The Last Mile: Use of Innovative Technologies to Attain the UNAIDS 90-90-90 Target

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Abstract

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Introduction

Multiple interventions and concerted efforts have led to an overall decline in the incidence of HIV. Despite these gains, new challenges emerge in sustaining the momentum of the fight against HIV. These challenges all call for creative approaches in enhancing implementation of the HIV care cascade to sustain the momentum and safeguard the gains made thus far. Linkage to care following HIV testing and counselling is a critical initial step in the HIV care cascade. However, lack of a unique patient identifier within HIV care services limits utilization of routine programme data due to inaccuracies associated with patient misidentification. e.g. use of testing data to obtain HIV incidence. Attainment and maintenance of viral suppression is the goal of the HIV care cascade. Type 2 diabetes (T2D), as a co-morbidity could affect viral suppression by reduced medication and clinical appointment adherence. With a high prevalence of HIV and an excess risk of T2D in PLHIV, prediabetes is an important target for screening and primary prevention in Sub-Saharan Africa.

Methods

In the first study, we evaluated feasibility and acceptance of an iris scan biometric system for unique patient identification integrated within the routine HIV care clinics in 4 centres in Kenya. All patients were offered the iris scanning and chose to opt-out. They would then proceed with their routine clinic services.

In the second study, we evaluated the prevalence and risk factors for T2D and prediabetes in 2 centres in Central Kenya, using point of care HbA1c and 2nd confirmatory test as per ADA guidelines. We also conducted a budget impact analysis on the cost and affordability of integrating this screening within routine HIV care services. For this, we compared universal screening vs risk-based screening, targeting people with hypertension and obesity.

Results

For unique identification, we offered biometric scanning to 8,794 unique people and a total of 14,942 scans issued an ID. About 1% of people approached refused to have their iris scanned, often due to privacy and confidentiality concerns. The system sensitivity was 94.7%. The system's limitation to issuing an ID was lack of internet connectivity. Time taken for the scanning and demographic profiling process was 3.5 min and this improved with time.

For HbA1c, among 600 participants, we observed an overall prevalence of 5% and newly diagnosed prevalence of 3.4% for T2D. The prevalence of prediabetes was 14.2%. Risk factors for hyperglycemia were age, familial history, hypertension, central adiposity and combination of Tenofovir/Efavirenz.

The unit cost of screening using HbA1c was 2018 USD ($) 42, and a confirmatory test was $6. Risk-based screening was slightly cost-efficient: the unit cost of identifying and confirming T2D per person was $892, needing to screen 21 people to identify one person with T2D, compared to universal screening at $ 1,705 and screening 25 people. Main drivers for unit costs were personnel and reagent costs.

Conclusion

Iris biometrics scanning is a feasible and highly acceptable among newly tested positive and PLHIV already engaged in care as a unique identifier and can be integrated with existing EMR systems for program implementation and scale-up. Screening for diabetes and prediabetes using POC HbA1c was feasible and showed a high prevalence of prediabetes, a modifiable risk factor for T2D and other cardiovascular conditions. It is also affordable if it were to be integrated within the HIV care program in Central Kenya, more so if it were risk-based.

Innovative technologies (iris biometric scanning, point of care HbA1c devices) can therefore be integrated within routine service delivery among PLHIV to improve the HIV care cascade, bring us closer to the end of the epidemic.

Dedication

To my angel Lauren; you inspired me to want this and work towards it, no matter what.

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List of Abbreviations

ADA	American Diabetes Association
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
BMI	Body Mass Index
BP	Blood Pressure
CCC	Comprehensive Care Clinic
CI	Confidence Interval
CKD	Chronic Kidney Disease
CRF	Case Report Form
DCCT	Diabetes Control and Complications Trial
EFV	Efavirenz
EMR	Electronic Medical Records
FBG	Fasting Blood Glucose
FTE	Full Time Equivalent
HCW	Healthcare Worker
HIV	Human Immunodeficiency Virus
HTC	HIV Testing and Counselling
IPSOR	International Society for Pharmacoeconomics and Outcomes Research
LMIC	Low- and Middle-Income country
NCD	Non-communicable Disease
NGSP	National Glycohemoglobin Standardization Program
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
OGTT	Oral Glucose Tolerance Test
PEPFAR	President's Emergency Plan for AIDS Relief
PI	Protein Inhibitor
PLHIV	People Living with HIV
POC	Point of Care
RR	Risk Ratio
SSA	sub-Saharan Africa
STI	Sexually Transmitted Illness
T2D	Type 2 diabetes
TDF	Tenofovir
WHO	World Health Organization

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Introduction

There is a growing global consensus that we can end the AIDS epidemic as a public health threat by 2030.[1]

Multiple interventions have been evaluated and found to be effective in improving various specific aspects of the HIV care cascade, particularly in sub-Saharan Africa.[2-4] This has led to an overall decline in the incidence of HIV. It has also led to reduced HIV-associated morbidity and mortality, with HIV-positive individuals now living longer.[5,6] Despite these gains, new challenges emerge in sustaining the momentum of the fight against HIV. ***Changing health priorities, reduced budgetary allocations specific to HIV and calls for integration of HIV programming into mainstream health systems for sustainability all call for creative approaches in enhancing implementation of the HIV care cascade to sustain the momentum and safeguard the gains made thus far***.[7-10] We must re-shape our thinking and approach to achieve the 90-90-90 targets.[11,12]

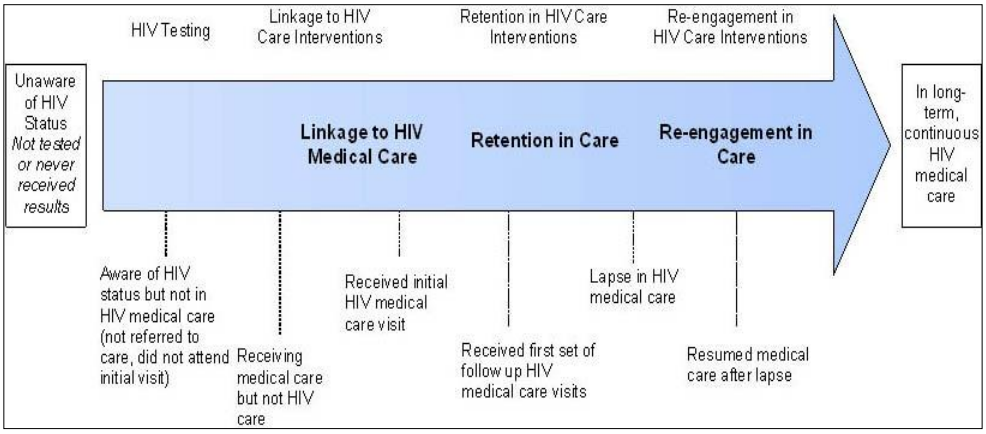


Figure 1: HIV Care Cascade

Linkage to care following HIV testing and counselling is a critical initial step in the HIV care cascade.[13-15] A challenge often encountered in this step is timely and accurate unique patient identification within health services. Patient misidentification could allow for unnecessary multiple HIV testing with wastage of resources as clients move from one testing facility to the next. Lack of a unique patient identifier within health services limits utilization of routine programme data due to inaccuracies associated with patient misidentification. Having a unique identifier within the routine data systems e.g. electronic medical record systems (EMRs) would be a key step in allowing for these data to be used for real-time surveillance and assessing where we are in achieving the 90-90-90 targets.

