abuse was found to be cannabis; 95% of tests detected this substance. According to the epidemiology of drug abuse treatment studies in SA (2010), the most frequent substance of abuse in the mentioned study was alcohol (51%) followed by cannabis (21%), cocaine (9.6%), heroin/opiates and methamphetamine (7.9% and 4.5%, respectively) (Ramlagan et al, 2010). It must be noted that these results were from patients in rehabilitation centers, where individuals may only have substance use/misuse disorders. Our study results

found high rates of substance use which is in keeping with the high rates referenced in the literature. However, our rates were at least double those in literature. For example, from our study, the prevalence of opiates was 21% compared to 7.9% in other South African literature (Ramlagan et al, 2010) and this may be explained by the existing comorbidities of each patient, including other chronic medical illnesses, which may act as perpetuating factors. Mane et al, (2015), cited that a high rate of substance abuse was most probably due to the patient self-medicating their chronic illness, especially psychiatric illnesses.

According to the Global Drug Survey (2012, 2017) findings, cannabis was among the top ten of substances of abuse internationally, with a lifetime prevalence of 77.8%. Peltzer et al, 2007 also described cannabis usage trends in SA and has demonstrated that cannabis is the most illicit substance used in the general population.

The high prevalence of cannabis in this study and in SA may also be explained by its high availability in townships. Cannabis is readily available as it is produced locally and from neighboring countries, such as Swaziland and Lesotho (UNODC, 2012). The price of the drug is fairly affordable and can be purchased from any place, be it in the streets and the so called "spaza" shops in townships (Leggett et al. 2002). Again a huge proportion of the patients were on ARTs, mostly Efavirenz (EFV) combinations, and with the controversy that EFV may cause false positive urine cannabis results (Koh et al. 2012), this may also have contributed to the high rates of positive urine cannabis results in our study population.

Opioid use was in the top ten of drugs of abuse globally as well, with a lifetime prevalence of 16.0% (Global Drug Survey 2012, 2017). It is however important to note that positive opioids results could also be iatrogenic if patients are on pain medication that contain opioids. The SACENDU (2017) project described an alarming increase in opioid use in different SA provinces. In 2011, the prevalence of opioid users nationally was as followers: the Western Cape (17%); Kwa-Zulu Natal (31%); Mpumalanga and Limpopo (28.3%) and Gauteng (12.7%). From our study, opioid use was the second most commonly used drug at 21.2%. The high rate, while in line with afore-mentioned research data, may also be explained by the fact that heroin is easily accessible and often mixed into cannabis (SAAMS ,2015).

5.3 MDUT and Demographic profile

Although our study population predominantly comprised of an older age range (35-55 years old), there was a strong association of substance use/misuse with younger age than those of older age generally (median age of 38 years). This may still be in line with countrywide data showing stronger links of substance use/misuse predominantly in lower ages as opposed to older counterparts within a particular population. The South African Stress and Health study (SASH, 2009) has shown high prevalence of substance use among young people (18-34 years old) and demonstrated high-risk behaviours in this population. Shisana et al, 2012 had linked the negative consequences of substance use in youth with violence, aggression and promiscuous behaviours resulting in HIV/AIDS infections.

A strong association between male gender and positive MDUT (51.4%) was found in our study. This is in keeping with the findings from a study in the United States, the Substance Abuse and Mental Health Services Administration study (SAMHSA, 2014), which found that illicit substance use was more common in young male participants than in females. Locally, William et al. 2008 and Weiss et al. 2015 also found that the high prevalence of illicit substances was consistently found in young males. Substance use has also been shown to have the highest prevalence in unemployed individuals residing in semi-or urban regions according to Herman et al, 2009. Our study however did not elicit any direct association between unemployment and positive MDUT tests, possibly because there was such a high rate of unemployment in our study sample.

5.4 MDUT and viral load suppression.

In our study, 99.4% of patients were on ART and 12.2% of these patients were already on a 2nd line treatment regimen. A total of 241 individuals from the sample (337) had a viral load documented at the same time a MDUT was done and in those with a positive MDUT, 44.8% were not virally suppressed.

There are several studies internationally which compared the relationship between a positive drug test and viral load suppression. The majority of these studies looked at the adherence to ART and have consistently found poor adherence associated with a positive drug test. In an American study by Arnstern et al. 2002, a mean overall adherence of only 53% was found from electronic monitors that were used in measuring adherence on ARTs in 85 HIV-infected drug

users. Rangarajan et al. 2016 in Vietnam found similar results, where almost half of the study participants were non- adherent to ART, and this was associated with a positive MDUT. Some European studies that looked specifically at cannabis as the substance of use, (Ware et al, 2003) found a threefold increase in non-adherence in HIV/AIDS patients who also used cannabis. Equally well, the study was also able to demonstrate the impact of substance use on adherence.

