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RESEARCH ARTICLE

Unmasking a silent killer: Prevalence of diagnosed and undiagnosed diabetes mellitus among people living with HIV in rural South Africa

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Abstract

Objectives: To document the prevalence of impaired glucose tolerance (IGT) and undiagnosed diabetes mellitus (DM) and to identify factors associated with undiagnosed DM in people living with HIV (PLWH).

Methods: Cross-sectional study performed at Ndlovu Medical Center, Limpopo, South Africa including PLWH aged ≥18 years. Between August and November 2017, 356 HIV-positive participants were included. Information was collected on socio-demographics, DM symptoms and risk factors for DM. IGT and DM were diagnosed using random plasma glucose and/or HbA1c. Factors associated with undiagnosed DM were assessed by comparing participants with newly diagnosed DM to participants without DM.

Results: IGT was diagnosed in 172 (48.3%) participants. Twenty-nine (8.1%) participants met the definition of DM, of whom 17 (58.6%) were newly diagnosed. Compared to participants without DM, participants with DM were on average 5 years older, were more likely to have a positive family history for DM, were less physically active and had higher systolic blood pressure, body mass index and waist circumference. Factors associated with undiagnosed DM included age ≥45 years (odds ratio [OR] = 3.59) and physical inactivity (OR = 3.17).

Conclusions: The prevalence of IGT and DM among PLWH is high and more than half of DM cases were undiagnosed. Regular screening for DM in PLWH is recommended, especially in an ageing population with additional cardiovascular disease risk factors.

KEYWORDS
diabetes mellitus, epidemiology, HIV, impaired glucose tolerance, sub-Saharan Africa

INTRODUCTION

The prevalence of diabetes mellitus (DM) is rising in South Africa. In 2019, the prevalence was estimated to be 12.8% in adults, making South Africa the country with the highest prevalence of DM in Sub-Saharan Africa (SSA) [1]. In 2017, DM was the leading cause of death among females (7.3%) in South Africa and the second leading cause of death for the entire population, accounting for 5.7% of all deaths [2]. Additionally, the prevalence of impaired glucose tolerance (IGT) was 9.0% in 2019 [3]. IGT is a form of prediabetes indicating increased insulin resistance and impaired insulin production. The 5-year progression rate to DM is estimated to be 26% [1, 4, 5]. Lifestyle modifications may prevent progression of IGT to DM by 58% [6, 7].

Zanele Xaba and Sehulong R. Moraba contributed equally to this work.

Sustainable Development Goal: Good Health and Wellbeing

The alarming increase in DM prevalence coincides with the increasing number of people living with HIV (PLWH). In 2019, an estimated 7.5 million PLWH were residing in South Africa, comprising 19% of the adult population [8]. Due to the rapid roll-out of antiretroviral therapy (ART) life expectancy of PLWH has increased substantially [9]. This results in an ageing HIV-positive patient population, who is thus also more exposed to complications of ageing like non-communicable diseases (NCD).

PLWH may be at an increased risk of developing IGT and DM through direct and indirect mechanisms. ART, and to a small extent the virus itself, may induce central obesity, increased insulin resistance, lipodystrophy, dyslipidaemia and endothelial dysfunction [5, 10–13], which are associated with a higher risk of developing DM and metabolic syndrome [14]. It might also be the case that a DM diagnosis is made more often in PLWH due to more regular medical visits and increased NCD screening in HIV treatment facilities [14]. In spite of this, in a population of Type 2 DM in Cameroon, HIV was associated with a higher likelihood of having a debilitating complication of DM in ageing, diabetic polyneuropathy [15].

Accordingly, DM might exert a greater impact on PLWH morbidity and mortality than on HIV-negative people. A study in Malawi found that PLWH with DM had a higher mortality rate than HIV-negative people with DM [16]. Despite the higher burden of DM, over 40% of cases in PLWH may remain undiagnosed [17]. The years of life lost due to long-term effects of DM such as cardiovascular disease could be reduced substantially by early diagnosis and adequate treatment [18].

Several initiatives have been undertaken in SSA to integrate NCD care in routine HIV care [19–21]. Integration seemed feasible and, despite challenges, several studies showed significant improvement in quality of DM care [19, 20, 22]. However, there are few reports addressing the prevalence of undiagnosed DM in HIV treatment facilities in South Africa [17]. Therefore, the primary objective of this study was to get insight in the prevalence of DM and undiagnosed DM in PLWH attending a Department of Health (DOH)-contracted HIV treatment facility in rural South Africa. As a secondary objective, this study assessed the prevalence of IGT and factors associated with undiagnosed DM.

METHODS

Study population and data collection

The DM-ALERT study is a cross-sectional study that was performed at Ndlovu Medical Center (NMC), located in Elandsdoorn, a rural area in Limpopo, South Africa. The NMC is a large rural HIV treatment facility that, at the time of the study, was contracted by the South African DOH to provide free-of-charge HIV and tuberculosis treatment. The NMC delivered ART to approximately 3700 HIV-positive patients. During the study period, ART care and monitoring was provided in accordance with the 2015 South African National Consolidated Guidelines for HIV Management [23].

Eligible participants were aged 18 years or older, HIV-positive and on stable ART for at least 6 months. Being on stable ART was defined as receiving ART for at least 12 months, with undetectable plasma HIV-RNA load (<400 copies/mL) in the last blood analysis and no change in ART regimen in the last 6 months. Patients were eligible regardless of a known DM diagnosis. Exclusion criteria were steroid therapy and serious unstable medical conditions, such as uncontrolled infections and current AIDS-defining events.

Systematic sampling was applied to recruit patients from the waiting area at the HIV clinic (one in every four patients) over a 4-month period (August to November 2017) with the intent to recruit as many patients as possible within this time frame. Participants were interviewed by a study nurse in their preferred language (Sepedi, IsiZulu or English) using a questionnaire based on a modified version of the WHO STEPS instrument and the short International Physical Activity Questionnaire (IPAQ) [24, 25]. Information was collected on socio-demographic factors, risk factors for DM and DM symptoms experienced in the past 6 months. Physical activity was defined as being active long enough to work up a sweat, based on the categories vigorous and moderate activities of the IPAQ. For known DM patients, information about diagnosis was obtained and self-reported current treatment methods and adherence to medical treatment for DM was assessed using the questionnaire.

Adherence to ART was assessed by pill count and HAART Questionnaire Score Index, which included questions about difficulty taking medication and missed doses [26]. The maximum score of the questionnaire was 16 and a higher score indicated better adherence. Information taken from the participant's medical files included relevant medical history, medication and ART therapy history (i.e. current ART regimen and duration on ART). In routine HIV care, plasma HIV-RNA load (viral load) and CD4-positive T-lymphocyte (CD4+) counts were measured once a year. The most recent plasma viral load and CD4+ counts were retrieved by retrospective chart review.

Physical examination included measurement of weight, height, waist and hip circumference by standard procedures [27]. Afterwards, the body mass index (BMI) was calculated as kg/m^2. Brachial blood pressure and pulse were measured three times after a 5-min rest on the left and the right arm and repeated at the arm with the highest value using an ambulatory blood pressure device (Rossmax, Berneck, Switzerland). For blood pressure and pulse, the mean of the three measurements was used.

Random plasma glucose (RPG) was assessed with a point-of-care finger prick test using the Accu-Chek Active® (Roche Diabetes Care). For analysis of haemoglobin A1c (HbA1c) levels, whole blood was tested using Dimension® EXL™ (Siemens Healthineers). IGT and DM were diagnosed using RPG and/or HbA1c, in accordance with the cut-off values of the American Diabetes Association: for RPG values between 7.8 and 11.0 mmol/L defined IGT as

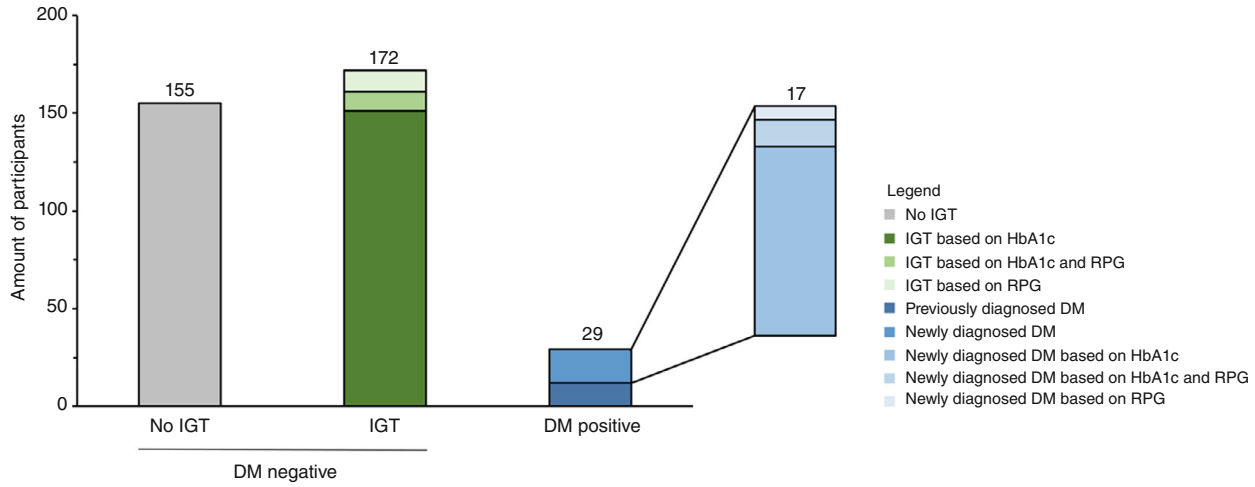

FIGURE 1 DM status and method of diagnosis of participants. DM, diabetes mellitus; IGT, impaired glucose tolerance; HbA1c, haemoglobin A1c; RPG, random plasma glucose.

well as values ≥11.1 mmol/L in the absence of classic DM symptoms, while values ≥11.1 mmol/L in the presence of classic DM symptoms defined DM. HbA1c values between 5.7% and 6.4% were regarded to reflect IGT and values ≥6.5% diagnosed DM [28]. For analysis, participants with IGT were included in the DM-negative group. The DM-positive group consisted of participants with newly diagnosed DM and previously diagnosed DM. For participants with a known DM diagnosis, controlled DM was defined as a HbA1c level of ≤7.0%. In case of abnormal laboratory findings, the participant was referred to one of the clinicians at the NMC.

Ethical approval

The DM-ALERT study was approved by the Human Research committee of the University of Pretoria, South Africa (ethics clearance number 60/2017) and conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki and ICH GCP Guidelines [29]. Written informed consent was obtained from all participants prior to study participation.

Statistical analysis

Data were imported into SPSS version 25 (IBM Corp., Armonk, NY) for analysis [30]. A two-sided p value <0.05 was considered statistically significant. Descriptive data were presented as mean with standard deviation (*SD*), median with interquartile range (IQR) or count with percentage (%), as appropriate.

Based on literature, factors associated with an increased risk of DM included age ≥45 years, BMI ≥30 kg/m^2, waist circumference ≥102 cm for men or ≥88 cm for women, physical inactivity, positive family history for DM and symptoms associated with DM like nightly polydipsia [28, 31–37]. Waist circumference was preferred to BMI as abdominal obesity is the form of obesity most strongly associated with metabolic syndrome.

To calculate the p value, the Chi-squared test was used for categorical variables. When ≥20% of the cells had an expected count less than 5, Fisher's exact test was used. The independent samples Student's t-test was used for normally distributed continuous variables. For non-normally distributed continuous variables, the Mann–Whitney U test was used. The previously mentioned factors associated with DM were assessed by comparing participants with newly diagnosed DM to participants without DM in a univariable logistic regression analysis.

RESULTS

A total of 356 HIV-positive participants were included in the study, of whom 29 (8.1%) had DM and 172 (48.3%) IGT (Figure 1). Of participants with DM, 12 (41.4%) were previously diagnosed and 17 (58.6%) were newly diagnosed. Of the participants with a new DM diagnosis, 14 were diagnosed based on HbA1c, 2 based on HbA1c and RPG and 1 based on RPG in the presence of classic DM symptoms. Diagnosis of IGT was based on HbA1c in 151 cases, based on HbA1c and RPG in 10, and based on RPG in 11. None of the IGT cases were diagnosed based on a RPG ≥11.1 mmol/L in the absence of classic DM symptoms.

The mean age of participants was 43.8 years (*SD* 9.5 years) and 69.9% were female (Table 1). DM positive participants were on average 5 years older than DM negative participants ($p = 0.008$) (Table S1). There was no difference in other socio-demographic factors or HIV-related characteristics. DM-positive participants were physically less active ($p = 0.026$), were more likely to have a positive family history for DM ($p = 0.013$) and more frequently displayed cardiovascular risk factors such as a higher systolic blood pressure ($p = 0.016$), higher BMI ($p = 0.038$) and larger waist circumference ($p = 0.012$) compared to DM negative

TABLE 1 Participant characteristics.

	No IGT ($n = 155$)	IGT ($n = 172$)	Newly diagnosed DM ($n = 17$)	Previously diagnosed DM ($n = 12$)
Demographics and socio-economic background				
Age, mean (*SD*), years	41.8 (8.7)	44.8 (9.8)	46.7 (9.7)	50.4 (8.6)
Female gender	111 (71.6)	117 (68.0)	14 (82.4)	7 (58.3)
Partnership status ($n = 355$)				
Married or life partner	52 (33.8)	68 (39.5)	7 (41.2)	7 (58.3)
Single, divorced or widowed	102 (66.2)	104 (60.5)	10 (58.8)	5 (41.7)
Highest level of education				
Primary or less	16 (10.3)	13 (7.6)	2 (11.8)	0 (0.0)
Secondary or matric	113 (72.9)	127 (73.8)	12 (70.6)	9 (75.0)
College or university	26 (16.8)	32 (18.6)	3 (17.6)	3 (25.0)
Employment ($n = 353$)				
Unemployed	47 (30.3)	36 (21.3)	3 (17.6)	2 (16.7)
Employed	98 (63.2)	112 (66.3)	12 (70.6)	9 (75.0)
Other (student, retired, disabled)	10 (6.5)	21 (12.4)	2 (11.8)	1 (8.3)
Source of income				
No income	6 (3.9)	5 (2.9)	1 (5.9)	1 (8.3)
Remittance	23 (14.8)	18 (10.5)	2 (11.8)	0 (0.0)
Grants or pension	32 (20.6)	34 (19.8)	2 (11.8)	2 (16.7)
Salaries	94 (60.6)	115 (66.9)	12 (70.6)	9 (75.0)
Lifestyle, diet and risk factors for DM				
Activity long enough to work up a sweat ($n = 354$)				
Never or rarely	43 (27.9)	42 (24.6)	9 (52.9)	5 (41.7)
Sometimes	91 (59.1)	97 (56.7)	5 (29.4)	5 (41.7)
Often	20 (13.0)	32 (18.7)	3 (17.6)	2 (16.7)
Diet with daily vegetables or fruits ($n = 351$)	69 (45.1)	75 (44.4)	6 (35.3)	6 (50.0)
Positive family history for DM ($n = 290$)	36 (27.7)	40 (28.2)	4 (23.5)	6 (50.0)
HIV-related characteristics				
Time on ART, months ($n = 355$)	74 [48–104]	74 [49–98]	67 [41–104]	68 [41–127]
CD4+ cell count, cells/mm^3 ($n = 355$)	514 [338–735]	529 [332–676]	590 [432–855]	648 [362–866]
Viral load, cp/mL ($n = 269$)	50 [20–281]	73 [20–295]	50 [20–73]	238 [20–1080]
Pill count ($n = 221$)	100 [98–100]	100 [98–100]	100 [94–100]	100 [95–100]
HAART adherence score ($n = 346$)	16 [15–16]	16 [15–16]	16 [14–16]	16 [15–16]
Physical examination				
Systolic blood pressure, mmHg	119 [110–126]	121 [113–131]	125 [118–139]	128 [119–134]
Diastolic blood pressure, mmHg	81 [74–89]	83 [74–93]	81 [76–100]	89 [82–98]
Heart rate, beats per minute	73 [67–78]	73 [67–82]	75 [70–85]	80 [69–96]
Body mass index, kg/m^2	25.1 [21.8–28.9]	24.8 [21.2–30.1]	27.7 [22.8–36.0]	28.1 [24.2–31.5]
Waist circumference, cm	80 [74–87]	83 [76–91]	89 [76–101]	93 [80–100]
Hip circumference, cm	101 [94–109]	100 [92–110]	103 [96–120]	100 [96–112]
Waist:hip ratio	0.79 [0.75–0.85]	0.82 [0.77–0.88]	0.81 [0.74–0.86]	0.88 [0.81–0.98]
Laboratory analysis				
Random plasma glucose, mmol/L	5.5 [5.0–6.3]	5.8 [5.3–6.8]	8.3 [6.0–10.6]	12.5 [8.0–15.8]
HbA1c, % ($n = 354$)	5.4 [5.2–5.5]	5.9 [5.7–6.1]	6.7 [6.5–7.3]	8.5 [6.6–10.5]