Biometric identification is a unique patient identifier option. Advantages of using biometrics include their ability to authenticate identity (confirm you are who you say you are),

are highly accurate, hard to forge and convenient, since they are always on the person and cannot be forgotten.[16-18] To our knowledge, our study is the first in SSA to evaluate use of biometrics for identification in a routine healthcare system.While fingerprint scanning has been used in SSA, this has largely been in controlled study/research settings.[19,20] We will contribute new knowledge on the feasibility and acceptability within a routine HIV care setting.

Attainment and maintenance of viral suppression, through retention in care is the goal of the HIV care cascade, for the health benefits to the patient and prevention of transmission to others.[21] To this end, chronic co-morbidities such as type 2 diabetes (T2D) and cardiovascular disease occurring in a HIV-infected individual play an important role. The dual disease burden is associated with increased morbidity and end-organ damage.[22-24] Advanced illness, as is expected with complications from diabetes e.g. diabetic nephropathy, is also associated with reduced adherence as they may be too sick to access healthcare services.[25] More so, multiple clinic appointments due to co-morbidities in addition to the regular HIV clinic visits, seem to be associated with poorer odds of being retained in care.[26,27] With a high prevalence of HIV and an excess risk of T2D in PLHIV, prediabetes is a modifiable risk factor that could be an important target for screening and initiation of therapy for primary prevention in Sub-Saharan Africa (SSA).[28]

The views on use of HbA1c for screening are varied. A HbA1c cut-off of 6.5% has a lower sensitivity compared to fasting glucose (126 mg/dL /7.0 mmol/L) or a 2h-OGTT (200mg/dl/11.1mmol/L) and numerous studies have confirmed that at these cut points the 2-h OGTT value diagnoses more screened people with diabetes.[29,30] However, in practice, a large portion of the diabetic population remains unaware of its status. Thus, the lower sensitivity of HbA1c at the designated cut point may well be offset by the test's greater practicality, and its wider application due to convenience may increase the number of diagnoses made. This may be particularly important among PLHIV who need an alternative to fasting as this can easily interfere with ART adherence since many antiretroviral drugs are often taken with food.

For HbA1c to be used as a diagnostic test, a method certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay must be used. Proficiency testing is not mandated for point of care (POC) testing, thus their use for diagnostic purposes has been challenged.[31] More so, due to the variability in environmental conditions that may affect their functionality, the precision of most POC devices is highly variable.[32] We chose the Cobas b101® analyzer manufactured by Roche®, a leading company in POC diagnostics.[33,34] This platform can assay both HbA1c and lipids. It undergoes NGSP certification annually, ensuring high calibration standards to maintain accuracy.

While there are several HbA1c POC devices in the market, their uptake has been limited due to their high costs. As an innovation, we partnered with Roche® to offer placement of the devices while we procured the test disks and control solutions; remarkably reducing the costs. We piloted this approach as one that can be adopted by the counties in future should they seek to integrate NCD screening in HIV care in their facilities. We chose a cost and budget impact analysis because in Kenya, essential HIV care is payed for by the ministry of health. It's therefore important to policy makers to know the affordability of such a screening program and estimated budgetary implications as they make decisions on whether it's feasible to integrate this within routine HIV services.

We therefore set out to evaluate the application of innovative technologies to these two ends of the HIV care continuum. Specific aims of this dissertation research were: -

1. To describe the feasibility, acceptability and performance of a biometric identification system using iris recognition in routine HIV services in Kenya
2. To evaluate diabetes point-of-care screening integration into routine adult HIV care; determining the prevalence and risk factors for diabetes and pre-diabetes among individuals engaged in HIV care in Central Kenya.
3. To determine the cost and budget impact of scaling-up point of care diabetes screening as delivered through existing HIV treatment programs in Kenya

Conceptual Framework

We framed our evaluations using the Implementation Outcomes Framework (Proctor et al,2011). [35]

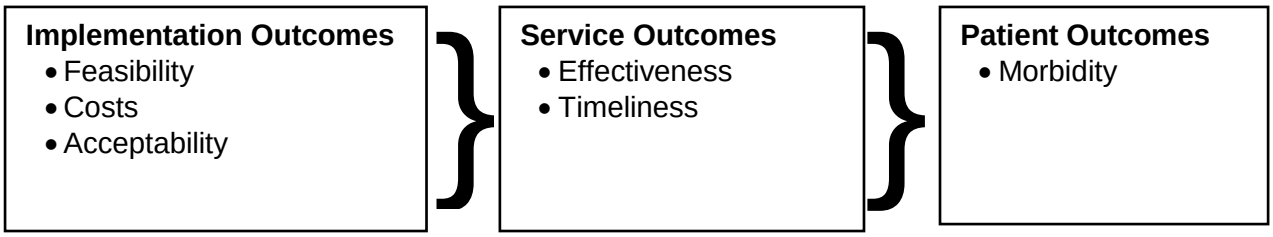


Figure 2: Evaluation of use of innovative technologies to attain the 90:90:90 targets using the Implementation Outcomes Framework

Across the aims, our outcomes were be based on the framework's definitions:

Feasibility: the extent to which an innovation can be successfully used or carried out within a given agency or setting.

Acceptability*:* the perception among implementation stakeholders (providers and recipients) that a given service, practice, or innovation is agreeable, palatable, or satisfactory.

Our service outcomes were i) improved timeliness in diagnosis of diabetes ii) effectiveness in the HIV care cascade through proper identification of those who linked to care after testing HIV-positive and iii) correct classification of people as diabetic or not. While we did not assess actual health outcomes, we posit that these service-level outcomes could be associated with improved patient morbidity among PLHIV.

Mechanism of Action

For Aim 1, our intervention/innovation was the iris biometric recognition system. (Figure 3) We hypothesized that for it to work, it needed to allow for unique identification of individuals entering the HIV care cascade. We observed the unique identifier link testing services to care and treatment services, and a patient could seek services in another facility that is not their "home" facility and be accurately identified.

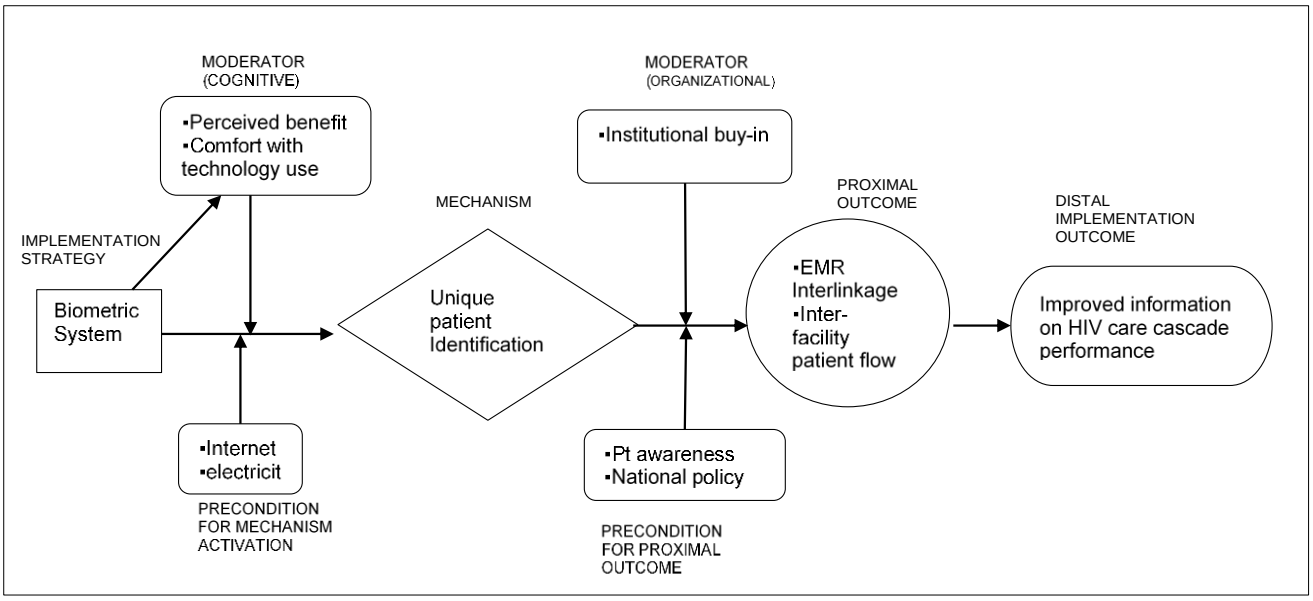


Figure 3:Hypothesized mechanism of action for the biometric system

For the 2nd aim, our intervention/innovation is the POC HbA1c screening. (Figure 4) We hypothesized that for it to work, it needed to correctly diagnose individuals with diabetes and pre-diabetes. We observed that these individuals linked to a clinic where they accessed diabetes care. Though not observed, this was hypothesized to overall lead to improved health outcomes due to early T2D diagnosis.

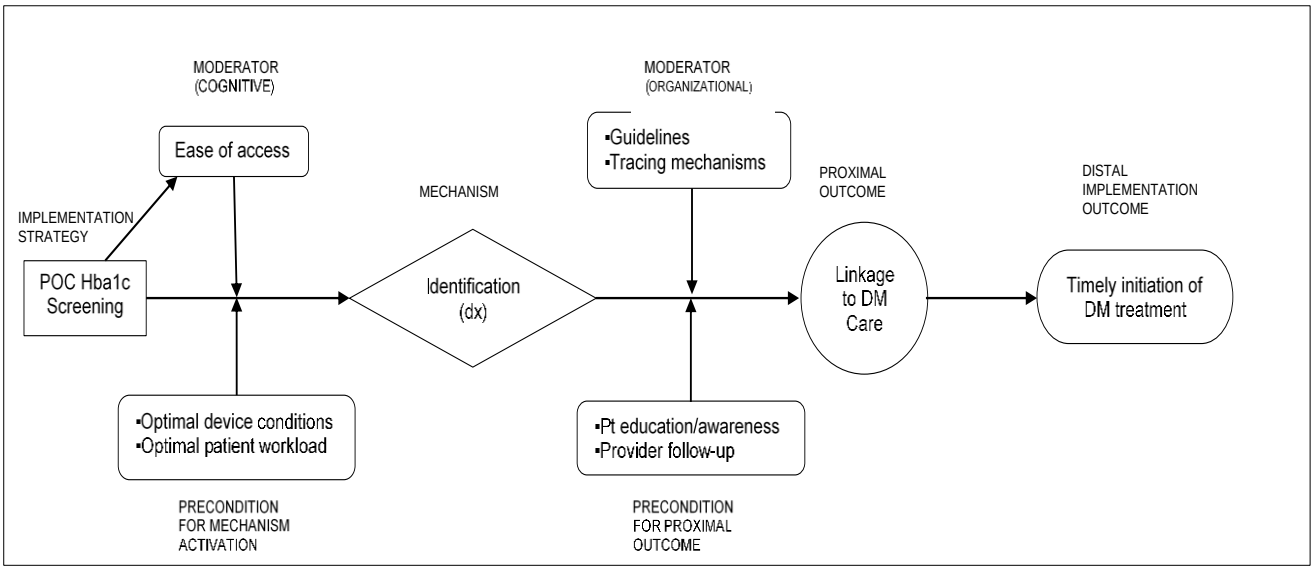


Figure 4:Hypothesized mechanism of action for point-of-care HbA1c screening

Each chapter in this report constitutes a research aim.

The first chapter describes the feasibility and acceptability of integrating an iris recognition biometric identification system into routine HIV care services at four high-volume hospital

facilities in Kenya. The study population were individuals newly testing HIV-positive and individuals known to have HIV and engaged in care at these health facilities.

The second chapter outlines the prevalence and risk factors of T2D and prediabetes in a cohort of 600 ART-experienced individuals enrolled from Kiambu and Kerugoya county referral hospitals.

The third chapter details the affordability of introducing annual point of care HbA1c screening, with a confirmatory fasting blood glucose among adults on ART engaged in care in Central Kenya (Kiambu and Kirinyaga counties), using costing data from the study in aim 2 and other publicly available information on costs and estimated disease prevalence.

Chapter 1: Unique patient identification: Feasibility and acceptability of an iris recognition biometric system in routine HIV services in Kenya

Abstract

Background

Use of routine HIV programme data for surveillance is often limited due to inaccuracies associated with patient misclassification which can be addressed by unique patient identification.