From our study, we found a significant association between MDUT outcome and viral load. This outcome was measured in two cases: (1) in patients with both viral loads performed at the same time with MDUT and (2) those with a viral load within a designated year period. The proportions of positive tests were greater in both cases, and amongst those with unsuppressed viral loads (44.8% and 46.1%, respectively). With the increase in prevalence of substance use in HIV patients, Kader et al. 2014 emphasized the impact of non-adherence to ARTs and the consequences thereof, including sub-optimal health with associated HIV-related complications amongst this group of individuals.

Patients who were on ART for a longer duration had fewer positive MDUTs. The median duration on treatment among patients with a positive MDUT was 34 months, as opposed to 46 months in those patients with a negative MDUT. There is no literature specifically looking at the duration of ART as a factor in substance use, but we hypothesize that the longer an individual is on treatment, the greater the chance of him/her accepting the diagnosis and abstaining from self-medicating practices (by use of illicit substances). Impulse control as a feature of cognition may also be an important factor in the decision to abstain from these illicit substances.

5.5 HIV, MDUT and psychiatry diagnosis

The results obtained from the study showed that the most commonly recorded psychiatric diagnosis was mood/psychosis (bipolar disorder) due to another medical condition (HIV) (73.9%), this however seemingly under-represent the number of psychotic disoders where the two disorders (mood and psychosis) are combined as bipolar disorder as depicted in figure 4. This was followed by bipolar disorder I and II collectively (18.4%). From our study, significant associations were established between positive MDUTs and diagnoses of major depressive/dysthymia disorder and bipolar disorder due to substance use. In contrast, Weich et al. 2009 had reported the greatest link being between primary psychotic disorders, namely,

schizoaffective and schizophrenia disorders and substance use/misuse. The least association of positive MDUTs was reported in major depressive disorder and adjustment disorders.

There are strong associations between substance use, specifically cannabis and psychosis from large cohort studies done in the Netherlands and Sweden (Koning et al, 2010). Likewise, Weich et al, 2009 results showed strongest association with cannabis use and psychotic disorders (schizoaffective and schizophrenia) but not with unipolar mood disorder.

Our results have shown the opposite compared with Weich et al (2009) findings. In our study, we found a strong substance use association with MDD. Satre et al, 2011 in a more similar study of patterns of substance use in depressed elderly psychiatric outpatients revealed a significant association between depression severity and cannabis use specifically. Hence while cannabis is mostly associated with psychosis, there is possibly evidence that some people may also self-medicate with it in depression, which may be the case in our setting. Nonetheless the results obtained from the study, provided a compelling evidence of an association between psychopathology and substance use (Sepehmmanesh et al, 2012; Miller et al, 2009).

Another interesting finding was that, none of the patients in the study was diagnosed with HIV-associated neurocognitive disorders (HAND) despite known alarmingly high rates in both international and South African populations (Joska et al, 2016) . Although the exact reasons were not picked up by our study, we speculated that our clinicians mainly tend not to screen for HAND.

We were able to establish an association between MDUT outcome and number of psychiatric diagnoses (i.e. two or three psychiatric diagnoses in an individual). There is support for a biological contribution to shared vulnerability to major psychiatric disorders (Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium, 2015). Furthermore, the Gross-Disorder Group of the psychiatric Genomics Consortium, (2013), identified common single nucleotide polymorphisms which collectively influenced liability of some major psychiatric illnesses, namely bipolar disorders, major depressive disorders, schizophrenia, autism spectrum and attention deficit and hyperactivity disorders. These illnesses are likely to be sharing the same genetic etiology; hence associations of substance use to one mental disorder might be linked to others sharing the same genetic etiology.

CHAPTER 6 LIMITATIONS

The research study hypothesized that a significant level of substance use, particularly cannabis, would occur in patients with a dual diagnosis (HIV/AIDS and mental illness). Cannabis was found to be the most commonly used substance in the study, with a large number of participants using substances. However, there were significant limitations associated with the research. Firstly, it is unfortunate that the study, in part due to its retrospective design was unable to describe the use of alcohol which from other multiple studies in the same field, it has been recorded as the most prevalent substance of abuse in this population.

The multi-drug urine test kit used to test for drugs of abuse are prone to false positives and false negative results and may not be an accurate reflection of the data. As such, it requires the use of gas chromatography or mass spectroscopy to confirm the validity. A positive multi-drug test does not necessarily mean a patient has a substance use disorder, but simply means that one has used a specific drug around the time of being tested. A more definitive quantitative serum testing may have been more beneficial in yielding the dosage of drugs used among other results including detection of alcohol.