Note: Data are expressed as median [IQR] or count (%) unless otherwise specified.
Abbreviations: ART, antiretroviral treatment; CD4+, CD4-positive T-lymphocyte; DM, diabetes mellitus; HbA1c, haemoglobin A1c; IGT, impaired glucose tolerance; viral load, HIV-RNA load.

participants. When comparing participants with IGT to participants without IGT, no significant differences in demographics or risk factors were observed.

Comparing DM-related symptoms, only polydipsia at night was more frequently seen in participants with DM ($p = 0.04$) (Table 2).

Of the 12 participants previously diagnosed with DM, four (33.3%) had reached the treatment goal (HbA1c ≤ 7.0%) (Table S2). All were treated with prescription tablets, although many had medication difficulties and missed doses. In addition to this, only 1 out of 12 participants reported to currently use a diet in addition to prescription tablets. None of the participants were on insulin therapy. The date of diagnosis was available for five participants and the mean time since diagnosis was 4.8 years.

Comparing participants with newly diagnosed DM to DM-negative participants, age ≥45 years (odds ratio [OR] = 3.591 [95% confidence interval [CI] 1.236–10.432], $p = 0.019$) and physical inactivity (OR = 3.176 [95% CI 1.187–8.497], $p = 0.021$) were associated with a DM diagnosis (Table 3).

TABLE 2 Symptoms of DM experienced in the past 6 months.

	DM positive ($n = 29$)	DM negative ($n = 327$)	*p* value
Polydipsia and polyuria	13 (44.8)	94 (28.7)	0.070
Nightly polydipsia ($n = 355$)	11 (37.9)	69 (21.2)	0.038
Increased hunger	10 (34.5)	75 (22.9)	0.162
Changed weight	4 (13.8)	50 (15.3)	1.000
Fatigue	12 (41.4)	90 (27.5)	0.114
Blurred vision ($n = 355$)	10 (34.5)	107 (32.8)	0.855
Slow-healing sores or frequent infections	4 (13.8)	20 (6.1)	0.120
Tingling or numbness in hands or feet	11 (37.9)	101 (30.9)	0.434
Any symptom of DM	25 (86.2)	272 (83.2)	0.800

Note: Data are expressed as count (percentage).
Abbreviation: DM, diabetes mellitus.

DISCUSSION

This study found an overall DM prevalence of 8.1% in a population of PLWH on ART attending clinical care in a rural South African setting. Undiagnosed DM was found in 4.8% of the participating PLWH. Moreover, IGT occurred in nearly half of the participating PLWH. Factors associated with undiagnosed DM were age from 45 years and physical inactivity.

The high burden of DM is alarming as DM predisposes to morbidity and premature mortality, including cardiovascular disease and death [18]. Of the PLWH with DM, 58.6% was undiagnosed, which is roughly in line with previous studies. A systematic review on DM in SSA covering publications from 1999 to 2011 concluded that over 40% of DM was undiagnosed [11]. A study performed in South Africa reported that 43% of PLWH with DM were previously undiagnosed, although they attended clinic visits regularly [17]. This high frequency of undiagnosed DM suggests that existing screening practices in general primary care clinics might be suboptimal. The South African Adult Primary Care guideline recommends screening for DM among PLWH when patients are first diagnosed with HIV, using urine dipstick on glucose as well as an assessment of CVD risk including a Random Plasma Glucose [38]. No further routine DM screening is incorporated in the South African HIV guideline [39].

Overall, the DM prevalence of 8.1% in our study corresponds with previous studies addressing DM in PLWH. A recent systematic review and meta-analysis reported a prevalence of DM among PLWH ranging from 1.3% to 18% in low-income and middle-income countries [40]. However, studies conducted in South Africa in PLWH reported a slightly lower prevalence of 1%–5% [12, 17, 41]. The difference between our study and these studies can be explained by differences in patient populations as studies were performed in different parts of South Africa, e.g. rural and urban areas [12]. Furthermore, one study excluded participants aged above 45 years [41]. Additionally, different methods for diagnosing DM were used (e.g. fasting plasma

TABLE 3 Possible predicting factors for newly diagnosed DM.

	DM negative ($n = 327$)	Newly diagnosed DM ($n = 17$)	OR (95% CI)	*p* value
Age ≥ 45 years	131 (40.1)	12 (70.6)	3.591 (1.236–10.432)	0.019
Female gender	228 (69.7)	14 (82.4)	2.026 (0.570–7.209)	0.275
Waist circumference: male ≥102 or female ≥88 cm	75 (22.9)	7 (41.2)	2.352 (0.866–6.391)	0.094
Symptoms of DM experienced in the past 6 months				
Nightly polydipsia ($n = 343$)	69 (21.2)	6 (35.3)	2.032 (0.726–5.688)	0.177
Changed weight	50 (15.3)	2 (11.8)	0.739 (0.164–3.330)	0.693
Blurred vision ($n = 343$)	107 (32.8)	4 (23.5)	0.630 (0.201–1.978)	0.428
Slow-healing sores or frequent infections	20 (6.1)	1 (5.9)	0.959 (0.121–7.605)	0.969
Physical inactivity ($n = 342$)	85 (26.2)	9 (52.9)	3.176 (1.187–8.497)	0.021

Note: Data are expressed as count (percentage).
Abbreviations: BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; OR, odds ratio.

glucose, HbA1c only and RPG and HbA1c) as well as more lenient cut-off points. This may all explain the lower DM frequency found in these studies.

Another finding of our study is a high frequency of IGT among PLWH of nearly 50%. This lies roughly in the same range as previous studies on IGT among PLWH where frequencies between 19% and 47% were reported [5, 7, 10]. This finding is alarming as IGT has been associated with progression to DM [5]. Early identification followed by lifestyle counselling addressing food choices, a healthy BMI and physical activity is important as lifestyle modifications decrease the likelihood of progression to DM [6, 7].

Factors associated with undiagnosed DM (age and physical inactivity) and variables with a p value <0.20 but not reaching statistical significance (waist circumference and nightly polydipsia), correspond with previously identified clinical risk factors for DM [28, 31, 32, 42–44].

A strength of this study is that we addressed the rate of undiagnosed DM among HIV-infected individuals in an HIV clinic in South Africa, where this was previously largely unknown. This reflects real life clinical care and adds to the knowledge gap of undiagnosed DM. Other strengths are the structured data collection and assessment of DM by means of RPG and HbA1c.

A limitation of our study is that it has a relatively small sample size which limited power and ability to examine associations in a multivariable way between risk factors and undiagnosed DM. Besides, although the study was conducted at a governmental HIV facility and hence reflects clinical care, the single-site nature of the study might limit the generalizability to other governmental clinics located in the same area or elsewhere in the county, as well as to private clinics. Furthermore, we did not have fasting blood glucose measurements and diagnosis was based on a single measurement. This can have resulted in an underestimation of the prevalence of DM, although most cases in our study were diagnosed based on HbA1c, which is a stable outcome as it reflects blood glucose levels over the course of the past 3 months [28]. However, studies suggest that using HbA1c to diagnose DM in South Africa can both underestimate and overestimate the prevalence of DM [45, 46]. In people with sickle cell trait, which may extend to more than 15% of the SSA population, HbA1c may underestimate past glycaemia due to the shorter life span of the red blood cells [47, 48]. However, another study reported that using HbA1c to define diabetes resulted in a four times increased prevalence of DM compared to the prevalence based on fasting blood glucose [46]. Finally, we did not distinguish between Type 1 DM and Type 2 DM, although no patient was on insulin therapy, suggesting that all cases were Type 2 DM.

The high rate of undiagnosed DM and IGT underlines the importance of screening for DM as part of routine HIV care. We would recommend to screen for DM at HIV diagnosis using Random Plasma Glucose or HbA1c in all patients, depending on available resources and infrastructure. The optimum screening interval has yet to be determined, but in line with the South African Adult Primary Care guideline triennial screening for patients over 45 years and yearly screening for patients with IGT would be recommended [38]. The co-existence of HIV and DM underlines the need for integrated health care, addressing both HIV and NCDs. To achieve this, a fundamental restructuring of available resources, and increase in capacity, both in human resources and available funding is needed. If regular testing for the development of IGT or DM in patients at risk (age >45 years and physical inactive) cannot be achieved, physicians should be alert to the development of DM-related complaints.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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