We assessed the feasibility and acceptability of integrating an iris recognition biometric identification system into routine HIV care services at 4 sites in Kenya.

Methods

Patients who had recently tested HIV-positive or were engaged in care were enrolled. Images of the iris were captured using a dual-iris camera connected to a laptop. A prototype iris biometric identification system networked across the sites, analyzed the iris patterns; created a template from those patterns; and generated a 12-digit ID number based on the template. During subsequent visits, the patients' irises were re-scanned, and the pattern was matched to stored templates to retrieve the ID number.

Results

Over 55 weeks, 8,794 unique patients were assigned an ID on their first visit. We had 6,148 repeat scans. Of the total 14,942 scans, 14,151 were issued with the correct ID, hence a sensitivity of 94.7%. The false acceptance rate (a new patient given the ID of another patient) was 0·5% while the generalized false rejection rate (re-scans assigned a new ID) was 4·7%. Overall, 9 (0·1%) agreed to enroll but declined to have an iris scan. The most common reasons cited for declining an iris scan were concerns about privacy and confidentiality.

Interpretation

Implementation of an iris recognition system in routine health information systems is feasible and highly acceptable as part of routine care in Kenya. Scale-up could improve unique patient identification and tracking, enhancing disease surveillance activities.

Introduction

Unique patient identification is an integral part of healthcare service delivery. Correctly identifying patients is critical when undergoing clinical procedures, reporting of test and procedure results, as well as managing administrative functions such as scheduling and billing.[36-38] Unique identification of individuals is essential in case-based disease surveillance. In HIV surveillance, for example, it is impossible to know if the UNAIDS 90-90-90 targets have been achieved if individuals are not uniquely identified and tracked through the care continuum.[11]

The continuum of HIV care spans across multiple access points within the healthcare system; it includes HIV counselling and testing (HTC), care and treatment, as well as antiretroviral therapy (ART) dispensing at the pharmacy, laboratory monitoring and other supportive services. Recent evidence suggests that improving the HIV care cascade and reducing loss to follow-up at each stage is critical for control and reduction of the global HIV epidemic.[39] Patients who default from care after testing HIV-positive are unable to receive the care and treatment required to control their infections, and thus are unable to achieve viral suppression. Throughout sub-Saharan Africa (SSA), estimates indicate that less than 33% of PLHIV are engaged in care from date of diagnosis to the time they begin ART[15,40] and even after ART initiation.[41-43]

Poor retention in HIV care is compounded by patient relocation or change of health facilities, where patients may change their primary healthcare facility and not be truly "lost to follow-up".[44] In the West, almost half of HIV patients lost to follow-up had relocated and remained engaged in care.[45] In Africa, studies show that a sizeable proportion of those classified as "lost-to follow-up" can be tracked to identify their vital status.[46-49] However, these studies have not described the proportion or characteristics of those who have been found to seek care from other facilities. Access to information from these multiple care settings and the retrieval and assembly of relevant patient care information from past episodes of care across different times is required not only for provision of quality healthcare services but also for accurate and timely surveillance. Linkage of this patient care information requires the use of a unique patient identifier.[50]

Globally, unique patient identification within health services is an operational challenge. Many HIV care and treatment programs use traditional text-based matching for patient identification, including personal identifiers such as name, date of birth, and clinic-issued numbers. This approach identifies patients by what they know or possess (e.g., medical ID cards) as opposed to identifying them by who they are; and is often unreliable and inaccurate.[20,51] Text-based matching is often associated with multiple registration: one patient may have multiple IDs or one ID may be associated with multiple individuals or incomplete registration. Misidentification not only compromises patient care at the individual level but also limits utilization of surveillance data from routine programme data due to inaccuracies.[52] Double-registration could lead to overestimation of HIV incidence, with HIV re-testers being counted as newly diagnosed cases. It could lead to misclassification of HIV patients as being "lost to follow up" if they have only changed their care provider yet tracing these subjects' demands significant amounts of effort by healthcare providers, reducing efficiency in already overburdened health facilities.[12] It is therefore imperative to develop and implement unique patient identifiers to improve both longitudinal and geographical patient information linkage.[53,54]

Biometric identification is recognized as one of the six unique patient identifier options by the US Health & Human Services department.[55] Others include the social security number, personal number based on bank card method and unique identifier based on personal immutable properties. These have limitations for use in healthcare, chiefly being the need for federal privacy legislation against unauthorized access and misuse of patient information as they are used beyond healthcare. In Kenya, all adults above 18 years are expected to have a national ID number, based off finger prints. However, this administrative number is not a requisite to receiving healthcare services and not everybody obtains one.

Use of biometrics for unique identification is rapidly growing in low and middle-income countries (LMIC). According to the Centre for Global Development, a significant percentage of large-scale biometrics initiatives are in LMIC.[56] In sub-Saharan Africa as of 2013, use of biometrics for identity authentication was largely in elections, followed by

social/cash transfers and thirdly in health.[16] Iris scanning, a biometric identifier, has great potential for integration with health information systems.[57] A large-scale iris identification system, especially if launched in combination with a patient registry and electronic medical record system, would allow for subjects to move more naturally through the health system, be recognized at any facility, and receive the care they need then rather than only at their "home" facility. Given the global burden and the stigma associated with HIV, understanding the uptake and performance of biometrics in this setting is important in assessing the utility of such technology.

We therefore assessed the feasibility and acceptability of integrating an iris recognition system into routine HIV testing and counselling (HTC) and linkage to HIV comprehensive care and treatment clinics (CCC) in Kenya.

Methods

Study design

This was a longitudinal study where iris scanning was used to uniquely identify individuals at study enrolment and at their routine clinic follow-up visits.

Study setting and population

The study was conducted in four high-volume hospital facilities in Kenya. Kenyatta National Hospital (KNH) and Kiambu District Hospital are in Central Kenya, serving largely an urban-poor and peri-urban population, respectively, while Kisumu East County Hospital and Kombewa Sub-County Hospital are in Western Kenya with largely rural catchment populations.

We recruited two populations: individuals newly testing HIV-positive at ambulatory testing sites and individuals known have HIV and engaged in care at the four health facilities. Participants were 18 years and older and those enrolled in other research studies were excluded. Participants were enrolled continuously from February 2015 to February 2016.

Procedures and follow-up of study participants

Potential participants were informed of the study by HTC counsellors and were taken through a scripted oral consent process. The consenting process emphasized the participants' voluntary participation and that opting out would not affect their clinical care. An

electronic version of the national HTC case report form used as part of standard care to assess patient risk factors and reasons for testing was administered by HTC counsellors. A detailed description of this case report form has been published previously.[58] Data was collected on tablets using custom-designed Open Data Kit forms.[59] Two versions of the HTC case report form were used; one for those who had just tested HIV-positive and another version for those known to be HIV-positive and already engaged in care. This information was encrypted and uploaded, via an encrypted connection, into a registry housed at the National AIDS & STI Control Programme (NASCOP). Once encrypted, the HTC counsellors on site no longer had access to identifiable patient information. The case report form (CRF) was only administered at intake. Only their names and telephone numbers were collected at subsequent visits as existing identifiers to validate the iris biometric ID.

Iris scanning and assignment of a unique identifier:

Binocular iris recognition cameras from CMITech® (model BMT-20) connected via USB to laptops were used to capture iris images. A prototype iris recognition system software designed by *iRespond® was* networked across the study sites to analyze the iris patterns; create a template from those patterns and generated a 12-digit ID number based on the template, which was used as the unique patient identifier. (Figure 5)

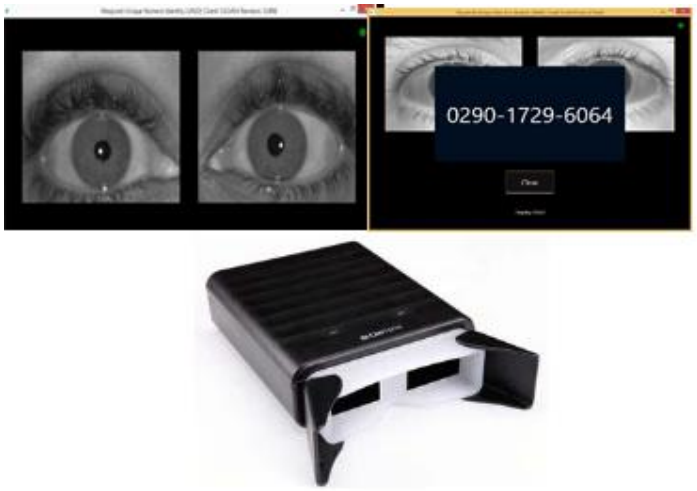


Figure 5:Iris Scan, Camera and ID generation as it appears on screen

This template was stored on the local laptop and uploaded to a secure server. When a patient was re-scanned, the system matched the iris pattern by searching against templates stored on the laptop first. If a match was not obtained locally, the system then searched the aggregate templates from all the enrolment sites on the server. For newly tested

participants, their irises were re-scanned, and the pattern matched to stored templates to retrieve the ID number if they linked to care at the CCC within the study hospital. Those who were already engaged in care were re-scanned and their ID number retrieved at any subsequent visit for routine care. This ID was then manually keyed into the electronic data collection form.

Assessment of feasibility and acceptability

Feasibility was assessed from two dimensions: infrastructure and human resource requirements for set-up and implementation of the system; marked by staff technological competence and average time spent per patient intake. Two biometric stations (camera, laptop, tablet and internet Wi-Fi dongle) were set up in each hospital; one at the HIV testing service delivery point and another at the HIV care clinic. Each biometric station was staffed by one HTC counsellor. Their average education level was diploma training and they were all conversant with use of smartphones/tablets. Training on the set-up, iris scanning, and set-down process was conducted over two days. Additional training on electronic data collection was over 2 days

The second dimension was the system performance as measured by hardware failures indicated by internet failure, camera failure or laptop malfunction and system accuracy as determined by the system false acceptance and false rejection rates. False acceptance was defined as issuance of an already existent ID to a new or different patient while false rejection was defined as issuance of a new ID to a client who had already been issued with a unique ID.

Acceptability was defined as the number of participants agreeing to iris scanning as a proportion of all the individuals approached. General reasons for declining iris scanning were elicited.

Ethical approval

Ethical review and approval were obtained from the University of Washington Institutional Review Board and the Kenyatta National Hospital-University of Nairobi Ethical Review Committee.

Results

The study enrolled 8,794 unique patients with HIV who agreed to have a biometric iris scan. 1,136 had newly tested HIV-positive, while 7,658 knew their HIV status and were already in care. Their demographic characteristics are summarized in Table 1. Overall, 5,663 (66%) were female; median age was 35 years [Interquartile Range (IQR): 29, 42]; 3.456 (39%) were from the rural facilities and 1,136 (13%) were enrolled at the time they received their HIV diagnosis for the first time (newly testing positive).

Characteristic	Rural (n=3,456) Median (IQR) or n (%)	Urban (n=5,338) Median (IQR) or n (%)
Age	33 (27-41)	36 (30-42)
Sex: Female	2,190 (65)	3,473 (66)
Pregnant (females)	398 (18)	491 (14)
Time when tested		
Newly testing positive	486 (14%)	650 (12%)
Known positive	2,970 (86%)	4,688 (88%)
Marital Status		
Single	320 (10%)	764 (15%)
Married Monogamous	1,822 (54%)	2,914 (55%)
Married Polygamous	474 (14%)	143 (3%)
Live-in Partner	6 (1%)	288 (5%)
Divorced	138 (4%)	630 (12%)
Widow/Widower	590 (17%)	546 (10%)
Initiated HIV test		
Provider-Initiated Testing	1,940 (58%)	3,488 (66%)
Client-Initiated Testing	1,410 (42%)	1,797 (34%)
Tested for HIV previously	697 (21%)	2,124 (40%)
Tested as a couple	541 (16%)	1,026 (19%)
Discordant couple	117 (26%)	355 (41%)
TB Suspect	140 (4%)	112 (2%)
TB-infected	491 (15%)	822 (16%)

Table 1: Demographic characteristics of participants by region

During subsequent clinic visits 4,242 had one re-scan; 1,262 had 2 re-scans and 574 were re-scanned 3 or more times, bringing the total number of iris scans conducted over the entire study to 15,457.

Of the 1,136 newly testing, 522 (46%) linked to care at the same CCC; while 2 were identified having linked to care at a different site within the 4 study sites. Two patients

presenting as newly testing for HIV were identified at the testing points as re-testers having been previously issued a unique ID at one of the 4 study sites.

Acceptability

Of the 8,894 patients approached, 100 (1%) declined to be enrolled in the study. Among those enrolled, 13 (0·14%) accepted to have their data collected electronically but declined to have the iris biometric scan. Four of these individuals later agreed to have an iris scan on a subsequent visit. There was no difference in age or gender comparing those who accepted iris scanning to those who declined.

Reasons for declining enrolment into the study were privacy concerns, as some clients did not feel safe about their medical details being transmitted via the internet and others expressed concern about confidentiality and accidental disclosure if records were accessed by other people. Another reason for declining was the lack of time; some believed the entire process would take too much of their time and they were in a hurry. For those who had just tested HIV positive, some declined study enrolment as they were in shock upon learning their HIV status and requested more time to process the results.

Of the 9 who enrolled in the study and then specifically declined iris scanning, 3 declined over privacy concerns; one cited religious/cultural concerns; one did not understand the technology; two feared the biometric camera; and one person had an eye problem and feared that the scan would exacerbate it. One person did not have any specific reason for declining.

Implementation

Time to complete iris scanning

The average time taken to fill the CRF, conduct the iris scan and obtain a unique ID, fill the ID on the CRF and send the encrypted form for an enrolment visit across all the sites was 6·4 min [IQR: 4·0, 15·7]. There was improvement in time taken as the HTC counsellors grew accustomed to the procedures, as shown in Figure 6.

The average time taken to conduct an iris scan and retrieve a previously issued unique ID (re-scan), fill the CRF and send the form for a re-visit across all the sites was 3·5 min.

[IQR:1·8, 5·8]. This retrieval time remained constant over the duration of the study despite the increase in size of the iris template database.

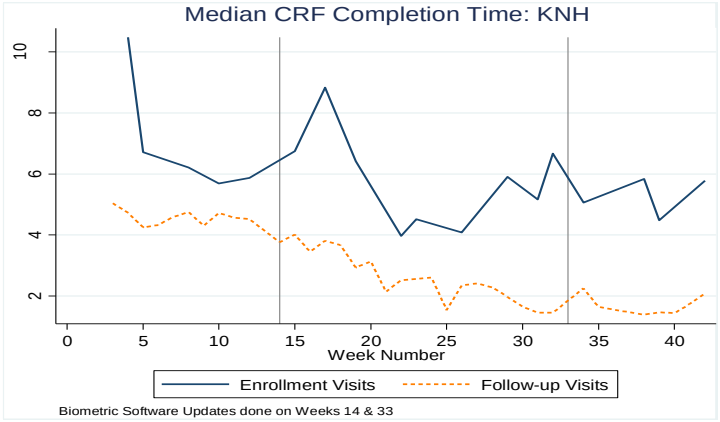


Figure 6: Time to complete iris scanning

System Performance

Of the 15,457 scans, the system issued a unique ID (both new identification and verification) 14,942 times. Of these instances, 14,151 were the correct IDs. The system's sensitivity was therefore 94·7%. (Figure 7)

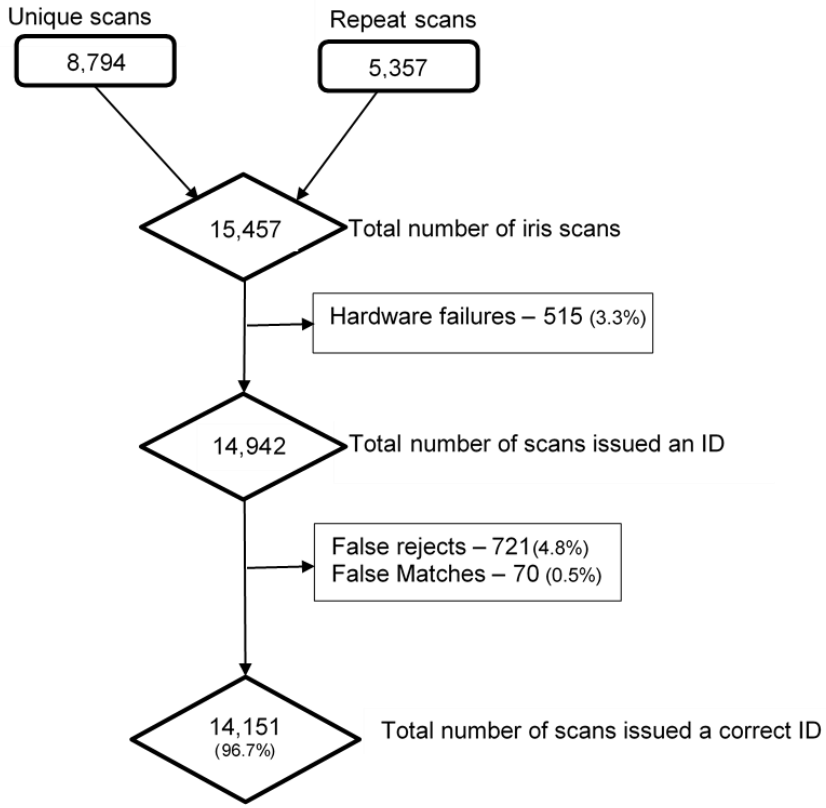


Figure 7: System Performance

Reasons for failure to issue a unique ID are summarized in Figure 8, with internet failure being the main one. Issue of an already existent ID to a new patient (false match rate) was 0·5% while the failure of the system to recall an existent ID (false reject rate) was 4·8%. These identification errors improved with time as the software algorithm was improved to match the populations' irises.

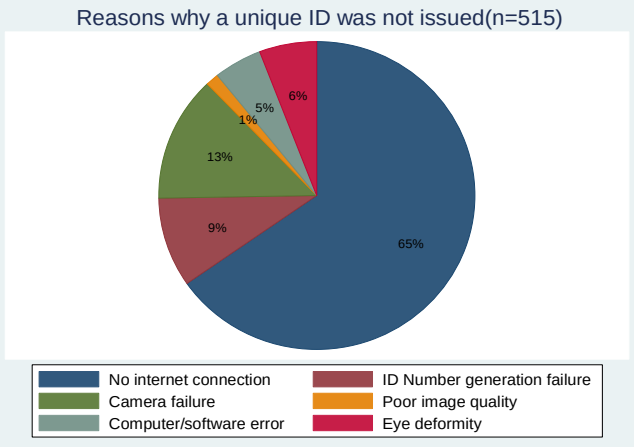


Figure 8: Reasons why a unique ID could not be issued

Discussion

Iris biometric scanning was highly acceptable in both rural and urban settings in Kenya with 8,794 unique patients accepting iris scanning at least once and 6,663 repeat scans obtained over the study period. While high acceptability of biometric identification has been noted among PLHIV populations, this has often been described in key populations and clinical research contexts.[60,61] Our high acceptability rate (98·9%) was remarkable since the project was integrated within routine programmatic service delivery of HIV testing and comprehensive care and treatment services. It was even higher than was observed in a HIV clinic in Los Angeles, California where upon survey, 72% of patients reported they would accept fingerprint biometrics for identification during their routine clinic visit.[60,61] Compared to fingerprints, iris scanning may be more acceptable in our setting because it is not used in any civil or government identification processes (e.g. Police records), thus eliminating fear of being arrested.[62] The high acceptability of multiple re-scans during clinic re-visits in our study shows that patients are willing to have their iris biometric data used for authentication during a clinic visit. To our knowledge, this is the first study in Africa demonstrating use of iris recognition in routine healthcare services.

Our low study participation refusal rate of 1·1% is comparable to other studies even in the US and Europe.[63] Among the few who declined to have an iris scan (9 out of 8,794), the main reason cited was privacy and confidentiality concerns as data would be transmitted over the internet. This may have been exacerbated by the obvious Wi-Fi dongle attached to the laptop during enrolment. Such dongles are commonly used for internet access locally and may have been associated with uses such as email or Facebook. For those who did not understand the technology or were afraid of the biometric camera, use of less intimidating gadgets (e.g. goggles or smartphones) could address their concerns.

Furthermore, our high biometric system sensitivity/accuracy (95%) is comparable to other studies using iris biometrics and is higher than the sensitivity observed with fingerprint biometrics in Ghana (68·7%) and Uganda(75.5%).[63] [64,65] The average system fail rate was low (~5%) and declined over time. This was because in the initial software development stage, all identity was set at the lowest matching thresholds. However, participants in this study tended to have high image contrast between the sclera (white area) of the eye and the surrounding skin tone. This led to a high proportion of new identities generated for existing participants (false rejects), demonstrating a need for biometric tuning of the rejection and matching parameters. Tuning included adjustments to image quality rejection due to out of range contrast ratios, to limit new ID generation for re-scanning participants. By reviewing these early issues and adjusting the software, the accuracy was continuously improved throughout the study.

This is one of the sentinel studies in Africa demonstrating such high levels of biometric identification system accuracy outside of a controlled trial context, showing that such systems can feasibly be optimized for use in 'real world' healthcare settings. Despite the small scale of the project (4 sites), we demonstrate the utility of a unique identifier in improving program data inaccuracies. By identifying two re-testers posing as first-time testers, the biometric identification allowed them to be correctly classified as re-testers. In the absence of the iris identification system, the two patients who linked to different CCCs from their testing sites could as well have been classified as having failed to link to care. If

used at-scale, this system allows for correct patient classification, improving the accuracy of programme data and could potentially support case-based HIV surveillance.

By the end of the study, in sites with a strong internet signal, the average time required for enrolment for a newly tested HIV-positive individual was 4·6 minutes, with the actual image capture and template generation taking about 20 seconds. This was even shorter during re-visits where only the biodata was collected. This is comparable to another study using fingerprint biometrics in Ghana that had an average of 7 min for a new enrolment.[64] Although ours was longer than the 2 minutes Corby et al observed in Brazil using iris scanning[63] , the length of their questionnaire and other enrolment procedures asides from ID assignment are not described. Unlike fingerprint scanning which sometimes requires scanning of multiple fingers to improve sensitivity; the iris scanning is faster as it is typically done once. A short transaction time (time taken to issue an ID) is important as the additional waiting time introduced into the system by use of the iris recognition time is minimal. In our case, it could be enhanced by boosting the internet signal to ensure constant internet connectivity.

Some important limitations need to be considered. Though small, the false acceptance error rates (4·7%) could cause duplication of patient counts while the false positive errors could lead to patients sharing IDs. Security questions incorporating other text unique identifiers e.g. national ID number could be added to the data input system as options to facilitate confirmation of matching without compromising identity. ID transcription errors (from screen to electronic medical record system) could also be eliminated by incorporating automated ID transfer technologies, such as Bluetooth transfer or on-screen scanning of data matrix from biometric software. Given that most of the system issues were attributable to lack of consistent internet connectivity particularly in rural areas, this could be improved by use of a system with offline functionality.

Conclusion

Our findings of high acceptability and system performance integrated within routine healthcare services demonstrate that use of iris biometrics for unique patient identification in routine HIV programmes is feasible.; supporting the UNAIDS position that “unique individual identifiers will strengthen fragmented health services in countries by linking data held within facilities and enabling the flow of information across the general health system and thereby also enhancing the quality, comprehensiveness and continuity of HIV-specific services”.[57] Our findings demonstrate potential for iris scanning to be scaled up as a unique patient identifier that can be effectively linked to electronic medical records and enhance individual tracking within the HIV care continuum, even in resource-limited settings.

Chapter 2: Risk Factors for Elevated Hemoglobin A1c among ART-experienced Kenyan adults with HIV

Abstract

Introduction

Findings on the burden of type 2 diabetes (T2D) among people living with HIV (PLHIV) in sub-Saharan Africa (SSA) are mixed, due to heterogeneity in antiretroviral therapy (ART) use among study populations and use of varied definitions of T2D. We assessed prediabetes and T2D prevalence and risk factors using HbA1c among ART-experienced PLHIV in Central Kenya.

Methods

We used a cross-sectional design enrolling PLHIV aged ≥ 35 years who had been on ART for at least 5 years, comparing a rural and urban site. Socio-demographics, family history of diabetes, and prior diagnosis and treatment of diabetes or hypertension were obtained through questionnaires. HbA1c was assayed using Cobas *b 101*®, a point-of-care platform. HbA1c levels ≥6.5% were confirmed using a random blood glucose. For HbA1c levels between 5.7% and 6.4%, participants were requested to return the following day for a fasting blood glucose (FBG). Risk factors were assessed using multivariable log-binomial regression.

Results

Of the 619 participants enrolled, 19 (17.4%) of the participants with prediabetic HbA1c levels failed to return for FBG. Of those completing study procedures, 83 (63.8%) were female. The median age was 46.8 years (interquartile range [IQR]: 41.6, 53.1). The median time since HIV diagnosis was 9.3 years (IQR: 7.6, 11.1) and median duration on ART was 8.1 years (IQR: 6.5 -10.0).

Overall prevalence of diabetes was 5% (30/600). Ten participants were known to be diabetic, hence the prevalence of newly diagnosed T2D was 3.4% (20/590). The prevalence of prediabetes (Hba1c 5.7%-6.4%), was 14.2% (84/590).

Significant predictors of elevated HbA1c were increased age (Prevalence ratio [PR]: 1.10, CI: 1.02, 1.18, p= 0.012), history of T2D in a first-degree relative (PR: 1.43, CI: 1.07, 2.3, p=

0.015), hypertension (PR: 1.43, CI: 1.07 to 2.3, p= 0.015) and central adiposity (PR: 2.11, CI: 1.57 to 2.84, p= <0.001).

Conclusion

The high prevalence of prediabetes, a significant predictor of T2D, and other risk factors among a population who attend clinic regularly highlights an opportunity for screening and early intervention.