The interpretation of results was affected by a small sample size with a precision of 5.3% instead of 5% that contributed to a slightly wider confidence interval. This forced us to combine some clinical and demographic variables so that statistical analyses could be performed. For example, psychiatric diagnoses like bipolar I and II disorders had to be combined. The sample size however was still rendered statistically adequate.

The study was a retrospective record review which can be prone to missing data. There were 13 patients who did not have MDUT records, thus affecting the outcome of the analyzed results. Some clinical features also had to be regrouped and clear associations between positive MDUT results and those individual variables could not be made (e.g. employment status and positive MDUT results).

The association of unsuppressed viral load and a positive MDUT, which was statistically significant, must be interpreted with care. There are a number of other factors which can contribute to virological failure, including non-adherence to ART for reasons other than

substance use to an individual's response to a specific ART regimen. However, substance use is a strong contributing factor, as previously proven in prior studies.

The fact that the study was conducted at a tertiary-level HIV clinic might have contributed to the most common psychiatric diagnosis among all participants being bipolar disorder due to HIV. This might have led to a biased result when compared to primary health care facilities. Therefore, results obtained may not be generalized when applied to other populations.

CHAPTER 7 CONCLUSION

There is a high prevalence of substance use, particularly cannabis, in patients attending Luthando Neuropsychiatric clinic. This has likely had an impact on clinical outcomes of our patients. Patients with positive MDUTs were more likely to have unsuppressed viral loads. Thus, the established high rate of substance use superimposed on the already vulnerable group of individuals with dual diagnosis has serious negative health implications.

It is essential that this group of individuals be identified early during clinic visits so that they can be properly diagnosed and managed. Integration of health services to provide efficient and effective health care is important in this type of population. Dual diagnostic clinics have proven to be effective, therefore, these particular individuals may benefit from triple diagnostic facilities.

Future studies may include patients with established substance use disorders rather than just screening for substance use at a particular time point, because the disorder is more likely to be associated with poor treatment adherence and multiple comorbid diagnoses, including both psychiatric and medical illnesses. Appropriate treatment modalities need to be formulated and tested. Qualitative analyses on the understanding and experiences of patients with triple diagnoses, including their treatment preferences, will be important to improve their overall care and management.

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Appendix 1:

Data Sheet

Section 1

Identifying Number……..

Demographic Characteristics

1.1 Age in Years:

1.2 Gender:

Female	Male	Unknown
1	2	3

1.3 Marital status:

Single	Married	Divorced	Widowed	Unknown
1	2	3	4	5

1.4 Education:

None	Primary	Secondary	Tertiary	Unknown
1	2	3	4	5

1.5 Employment:

Employed	Unemployed	Unknown
1	2	3

Section 2

Clinical Characteristics

2.1 Positive Multi-drug urine test (MDUT):

Yes	No	No record
1	2	3

2.2 Positive MDUT in Question 2.1, if so what substance:

Cannabis (THC)	1
Opiates (Nyaope/heroin)	2
Phencyclidine (PCP)	3
Stimulants (amphetamine/methamphetamines)	4
Cocaine	5
Other	6

2.3 Number of tests over study period:

Total number of tests.	**1**	**2**	**3**	**4**	**5**	**6**

2.4 CD4 within one year of study Period:

2.5 Viral load available at the time of MDUT screening.

Yes	NO	Unknown
1	2	3

2.6 If Yes to Question 2.5 and MDUT is +VE;

Current Viral load:

Suppressed	**Not Suppressed**
1	2

2.7 If NO to Question 2.5 and MDUT is +VE;

Latest viral load within 1 Year of MDUT screening:

Suppressed	Not Suppressed
1	2

2.8 If MDUT is -VE;

Viral load within 1 year of MDUT screening:

Suppressed	Not Suppressed
1	2

2.9 HIV Treatment (ARTs):

Yes	No
1	2

2.10 Date started on ARTs…….

2.11 Previous change of ARTs regimen due to immunological and/or virological failure:

Yes	No
1	2

2.12 Psychiatric Diagnosis (mark all relevant boxes):

Schizophrenia	1
Schizoaffective disorder	2
Bipolar disorder 1 or 2	3
Major depressive/dysthymic disorder	4
Substance Use disorder	5
Mood/psychosis due to substances	6
Mood/psychosis due to HIV	7
Post-traumatic stress disorder	8
Other	9

R14/49 Dr Moeketsi Eliiot Khabisi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160606

NAME: (Principal Investigator)	Dr Moeketsi Eliiot Khabisi
DEPARTMENT:	Psychiatry Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	The Prevalence of a Positive Urine Multi-Drug Test among Outpatients with both HIV and Psychiatric Illnesses at Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	24/06/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Janice Buckley
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	27/06/2016

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 in Room 10004, 10th floor, Senate House/2nd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized 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 the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in June and will therefore be due in the month of June each year.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES