Tracking the next co-epidemic

The relationship between HIV and non-communicable diseases

Brief 6

Authors:
Percept Actuaries and Consultants

31 August 2020

31
08
20

Research briefs on non-communicable diseases in South Africa

We have developed a series of briefs aiming to explain, explore and quantify the burden of non-communicable diseases (NCDs) in South Africa. Throughout the briefs, we draw together both existing quantitative data as well as emerging qualitative data. The primary qualitative data presented in the form of vignettes, has been collected by Dr Beth Vale, through in-depth ethnographic research. These briefs are timely, given the rising global burden, and particularly the rising burden in low- and middle-income countries (LMICs), of NCDs. Given South Africa's high prevalence of HIV, there has also been a recent focus on the link between HIV and NCDs as the population living with HIV grow increasingly older with the successful uptake of antiretrovirals. An ageing population is more at risk for NCDs as we will explain in our briefs. As we move towards universal health coverage (UHC) it is imperative that we understand the needs of our population now and how these may change going forward. We have produced twelve briefs in this series.

This work was funded by the following partners, although the views are the authors' own:

- Actuarial Society of South Africa (ASSA): ASSA has an interest in being part of the development of high-quality evidence to support resource allocation and decision-making and the interplay between the supply and demand sides of the health system

- RGA Reinsurance Company of South Africa Ltd (RGA): RGA has an interest in the ways in which life insurance can be responsive to the changing burden of disease and the ways in which we can use data to drive decision-making

- Board of Healthcare Funders (BHF): BHF has an interested in an affordable, accessible, and high-quality private health sector.

Introduction

The early story of HIV infection was that it was a death sentence. An HIV infected person would eventually develop AIDS and their life would be cut short. Combination antiretroviral treatment (ART) has managed to improve the health of people living with HIV (PLWHIV), extend their lives and substantially reduce the risk of transmission. This has increased the life expectancy of PLWHIV, and those that enrol and adhere to treatment have a life expectancy not much shorter than people without HIV.[1] Furthermore, early initiation and adherence to treatment can suppress the viral load to an undetectable level so that an HIV infected person will not be able to transmit the virus, thereby reducing the incidence (new infections) of HIV.[2] This is referred to as 'treatment as prevention' (TasP) because by PLWHIV remaining in care and on treatment, new cases are prevented.[3]

South Africa has one of the highest adult HIV prevalence rates in the world (20.4%) and the highest number of PLWHIV in the world (7.7 million people).[4] South Africa follows the World Health Organization's (WHO) test and treat policy[5], which means that as soon as someone tests positive for HIV, they are initiated on treatment. This further improves life expectancy, decreases HIV-related morbidity, and reduces incidence of HIV in the general population.

Despite these policies, HIV still forms part of South Africa's 'quadruple burden of disease'. This refers to the

burden of HIV, NCDs, maternal, newborn and child-health related incidents, and a high prevalence of injuries from accidents and interpersonal violence[6], but it should be noted that these four disease burdens are **not mutually exclusive**. From an infectious disease perspective, the epidemiology and comorbidity of HIV and TB is well documented and widely understood, and South Africa is considered the epicentre of the HIV-TB co-epidemic.[7] However, concurrently to this co-epidemic, another has emerged – that of HIV and NCDs. The drivers of the "multimorbidity" of HIV and NCDs are multifaceted and this brief aims to estimate the prevalence of the comorbidity of HIV and NCDs, unpack how this multimorbidity has come to be and how it manifests itself in the SA context, and to understand what the implications are for the South African (SA) healthcare system.

What drives the multimorbidity of HIV and NCDs?

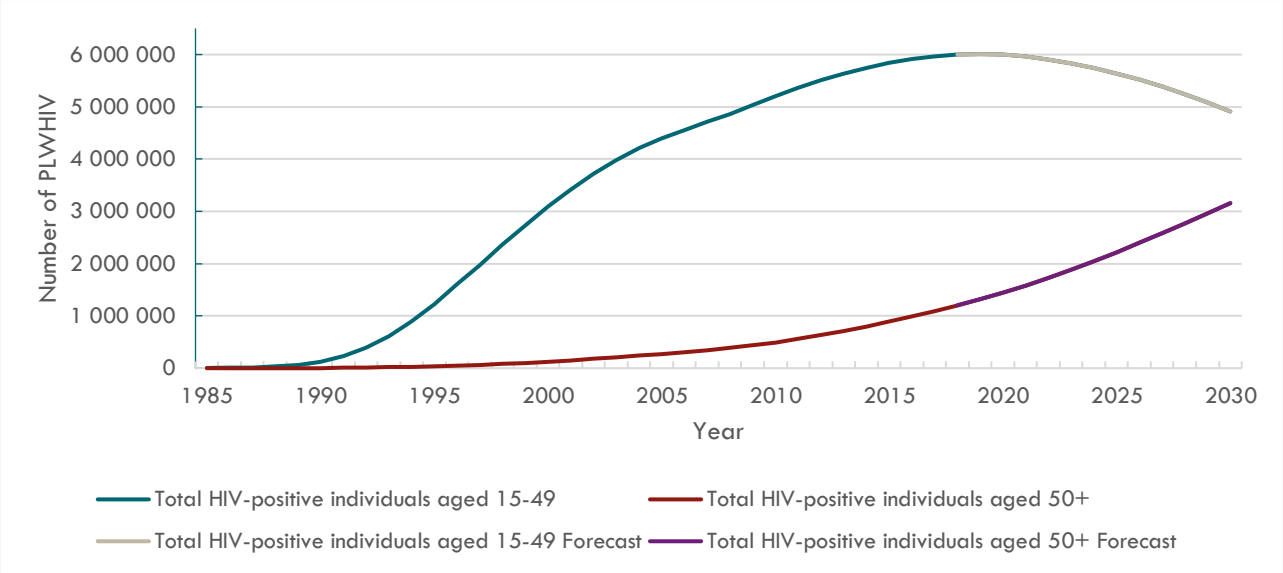
Multimorbidity refers to the presence of one or more diseases at the same time. Due to the life-extending effects of ART and the side-effects of prolonged ART use, there are often multiple illnesses which end up requiring treatment, in addition to HIV itself, in the long-term.[1] This may have an effect on the healthy aging of PLWHIV.

We discuss four channels through which NCDs develop in PLWHIV. The first two are linked to ART, through the life prolonging effects of ART and also the side effects and cumulative toxicity caused by prolonged ART use. The third and fourth relates to HIV infection itself. HIV infection has been linked to premature aging and also increases the likelihood of developing certain types of cancer.

The effects of ART: ART extends life

Public roll-out of ART in South Africa began, in earnest, in 2004. Since then, all AIDS-related deaths are a quarter of what they were at their peak in 2006[8] and the life expectancy of PLWHIV, who adhere to treatment, has increased to that comparable to those without HIV.[1] While HIV prevalence and incidence on the whole are declining, there is an increase in women between 15-24.[9] Consequently, this sub-population has become a focus point for HIV prevention and control. Meanwhile those aging with HIV, who are stable and adherent, are often neglected, despite the fact that the number of people over 50 with HIV is increasing, due to the life extending effects of ART (**Error! Reference source not found.**).[10] Although the vast majority of PLWHIV are in the 15 to 49 age group, this number is predicted to have peaked in the South African population. This means that in future years, the fastest growing population with HIV will be those over 50. The life prolonging effects of ART also have an impact on South Africa's population pyramid, moving the country away from the bottom-heavy pyramid it has previously had. The implications for this for population health and resource allocation is therefore important to analyse and forecast, particularly as the country contemplates universal health coverage (UHC).

Figure 1: HIV prevalence by age group in South Africa[9]



NCDs are considered the most important health issue for those over 60, and the aging population with HIV are not protected from this NCD "pandemic".[10] NCDs cause 55% of premature mortality (deaths occurring before the age of 70), in South Africa.[11,12]

As is the case for those without HIV, older people have a higher prevalence of NCDs such as diabetes, hypertension, chronic lung disease and cancer.[13] Therefore, as ART extends people's lifespan, it also opens them up to diseases of old age, making PLWHIV likely candidates for multimorbidity. However an Italian study of "geriatric" HIV positive individuals found that multimorbidity was more closely linked with duration of HIV infection rather than the age of the PLWHIV, so the higher prevalence of these NCDs among older PLWHIV **may not simply be a function of aging**.[14]

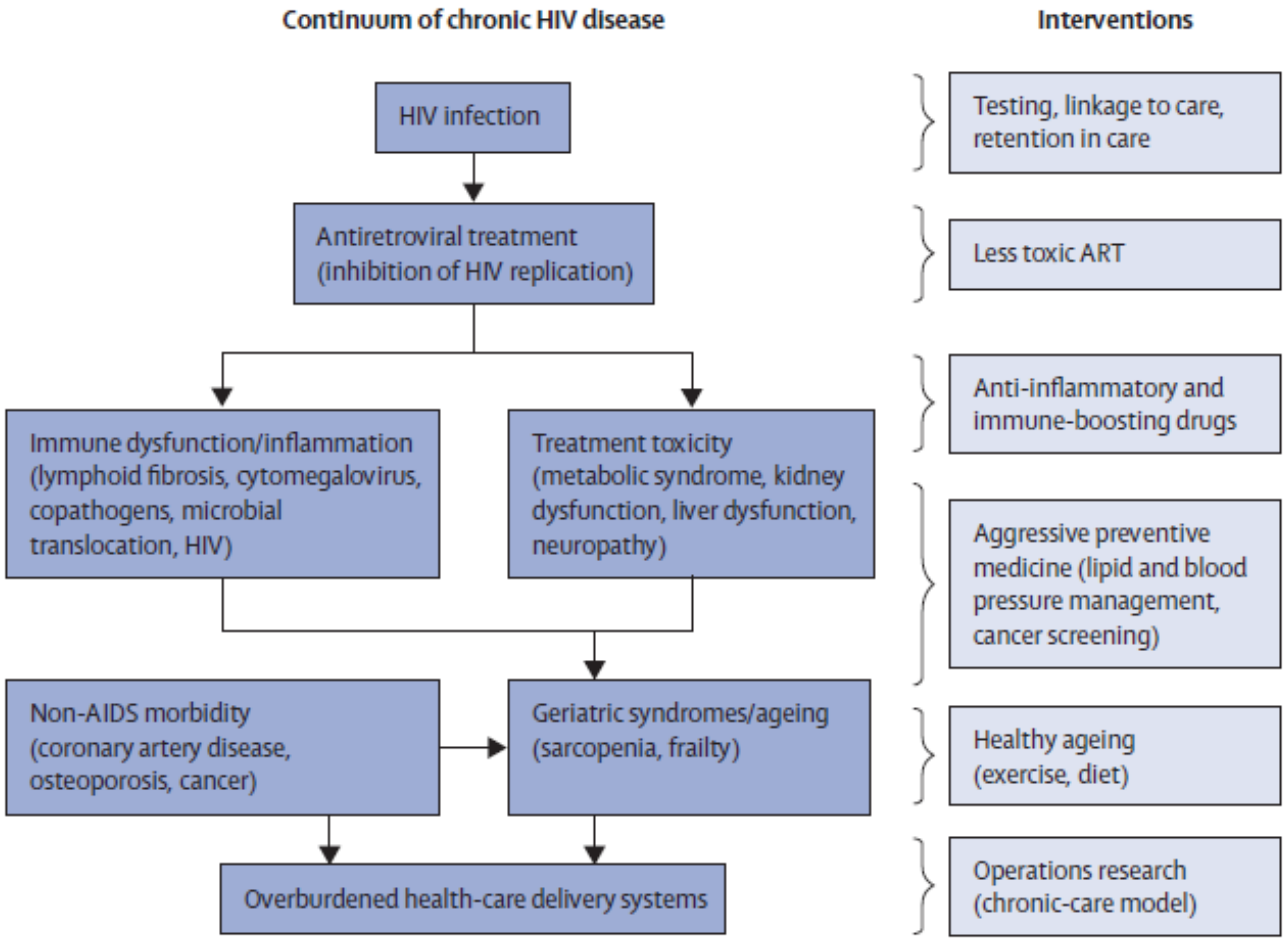
The effects of ART: ART associated with development of NCDs and NCD-risk factors

When PLWHIV are adherent on ART, viral loads are suppressed, and the person is healthier and more resilient to secondary infections. However, ART does not completely restore health. Long term exposure to ART can lead to cumulative drug toxicity, which can cause disorders of the metabolic system and end organ damage.[1,15] In recent years, it has become clear that prolonged use of ART is associated with diseases that have no direct relationship with HIV infection (referred to as 'non-AIDS morbidities'[1]).[16] These diseases include cardiovascular disease, liver disease, and non-AIDS defining cancers.[16] Systematic reviews also confirmed that PLWHIV had higher blood pressure and an increased risk of hypertension.[17] Figure 2 below shows the continuum of how chronic disease may develop in PLWHIV and the interventions which may be implemented at each stage to treat or prevent the development of these illnesses. The last intervention suggested by Deeks et al (2013) is operations research, which would help to inform the health system on how to treat and manage the ageing and

[1] AIDS defining morbidities or illnesses are diseases which are more prevalent among HIV positive people and may be an indication that they are in the more advanced stage of HIV infection called AIDS. Non-AIDS defining morbidities are those that fall outside of this category.

multimorbid population living with HIV.[1]

Figure 2: HIV Infection and Chronic Disease[1]



A side-effect of long-term ART is HIV-related fat redistribution syndromes or lipodystrophy syndrome.[18,19] This is when PLWHIV develop abnormal or excessive amount of fat, including visceral fat, in the trunk, upper back and neck. Fat redistribution syndromes resulting from long-term ART exposure are associated with many of the same NCD risks as metabolic syndrome, such as obesity (particularly fat accumulation around the waist), insulin resistance and diabetes, high blood pressure and high cholesterol.[1,18,20]

As new generations of drugs are released, these toxic side effects of prolonged exposure to ARTs are becoming fewer.[15] However, given that these drugs are taken for decades, even small levels of toxicity add up over time, therefore the treatment guidelines need to account for this and the NCD risks of the drugs prescribed.[1] PLWHIV should be regularly screened for common NCDs and their risk factors managed and counselled during interactions with healthcare providers.

Not all of the risks of developing non-AIDS morbidity can be fully attributed to ART toxicity.[1] Studies show that

PLWHIV on ART have higher levels of several different types of inflammatory markers[2] compared to individuals of similar age who do not have HIV.[1] These inflammatory markers are associated with all-cause mortality, coronary artery inflammation and atherosclerosis.[1,21]

Vignette 1: HIV and Hypertension

In June 2019, I spent a day observing consultations at a small-town primary healthcare clinic in the Eastern Cape Karoo. One of our patients was a petite woman in her fifties, who'd come to enquire about a disability grant:

'*What's wrong with you?*' The doctor asked. '*There needs to be something wrong.*'

'*I'm very sick*', she answered.

The patient, who I will call Sonnette, was HIV-positive and on ARVs, but appeared otherwise healthy.

'*But you're controlling your HIV well,*' the doctor said.

The patient was silent for a moment, while the doctor took her blood pressure. As the blood pressure monitor depressed, the doctor's expression switched from bemusement to one of deep concern:

'*Do you get blood pressure pills?*' she asked.

'*No,*' the woman answered, matter-of-factly.

'*This blood pressure is very high.*'

The diastolic reading was 130, far above the normal range (which would be below 80). The doctor grew agitated:

'*I think you must go to hospital. I'm worried you're going to have a stroke.*'

By this point, I'd seen many patients with co-morbid hypertension and HIV — one of the ways in which NCDs and infectious diseases collude. If unmanaged, the consequences of this collusion could be severe. In fact, in one municipal hospital ward, I'd even met a 44-year-old woman on antiretroviral treatment (ART) who'd suffered four debilitating strokes.

However, Sonnette was in her fifties – a testament to the victories of South Africa's ART roll-out. One primary healthcare nurse suggested to me that when HIV-positive patients had multiple conditions, HIV was prioritised:

'*When there is both HIV and hypertension, say, you focus on HIV. You almost forget about those other things.*'

Without thinking about the ways in which HIV might render patients more vulnerable to NCDs, patients like Sonnette might fall through the cracks.

The effects of HIV infection: premature aging

Given that many of the comorbidities associated with HIV infection are considered diseases of aging, there is

[2] One explanation for the causal process of this increased immune activation and chronic inflammation is as follows: Microphages are white blood cells that act as HIV reservoirs[2,21]. They exist in many of the tissue and organs which are associated with many age related comorbidities, such as fat, liver, bone, and brain tissue, and vascular walls [21]. If these infected microphages (white blood cells) release cytokines[2] that cause inflammation inside of these tissue, they may cause local inflammation and related comorbidities [21].

a debate about whether HIV infection causes premature aging or simply makes the occurrences of these diseases more likely at any age.[1]

Increased immune activation and long-term chronic inflammation are important contributors to the progression of aging. Among patients with HIV, these processes are more prevalent and as a result they are more prone to developing age related illnesses, even when the infection is adequately controlled.[21]

Another way in which premature aging is understood is by measuring the "frailty" of PLWHIV.[1] There is no universal definition for frailty, but it is generally defined as a "vulnerability in aging" which makes one unable to perform the normal functions of daily living when faced with physical, social or emotional stress.[16,22] Studies show that older PLWHIV are frailer than those do not have HIV, due to the high prevalence of HIV related co-morbidity, and this frailty is a predictor of morbidity and premature mortality among PLWHIV.[16,22]

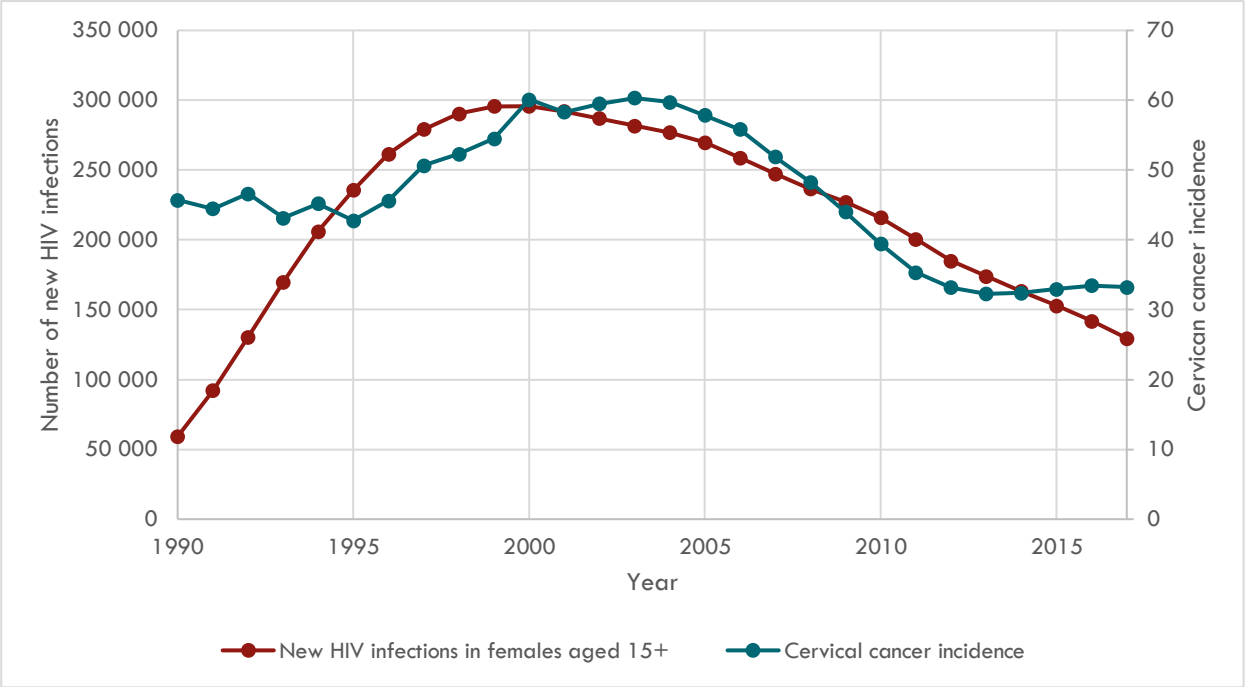
The effects of HIV infection: Cancer

In high-income countries, cancer is a leading cause of death among people with HIV.[23] Cancers which affect PLWHIV are divided into AIDS defining (ADC) and non-AIDS defining cancers (NADC).[23] Kaposi Sarcoma, non-Hodgkin's Lymphoma (NHL) and cervical cancer are classified as ADC, while all other cancers which affect PLWHIV are classified as NADC.[23]

Although HIV does not directly cause cancer, it does creates an immunosuppressed environment which enables malignancies caused by other viruses to develop.[24,25] This is why ADCs are primarily caused by tumour viruses, such Epstein–Barr virus (EBV) which causes NHL, Kaposi's Sarcoma herpesvirus (KSHV) that cause Kaposi Sarcoma cancer (which prior to the HIV/AIDS pandemic was a very rare cancer, but its incidence has increased by many magnitudes since), and human papillomavirus (HPV) which causes cervical cancer.[24,25] Despite the dichotomy between ADC and NADC, many NADC can be biologically and epidemiologically linked to HIV infection.[23] Silverberg et al (2011) find that PLWHIV are at higher risk of developing melanoma, anal and liver cancer.[26] Both liver and anal cancer are known to be caused by viruses.[26]

In line with the findings in more high resource settings, PLWHIV in South Africa show elevated risk of developing Kaposi Sarcoma, NHL, and cervical cancer.[27] Of the NADCs, PLWHIV are also at increased risk of developing conjunctival cancer and cancers associated with HPV infections such as, penis and vulva cancer.[27] Figure 3 illustrates how the incidence of HIV and cervical cancer, which is the second most common cancer among South African women, have tracked each other.

Figure 3: Incidence of HIV and cervical cancer among South African women from 1990 to 2017[28]



Adherence to ART and maintaining a high CD4 count has been shown to reduce the incidence of these AIDS and non-AIDS defining cancers, but the risk of developing them is still elevated among PLWHIV.[23,26] This has implications for policy and for resource-need forecasting.

The resultant multimorbidity in PLWHIV

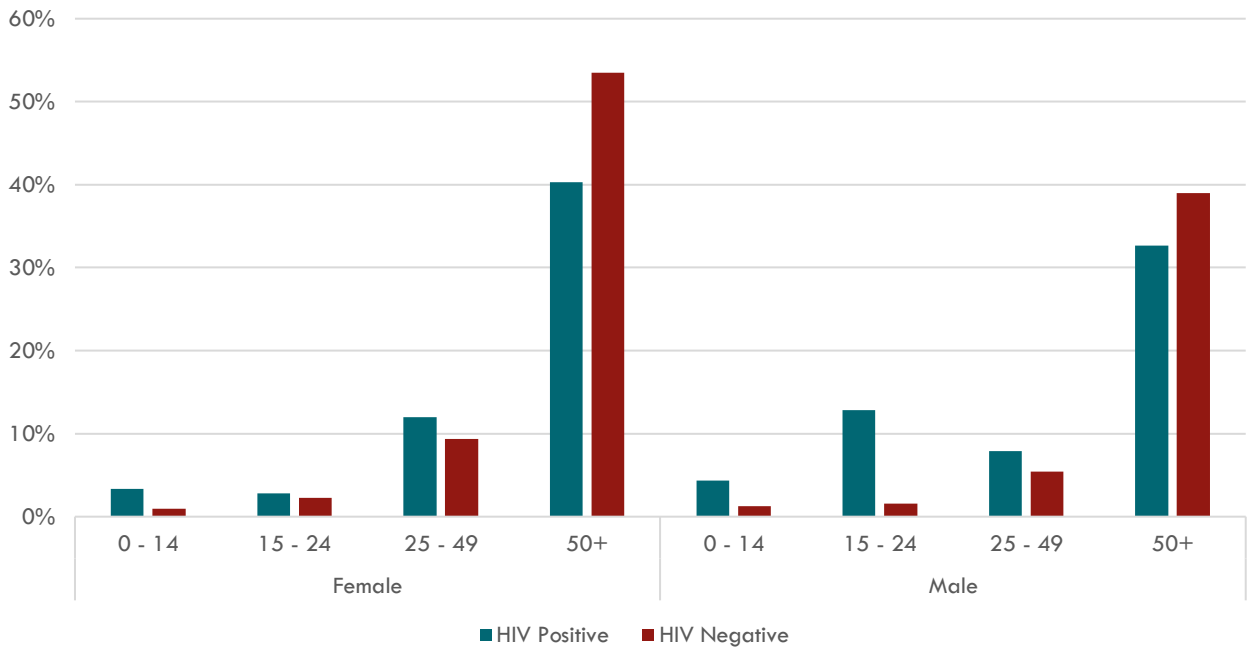
Studies indicate the prevalence of the comorbidity of NCDs and HIV in South Africa is high, particularly in older age groups. Negin et al. (2012) estimate that 30% of PLWHIV that are 50 years and older have two or more chronic conditions, this finding is based off of a nationally representative study.[10] In a study of the prevalence of multimorbidity using data from a primary healthcare facility in the Western Cape, South Africa, Oni et al. (2015) found that 26% of PLWHIV aged 18 to 35 and 30% of PLWHIV aged 36 to 46 who were on ART reported having multimorbidity.[3,29] Van Heerden et al (2017) found that 80% of PLWHIV in their study had comorbid obesity, hyperglycaemia, hyperlipidaemia, or hypertension.[30]

Using the South African Demographic Health Survey (SADHS) 2016 and the General Household Survey (GHS) 2018, which are both national representative datasets, we attempt to estimate the prevalence of the comorbidity of HIV with hypertension and diabetes, respectively. We then estimate the prevalence of comorbidities among the medical scheme population and compare those with the general population. We use both objective and self-reported measures of disease, therefore it should be noted that it is likely that each of these measures are underestimated as not all participants would have consented to revealing their HIV status or being tested for the objective measurements of NCDs. And, as always with self-reported data, respondents may inadvertently give false information because they may be unaware of their health status or may also refuse to reveal this information.

Household survey data

The graphs below compare the **self-reported** prevalence of NCDs among PLWHIV and those who do not have HIV using GHS and SADHS datasets. These NCDs include hypertension, heart attack or heart problems, cancer, stroke, diabetes, and asthma. In addition to these, the GHS also includes arthritis and mental illness. In Figure 4, the GHS data shows that NCDs are more prevalent among PLWHIV who are under the age of 50, compared to those who do not have HIV. For those over the age of 50, the prevalence of NCDs is much higher in the non-HIV positive population, although prevalence rates are very high for both groups compared to the younger population. The prevalence of NCDs also appears to differ by gender. Among those 25 years of age and older, NCDs are more prevalent in women compared to men in both the HIV negative and positive populations. Given what we know about health seeking behaviour in men, these differences by sex are not necessarily a true reflection.

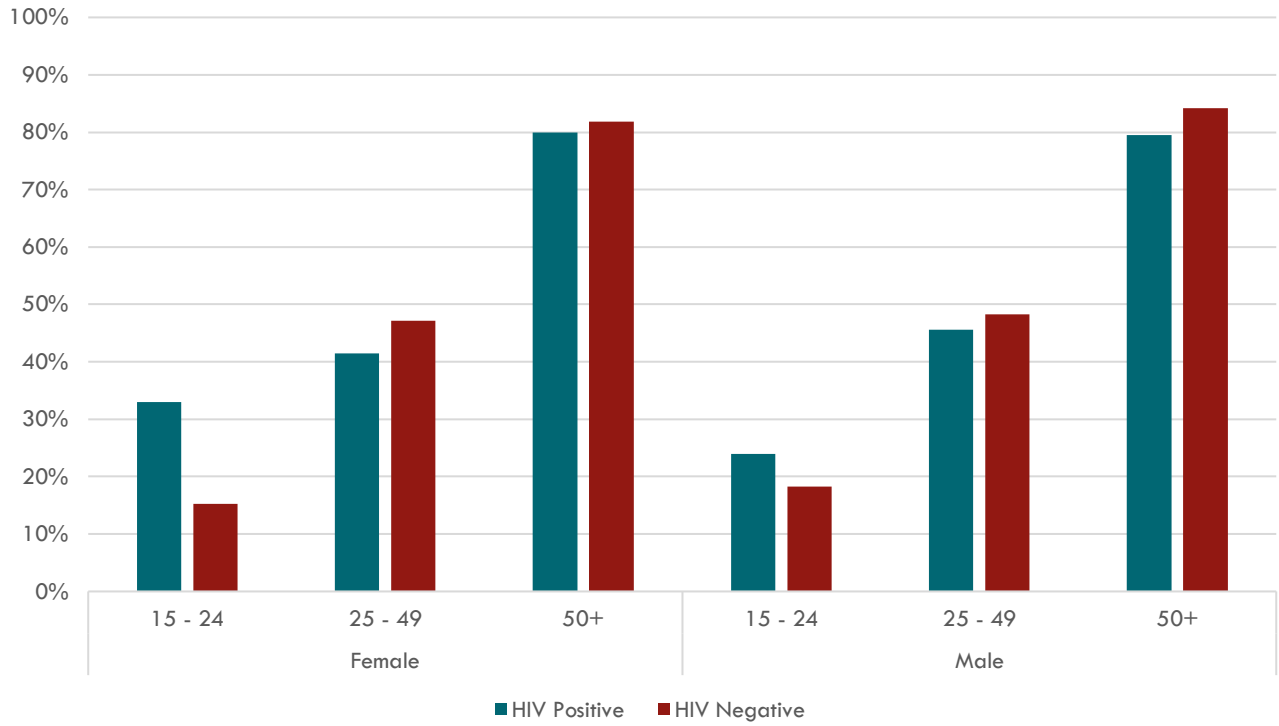
Figure 4: Self-reported prevalence of any NCD in HIV positive vs HIV negative population, GHS 2018[31]



Hypertension, diabetes, and HIV

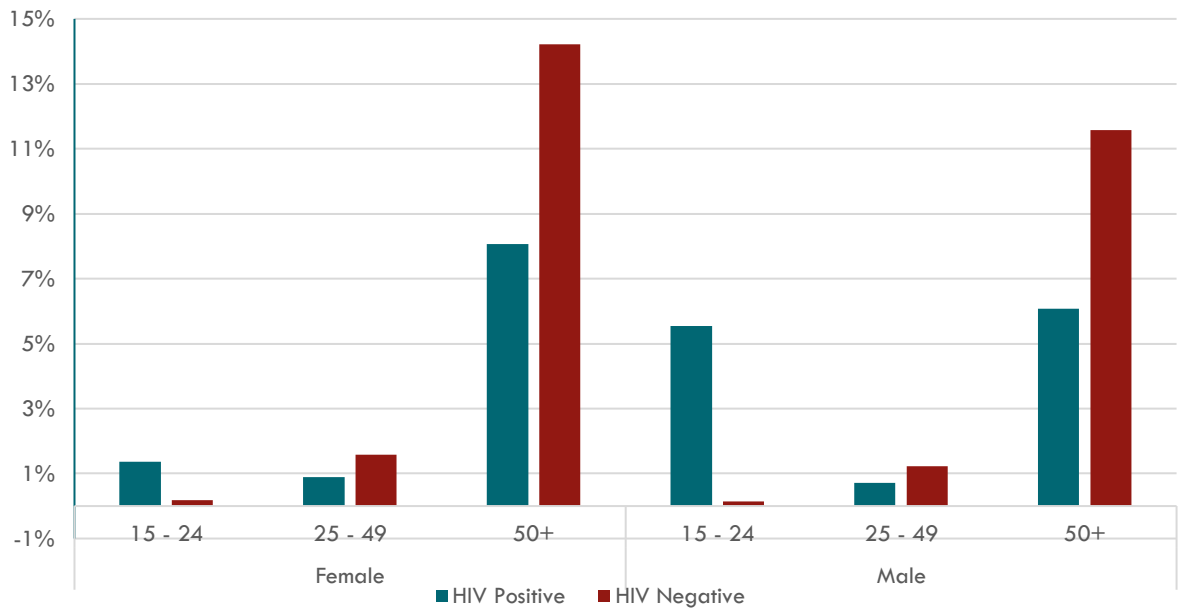
The SADHS' **objective measures** of hypertension (Figure 5) show that PLWHIV between the ages of 15 and 24 have a higher prevalence of hypertension compared to their peers who do not have HIV. For all other age groups PLWHIV have lower rates of hypertension, compared to people without HIV.

Figure 5: Hypertension prevalence in HIV positive vs HIV negative population, SADHS 2016



Self -reported estimates of diabetes from the GHS survey in Figure 6 show that the prevalence among PLWHIV under the age of 25 is much higher than that of HIV negative people of the same age group- matching the findings from the objective measure in the graph above. Again, these prevalence rates are lower than those of HIV negative people in older age groups, despite increasing with age.

Figure 6: Self-reported diabetes prevalence in HIV positive vs HIV negative population, GHS 2018



The survey data appears, to an extent, to echo the findings of much of the literature. Much like people who do not have HIV, PLWHIV are developing more NCDs as they age. PLWHIV also seem to be developing these NCDs, such as hypertension and diabetes, at a younger age compared to HIV negative people of the same age. However, the survey data findings don't seem to show that older PLWHIV have higher rates of NCDs compared to those without HIV. This may be explained by self-reporting bias, as survey respondent may not want to disclose or may be unaware of their health status. This would result in these prevalence estimates being underestimated. On the other hand, young PLWHIV may be in contact with the health system more often, therefore they are more likely to know about their comorbidities compared to those without HIV who have relatively little contact with the health system. This may also explain why the prevalence of NCDs among women is reportedly higher than that of men, as illustrated in Figure 4. Women, particularly those in their reproductive years, are more likely to have more contact with the health system and are therefore more likely to be aware of their health status compared to men, and this is likely to hold for WLHIV as well.

Comorbidity in the medical scheme population

The medical scheme population differs from the uninsured population in South Africa most often in terms of socio-economic status. As a result, the diseases of those who are covered by medical schemes tend to be different from the uninsured population. For example, HIV prevalence is far lower in the medical scheme environment but NCDs are more prevalent, given that the medical scheme population is much older than the general population.

Therefore, we have asked the Council for Medical Schemes and several medical schemes for data to allow us to analyse NCDs and their comorbidities, for this project. We will include this data and analysis once it has been received.

NCDs and HIV as syndemic

Perhaps the most useful conceptual framework for thinking of how the NCD and HIV epidemics are related is to understand them as "synergistic epidemics" or "syndemic". The term syndemic was coined by medical anthropologist, Merrill Singer, to describe "a closely interrelated complex of health and social crises".[35] The terms speaks to the comorbidity of two or more diseases which mutually reinforce each other to negatively impact morbidity and progression of each respective disease, but are also deleteriously affected by socioeconomic inequalities.[36,37] Syndemics specifically refer to both the biological interaction of these diseases in addition to how they are affected by the social, cultural, economic and physical environments in which people live.[36]

In the previous sections we described the biological mechanisms through which the HI virus itself, the treatment for HIV and the lack of adherence to treatment can cause or be associated with the development of NCDs. In this section we aim to describe the socioeconomic factors which cluster together to create these clusters of chronic illness and NCDs among PLWHIV using the syndemic framework.

Although ART is associated with certain NCD risk factors, adherence to ART and maintaining a healthy CD4 count is crucial to the prevention and managing the treatment of NCDs among PLWHIV. Therefore, when considering the socioeconomic factors which give rise to the NCD-HIV syndemic, **one needs to understand what socioeconomic factors affect access and adherence to HIV treatment**.

Poverty and rurality

Studies which analyse the barriers to ART adherence in South Africa identify that many of the primary impediments are related to poverty. Poverty is associated with food insecurity, which is one of the most important barriers to ART adherence.[38,39] Food insecurity which leads to poor nutrition, not only impacts adherence, but also treatment efficacy.[38] Young et al. (2014) describe three mechanisms through which food insecurity impacts treatment adherence. Firstly, the fear or the experience of increased or "intractable" hunger as a side effect of taking ART on an empty stomach.[40] Secondly, the fear of exacerbated ART side effects, such as nausea, vomiting and stomach pain, when ART is taken while inadequately nourished.[40] Lastly, in situations where resources are limited, PLWHIV often have to make the trade-off between getting their medication and getting food for themselves and their families because of the time and costs required to visit a health facility.[40] The combination of undernutrition and the lack of adherence to treatment due to food insecurity leads to worse clinical outcomes for PLWHIV.[39,40] This creates a vicious cycle as PLWHIV who are food insecure are unable to get healthy enough to look for or retain work which makes them unable to earn a living in order to purchase food, creating a trap of both poverty and morbidity.[39,40]

Poverty also forces people to make challenging trade-offs with regard to their health in order to survive. In South Africa, PLWHIV can receive disability grants of R1,860 if their CD4 count falls below 200.[41,42] This creates the potential for perverse incentives where some patients who are administered ART wilfully neglected to take their medication in order to suppress their CD4 count and continue receiving disability grants.[38,42] In an analysis of data from the Africa Health Research Institute Demographic and Health Surveillance System (AHRI DSS) in rural KwaZulu-Natal, Haber et al. (2018) were able to show that the rules for qualifying for the state disability grant appear to unintentionally cause slower CD4 count recovery for patients that are close to the threshold of qualification for the grant. The study attributes slower CD4 count recovery to change in adherence to ART when patient CD4 count are low enough to qualify them for the disability grant.[42] As described in the previous section, having a low CD4 count is strongly related to developing NCDs, particularly cancer, among PLWHIV.

Peltzer et al (2010) found that those who lived in urban areas were almost three times more likely to adhere to treatment than those who lived in rural areas. Rurality is also associated with lower levels of adherence and this has been attributed to higher transport costs in rural areas, which make accessing treatment more costly in those areas.[43]

Gender

Poverty and gender interact to create conditions which put women at higher risk of contracting HIV and create barriers to treatment adherence among women living with HIV (WLHIV).[44] Patriarchy and gender-related power dynamics can make it difficult for women to negotiate safe sex, forces them to remain in abusive relationships, and leads many women to engage in transactional sex to fend for themselves and their families.[44,45] In South Africa, women aged 15 to 24 are two and a half times as likely to contract HIV as men in the same age group, and transactional sex is considered a major driver of this phenomenon.[46,47] This puts WLHIV at risk of contracting STIs, such as HPV, which cause cervical cancer[48]; the combination of immune suppression caused by HIV and compounded by lack of adherence to treatment, and exposure to STIs is what makes cervical cancer one of the most common cancer among WLHIV.

In a study of treatment adherence among HIV positive pregnant women in rural KZN, issues related to domestic

violence were cited as a reason for lack of treatment adherence.[45] Some women reported that their partners threatened to beat or kill them if they found out they were HIV positive, others were discouraged from participating in the study by their partners, and one was threatened with violence for receiving calls from male nurses who were following up on whether they were adhering to treatment.[45]

Stigma

Stigma related to HIV status prevents people from being open about their status with their family, friends and employers.[38] These feelings of stigma and fear of discrimination are associated with lower levels of HIV treatment adherence.[43] In an attempt to hide their status, some people choose to receive treatment in health facilities far from where they live, so that their community does not find out about their status, this makes adherence more difficult.[38] The timing of when ART is taken is also important for treatment efficacy and when PLWHIV are unable to take their medication openly in front of friends, family and colleagues this also compromises treatment adherence and efficacy.[38]

Internalised stigma among PLWHIV has been found to be associated with lower CD4 counts and depression whereas high levels of social support are associated with treatment adherence.[43,49] Therefore destigmatising HIV is not only important for ensuring adherence, but also reducing the comorbidities of HIV since adherence is a crucial part of maintaining immune health.[49]

Mental health

There is a large body of literature, of both local and international studies, which show a strong relationship between mental health and HIV treatment adherence.[50–52] A systemic review of studies which estimated the relationship between ART adherence, and depression and alcohol use in sub-Saharan Africa showed that depression was associated with a 55% reduction in treatment adherence.[51] In a study of 101 PLWHIV who were on ART, Nel and Kagee (2013) found that 40% and 29% of participants showed moderate or severe symptoms of depression and anxiety, respectively.[53] They also found that those who reported imperfect adherent to ART were almost three times as likely to have moderate to severe symptoms of depression compared to those who reported perfect adherence.[53] There are several symptoms of depression and anxiety which may cause poor adherence to medication such as low motivation, poor concentration, fatigue or loss of energy and feelings of worthlessness.[53] These symptoms may cause PLWHIV to fail to attend clinic visits, forget to take medication or even wilfully neglect taking medication due to feelings of hopelessness.[53]

The factors mentioned in the sections above can also be considered to be social determinants of mental health, as people who live in poverty, face stigma and gender based violence are likely to experience poor mental health too, therefore it is likely that all of these factors work together to reduce adherence to treatment. It then follows that the treating depression and anxiety alone, although important and necessary, may not be the whole solution and a more integrated approach is necessary.

Leveraging existing HIV treatment infrastructure to treat NCDs

Life-prolonging effects of ART have meant that HIV is now managed as a chronic illness and given that many of the comorbidities associated with HIV are chronic illnesses too, their management aligns. To this end the

National Department of Health (NDoH) developed and implemented the Integrated Chronic Disease Management (ICDM) model. The ICDM is a model of integrated managed care which incorporates prevention, treatment and care of patients with chronic communicable and noncommunicable diseases at primary healthcare (PHC) level within their communities.[54] This has meant leveraging existing PHC infrastructure, which was previously geared towards treatment and management of HIV, to treat other chronic illnesses.[55]

The aspects of HIV care which can be leveraged for the control and treatment of other chronic illnesses are program approaches, such as defaulter tracing and peer support programmes, tools used to register patients and capture their medical records, and systems, such as monitoring and evaluation, drug procurement, referral and specimen processing.[55] In addition to this existing infrastructure, new structures such as the Central Chronic Medicine Dispensing and Distribution (CCMDD) programme were created to enable patients to collect repeat prescriptions for chronic medications at alternative, more convenient pick up points to assist in maintaining treatment adherence.[56]

There have been shortcomings reported by both patients and staff in the implementation of the ICDM model at PHC facilities which include, but are not limited to, long waiting times for patients, lack of or malfunctioning equipment, overburdened nurses due to increased workload created by integrated services, and sometimes even shortages of drugs. Despite this, ICDM model has achieved small but significant improvement in the control of CD4 counts and blood pressure, however the strengthening of these shortcoming is a necessary condition for the further improvements in chronic diseases management outcomes.[55]

Where to from here

Using the syndemic framework to understand the comorbidity of HIV and NCDs forces one to consider not only the medical conditions which cause the conditions to co-occur, but also the social conditions. This approach allows for effective intervention at both the policy and clinical level to address the root causes of morbidity and the inequalities that give rise to them.[36,57]

Despite beliefs around the perverse incentives created by them, disability grants provided to PLWHIV are one such attempt at bridging the gap between social and biological causes of these comorbidities. A study by Cluver et al (2016) showed that providing social protections to adolescents improved ART adherence.[58] The CCMDD program aimed to address the inconvenience and cost of collecting chronic medication for patients which also has the effect of increasing access to treatment and improving adherence.

As Goudge and Ngoma (2011) state, "multi-dimensional, inter-sectoral programs that tackle the social determinants of health, such as food insecurity, poverty, gendered inequities, and treatment adherence are more likely to be successful, than single interventions to support adherence." Although South Africa's integrated chronic disease model has been successfully implanted[59], more is needed to tackle these social determinants of the multimorbidity of these chronic diseases.

Conclusions

HIV is now a manageable chronic illness and PLWHIV are living longer, thus developing diseases of old age. However, PLWHIV are also more prone to developing comorbid NCDs as a result of ART side effects and HIV infection compromising their immune systems, particularly when CD4 counts are low. The susceptibility of PLWHIV

to NCDs is not only a function of biology, but there are also social factors that impact treatment adherence which make the likelihood of developing NCD among PLWHIV higher. Therefore, in addition to the integrated treatment approach to NCDs and HIV, societal and socioeconomic factors which affect treatment adherence also need to be understood in order to successfully treat the HIV NCD syndemic.

References

1. Deeks SG, Lewin SR, Havlir D V. The end of AIDS: HIV infection as a chronic disease. *Lancet*. 2013;382(9903):1525-1533. doi:10.1016/S0140-6736(13)61809-7

2. World Health Organisation. Viral suppression for HIV treatment success and prevention of sexual transmission of HIV. WHO. Published July 2018. Accessed July 23, 2020. http://www.who.int/hiv/mediacentre/news/viral-supression-hiv-transmission/en/

3. US Government. HIV Treatment as Prevention. HIV basics.

4. UNAIDS. South Africa | UNAIDS. Published 2020. Accessed July 2, 2020. https://www.unaids.org/en/regionscountries/countries/southafrica

5. World Health Organization. *Treat All: Policy Adoption and Implementation Status in Countries*. World Health Organization; 2019.

6. Bradshaw D, Groenewald P, Laubscher R, et al. Initial burden of disease estimates for South Africa. *South African Med J*. 2000;93(9):682-688. Accessed July 23, 2020. https://journals-co-za.ez.sun.ac.za/content/m_samj/93/9/EJC68039?fromSearch=true

7. Lawn SD, Churchyard G. Epidemiology of HIV-associated tuberculosis. *Curr Opin HIV AIDS*. 2009;4(4):325-333. doi:10.1097/COH.0b013e32832c7d61

8. UNAIDS epidemiological estimates. South Africa | UNAIDS. Published 2020. Accessed July 13, 2020. https://www.unaids.org/en/regionscountries/countries/southafrica

9. Johnson LF, May M, Dorrington RE, et al. Estimating the impact of antiretroviral treatment on adult mortality trends in South Africa: a mathematical modelling study. *PLoS Med*. 2017;14(12).

10. Negin J, Bärnighausen T, Lundgren JD, Mills EJ. Aging with HIV in Africa: The challenges of living longer. *AIDS*. 2012;26(SUPPL.1):S1. doi:10.1097/QAD.0b013e3283560f54

11. World Health Organisation. *Preparing for an Ageing Population.*; 2019.

12. Bennett JE, Stevens GA, Mathers CD, et al. NCD Countdown 2030: worldwide trends in non-communicable disease mortality and progress towards Sustainable Development Goal target 3.4. *Lancet*. 2018;392(10152):1072-1088. doi:10.1016/S0140-6736(18)31992-5

13. Rabkin M, Kruk ME, El-Sadr WM. HIV, aging and continuity care: strengthening health systems to support services for noncommunicable diseases in low-income countries. *AIDS*. 2012;2012(1):77-83. doi:10.1097/QAD.0b013e3283558430

14. Guaraldi G, Malagoli A, Calcagno A, et al. The increasing burden and complexity of multi-morbidity and polypharmacy in geriatric HIV patients: A cross sectional study of people aged 65 - 74 years and more than 75 years. *BMC Geriatr*. 2018;18(1):1-10. doi:10.1186/s12877-018-0789-0

15. Chawla A, Wang C, Patton C, et al. A Review of Long-Term Toxicity of Antiretroviral Treatment Regimens and Implications for an Aging Population. *Infect Dis Ther*. 2018;7(2):183-195. doi:10.1007/s40121-018-0201-6

16. Deeks SG, Phillips AN. HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. *BMJ*. 2009;338(7689):288-292. doi:10.1136/bmj.a3172

17. Nduka CU, Stranges S, Sarki AM, Kimani PK, Uthman OA. Evidence of increased blood pressure and hypertension risk among people living with HIV on antiretroviral therapy: A systematic review with meta-analysis. *J Hum Hypertens*. 2016;30(6):355-362. doi:10.1038/jhh.2015.97

18. Lichtenstein K, Balasubramanyam A, Sekhar R, Freedland E. HIV-associated adipose redistribution syndrome (HARS): Definition, epidemiology and clinical impact. *AIDS Res Ther*. 2007;4(1):16. doi:10.1186/1742-6405-4-16

19. Domingo P, Estrada V, López-Aldeguer J, Villaroya F, Martínez E. *Fat Redistribution Syndromes Associated with HIV-1 Infection and Combination Antiretroviral Therapy*. Vol 14.; 2012.

20. Paula AA, Falcão MCN, Pacheco AG. Metabolic syndrome in HIV-infected individuals: Underlying mechanisms and epidemiological aspects. *AIDS Res Ther*. 2013;10(1):1-8. doi:10.1186/1742-6405-10-32

21. Capeau J. Premature Aging and Premature Age-Related Comorbidities in HIV-Infected Patients: Facts and Hypotheses. *Clin Infect Dis*. 2011;53(11):1127-1129. doi:10.1093/cid/cir628

22. Willig AL, Overton ET, Saag MS. The Silent Epidemic - Frailty and Aging with HIV. *Total patient care HIV HCV*. 2016;1(1):6-17. Accessed July 27, 2020. http://www.ncbi.nlm.nih.gov/pubmed/28386608

23. Gopal S, Achenbach CJ, Yanik EL, Dittmer DP, Eron JJ, Engels EA. Moving forward in HIV-associated cancer. *J Clin Oncol*. 2014;32(9):876-880. doi:10.1200/JCO.2013.53.1376

24. Moore PS, Chang Y. Why do viruses cause cancer? Highlights of the first century of human tumour virology. *Nat Rev Cancer*. 2010;10(12):878-889. doi:10.1038/nrc2961

25. Simard EP, Engels EA. Cancer as a Cause of Death among People with AIDS in the United States. *Clin Infect Dis*. 2010;51(8):957-962. Accessed July 14, 2020. https://watermark.silverchair.com/51-8-957.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAokwggKFBgkqhkiG9w0BBwagggJ2MIICcgIBADCCAmsGCSqGSIb3DQEHATAeBglghkgBZQMEAS4wEQQMgGot-T-DkHgglDrfAgEQgIICPBnroJTI2Ss-3asbOgU2gU_9axFr-wTX5kpZCD2g1PDj-UyekrgTc0A-xjQbtBhLlgaD_iAIXGISBv_iyOTgCsmPAaS1Hm-bSPBuj7U2hD93iCfjaRhZCpqS_OPRt6S1I9LFNhc0QS3qj8oY0zgVdGxAQHDdJ7TNejTSX2HnDD2hK1vpjPSLz1J89Aj3kA4SdxdClmA-Izs3YK-kXX6v5anlMKJAkPKeOLkJunCnUzx3_Bw5OiDAcnHBM38pvPs-qLfTh3GFajgzv2gKZnM6mXR2gN6MfjE1EQLaRTthJxDljyLDEzkPdGwBc2Tp5cWO11_c0eiLZQy780Z3aojQfxLvLBbx4y2cmPxuSquoERPCL3LN0BkBmUXUvTlgHYJ18KoAx3ZTPP5Q6JFl_xfyR6Gy5WgLw0xFF__xrylkpJpTQL0fC5YxHA4whlkgEmhQ2qd3ahio6MFJlnZZRDoUFzKUsUGkdyagdchXKFE2vJE28wVxSopRRVwjRMCOUjg68zaXRehY8Q-PsLe2M_PJzNp4ZO3Ym6o7GyF_4psw70W3ryh3EVgEO4QyG7c9BkjqA9X6BiCbBbPAq3JTH-1HXm5enryjTukE036dK18pd27WyooTDeQudRsqL-qWrzW4CQtkoTsXT0pU2RXDQjVxri4UVcdcBUVyfo9Qodon9-08zu6LhxVFgkAwqX5B5WTTikfb7_iz83uZmxgYmMXzvBx4nDQVOlzGpbUHZNmRwwQlhmsCN5WzejY2noWS

26. Silverberg MJ, Chao C, Leyden WA, et al. HIV Infection, Immunodeficiency, Viral Replication, and the Risk of Cancer. *Cancer Epidemiol Prev Biomarkers*. 2011;20(12):2551-2559. Accessed July 14, 2020. https://cebp.aacrjournals.org/content/cebp/20/12/2551.full.pdf

27. Dhokotera T, Bohlius J, Spoerri A, et al. The burden of cancers associated with HIV in the South African public health sector, 2004-2014: A record linkage study. *Infect Agent Cancer*. 2019;14(1):12. doi:10.1186/s13027-019-0228-7

28. Institute for Health Metrics and Evaluation (IHME). *South Africa Profile*.; 2018. Accessed July 29, 2020. http://www.healthdata.org/south-africa

29. Oni T, Youngblood E, Boulle A, McGrath N, Wilkinson RJ, Levitt NS. Patterns of HIV, TB, and non-communicable disease multi-morbidity in peri-urban South Africa- a cross sectional study. *BMC Infect Dis*. 2015;15(1):1-8. doi:10.1186/s12879-015-0750-1

30. Van Heerden A, Barnabas R V., Norris SA, Micklesfield LK, Van Rooyen H, Celum C. High prevalence of HIV and non-communicable disease (NCD) risk factors in rural KwaZulu-Natal, South Africa. *J Int AIDS Soc*. 2017;20(2). doi:10.1002/jia2.25012

31. Statistics South Africa. *General Household Survey 2018 [Dataset]. Version 1*.; 2019. doi:10.25828/9tmn-fz97

32. Statistics South Africa. *General Household Survey 2018 [Dataset]*.; 2018.

33. South African Labour and Development Research Unit. *National Income Dynamics Study 2017, Wave 5 [Dataset]. Version 1.0.0.*; 2018. doi:https://doi.org/10.25828/fw3h-v708

34. National Department of Health (NDOH), Statistics South Africa (Stats SA), South African Medical Research Council (SAMRC), ICF. *South Africa Demographic and Health Survey 2016.*; 2019.

35. Singer M. A dose of drugs, a touch of violence, a case of AIDS: conceptualizing the SAVA syndemic. *Free Inq Creat Sociol*. 2000;28(1):13-24.

36. Mendenhall E, Kohrt BA, Norris SA, Ndetei D, Prabhakaran D. Non-communicable disease syndemics: poverty, depression, and diabetes among low-income populations. *Lancet*. 2017;389(10072):951-963. doi:10.1016/S0140-6736(17)30402-6

37. The Lancet. Syndemics: health in context. *Lancet*. 2017;389(10072):881. doi:10.1016/S0140-6736(17)30640-2

38. Coetzee B, Kagee A, Vermeulen N. Structural barriers to adherence to antiretroviral therapy in a resource-constrained setting: The perspectives of health care providers. *AIDS Care - Psychol Socio-Medical Asp AIDS/HIV*. 2011;23(2):146-151. doi:10.1080/09540121.2010.498874

39. Goudge J, Ngoma B. Exploring antiretroviral treatment adherence in an urban setting in South Africa. *J Public Health Policy*. 2011;32(SUPPL. 1):S52-S64. doi:10.1057/jphp.2011.22

40. Young S, Wheeler AC, McCoy SI, Weiser SD. A Review of the Role of Food Insecurity in Adherence to Care and Treatment Among Adult and Pediatric Populations Living with HIV and AIDS. *AIDS Behav*. 2014;18(5):505-515. doi:10.1007/s10461-013-0547-4

41. South African Government. Disability grant. Published 2020. Accessed July 23, 2020. https://www.gov.za/services/social-benefits/disability-grant

42. Haber N, Bärnighausen T, Bor J, et al. Disability for HIV and Disincentives for Health: The Impact of South Africa's Disability Grant on HIV/AIDS Recovery. *Cornell Univ Work Pap*. Published online October 3, 2018. Accessed July 23, 2020. http://arxiv.org/abs/1810.01971

43. Peltzer K, Friend-Du Preez N, Ramlagan S, Anderson J. Antiretroviral treatment adherence among HIV patients in KwaZulu-Natal, South Africa. *BMC Public Health*. 2010;10(1):1-10. doi:10.1186/1471-2458-10-111

44. Chop E, Duggaraju A, Malley A, et al. Health Care for Women International Food insecurity, sexual risk behavior, and adherence to antiretroviral therapy among women living with HIV: A systematic review. *Health Care Women Int*. 2017;38(9):927-944. doi:10.1080/07399332.2017.1337774

45. Mepham S, Zondi Z, Mbuyazi A, Mkhwanazi N, Newell ML. Challenges in PMTCT antiretroviral adherence in northern KwaZulu-Natal, South Africa. *AIDS Care - Psychol Socio-Medical Asp AIDS/HIV*. 2011;23(6):741-747. doi:10.1080/09540121.2010.516341

46. Mampane JN. Exploring the "Blesser and Blessee" phenomenon: young women, transactional sex, and HIV in rural South Africa. *Sage Open*. 2018;8.4. Accessed July 25, 2020. https://journals.sagepub.com/doi/pdf/10.1177/2158244018806343

47. Stoebenau K, Heise L, Wamoyi J, Bobrova N. Revisiting the understanding of "transactional sex" in sub-Saharan Africa: A review and synthesis of the literature. *Soc Sci Med*. 2016;168:186-197. doi:10.1016/j.socscimed.2016.09.023

48. Maree JE, Lu XM, Wright SCD. Cervical cancer: South African women's knowledge, lifestyle risks and screening practices. *Africa J Nurs Midwifery* . 2012;14(2):104-115. Accessed July 25, 2020. https://www.researchgate.net/publication/275152859

49. Peltzer K, Ramlagan S. Perceived stigma among patients receiving antiretroviral therapy: A prospective study in KwaZulu-Natal, South Africa. *AIDS Care - Psychol Socio-Medical Asp AIDS/HIV*. 2011;23(1):60-68. doi:10.1080/09540121.2010.498864

50. Gonzalez JS, Batchelder AW, Psaros C, Safren SA. Depression and HIV/AIDS treatment nonadherence: A review and meta-analysis. *J Acquir Immune Defic Syndr*. 2011;58(2):181-187. doi:10.1097/QAI.0B013E31822D490A

51. Nakimuli-Mpungu E, Bass J, Alexandre PK, et al. Depression, Alcohol Use and Adherence to Antiretroviral Therapy in Sub-Saharan Africa: A Systematic Review. *AIDS Behav*. 2012;16(8):2101-2118. doi:10.1007/s10461-011-0087-8

52. Uthman OA, Magidson JF, Safren SA, et al. Depression and Adherence to Antiretroviral Therapy in Low-, Middle-and High-Income Countries: A Systematic Review and Meta-Analysis. *Curr HIV/AIDS Rep*. 2014;11(3):291-307. doi:10.1007/s11904-014-0220-1

53. Nel A, Kagee A. The relationship between depression, anxiety and medication adherence among patients receiving antiretroviral treatment in South Africa. *AIDS Care - Psychol Socio-Medical Asp AIDS/HIV*. 2013;25(8):948-955. doi:10.1080/09540121.2012.748867

54. Asmall S, Mahomed O. *Integrated Chronic Disease Management Manual*.; 2013.

55. Ameh S. Evaluation of an integrated HIV and hypertension management model in rural south africa: a mixed methods approach . *Glob Health Action*. 2020;13. doi:10.1080/16549716.2020.1750216

56. National Department of Health. Alternative Chronic Medicines Access Programme for Public Sector Patients. In: *Civil Society Stakeholder Meeting*. ; 2014. http://www.differentiatedservicedelivery.org/Portals/0/adam/Content/5zkRswkhdUCwztOtMVmPKg/File/DOH_CCMDD civil society presentation_20140512_TO MSF.pdf

57. Peprah E, Caler E, Snyder A, Ketema F. Deconstructing syndemics: The many layers of clustering multi-comorbidities in people living with HIV. *Int J Environ Res Public Health*. 2020;17(13):1-7. doi:10.3390/ijerph17134704

58. Cluver LD, Toska E, Orkin FM, et al. Achieving equity in HIV-treatment outcomes: can social protection improve adolescent ART-adherence in South Africa? *AIDS Care*. 2016;28(2):73-81. doi:10.1080/09540121.2016.1179008

59. Mahomed OH, Asmall S, Voce A. Sustainability of the integrated chronic disease management model at primary care clinics in South Africa. *African J Prim Heal care Fam Med*. 2016;8(1):1248. doi:10.4102/phcfm.v8i1.1248