Introduction

Globally, PLHIV have been shown to have a higher prevalence of T2D and prediabetes relative to those without HIV.[66] Chronic systemic inflammation associated with the virus and toxicity related to antiretroviral therapy (ART) have been linked to pancreatic insufficiency and peripheral insulin resistance.[67-74] With the test-and-treat approach, PLHIV are also experiencing age-associated metabolic conditions, including T2D and cardiovascular disease, due to increased life expectancy following early initiation of ART. [75-77] We sought to characterize the prevalence of prediabetes, T2D and associated risk factors for hyperglycemia among ART-experienced PLHIV in in a rural and urban environment in Central Kenya.

In other regions, the burden of diabetes and prediabetes among PLHIV is high, with T2D incidence ranging from 3.4 to 11.1 per 100 person years. More so, prediabetes is important as it has a better predictive value for developing T2D than individual risk factors including obesity and familial history. This highlights the need for screening and early treatment in this sub-population. However, findings on prevalence of T2D among PLHIV in sub-Saharan Africa (SSA) are mixed. While earlier studies found up to 4-fold increased risk for T2D among PLWH compared to HIV-negative individuals,[78-80] a review of recent studies in SSA reported T2D prevalence ranging from 0.5% to 9.3% among HIV positive and 0.5% to 3.6% among HIV-uninfected individuals.[81] These conflicting findings could be due to diversity in tests or different criteria for diagnosis of T2D. Heterogeneity in ART use, for example including both ART-naïve and ART-experienced patients could also explain the mixed findings.[82,83] The earlier studies also showed being on protease inhibitors (PI), high viral load and low CD4 count as predictors of T2D among PLHIV. With universal ART roll-out, we need to identify persistent risk factors for T2D among PLHIV who have immune reconstitution and viral suppression, including newer classes of ART drugs.

Optimal screening approaches for diabetes suitable for PLHIV in resource-limited settings need to be identified. Glycated hemoglobin (HbA1c) captures the glycemic status over a 3-month period and does not require fasting, making it a feasible and acceptable screening tool in this population.[84] While older studies reported that HbA1c underestimated

T2D prevalence in PLHIV populations, these were among adults with severe HIV-associated immunosuppression.[85-87] Recent studies that include PLHIV on ART have found similar test performance comparing HbA1c to other screening tests.[88-90] Availability of stable and standardized point of care (POC) HbA1c devices has increased access to HbA1c testing and POC HbA1c could be a feasible screening tool in the Kenyan population.[33,34,91-93]

Based on these mixed findings, we conducted a cross-sectional study used screening via HbA1c and a confirmatory fasting blood glucose to assess the burden of prediabetes and T2D and associated risk factors for hyperglycemia among ART-experienced PLHIV in Central Kenya.

Methods

Study Setting and Participants

During a routine clinic visit, PLHIV aged ≥ 35 years were recruited from the HIV Comprehensive Care Centers at Kiambu, an urban and Kerugoya, a rural referral hospital(s) through systematic random sampling from January through July 2018. Eligibility criteria included having been on ART for at least 5 years and having had a clinical review within the previous 6 months. Patients with a history of blood transfusion or anemia in the preceding six months and pregnant women were excluded. Written informed consent was obtained by a dedicated study nurse. The study was approved by the Kenyatta National Hospital/University of Nairobi Ethics Review Committee and the University of Washington Human Subjects Division.

At enrolment, a questionnaire adapted from the World Health Organization (WHO) Stepwise Approach to Surveillance (STEPS) instrument was administered to obtain demographics, risk factors such as smoking and alcohol use, family history of diabetes, knowledge of diabetes screening recommendations and prior diagnosis or treatment of diabetes and/or hypertension. Factors influencing hemoglobin levels such as other medications and self-reported hemoglobinopathies, including sickle cell anemia, were obtained.

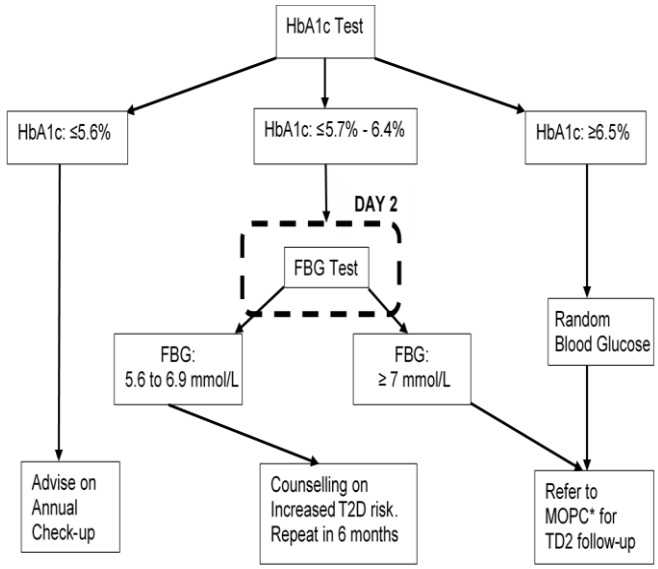
HIV-specific data including the date of HIV diagnosis, current and previous ART regimens and blood pressure (BP) readings from the two previous clinic visits were extracted

from participants' clinical charts and confirmed from the electronic medical records. Weight, height, waist and hip circumferences were measured according to WHO international standards.[94] A blood pressure reading was obtained with the participant seated and legs uncrossed, as part of routine clinic visit procedures.

Glucose Screening

An HbA1c assay was done using Cobas *b 101*® by Roche©, a point-of-care instrument which measures percent HbA1c and mmol/mol HbA1c by photometric transmission measurement. Internal quality controls were implemented as per the device manufacturer's instructions and run every two weeks. The device coefficient of variation provided by the manufacturer was 0.19%. Venous samples were obtained from 1% of the participants and assayed in an accredited laboratory for comparison with the POC values, showing good collinearity, with a coefficient of correlation of 0.97 and a %mean difference of 2%.

For HbA1c levels between 5.7% and 6.4%, participants were requested to return fasting the following day for a fasting blood glucose using Accu-Check® by Roche©. For HbA1c levels ≥6.5%, a random blood glucose was used to confirm T2D diagnosis, as per the American Diabetes Association (ADA) guidelines where a diagnosis needs to be confirmed using a different test. [Figure 9]. Some patients who needed a fasting lipid profile also got a fasting blood glucose regardless of their HbA1c level.



FBG – Fasting Blood Glucose, HbA1c – Glycated Hemoglobin, MOPC -Medical Out Patient Clinic, T2D – Type 2 Diabetes, RBG-Random Blood Glucose

*MOPC-Primary care clinic where all diabetic patients are followed up and routinely reviewed every 3-6 months.

Figure 9: Study Flow

Definitions of diabetes and hypertension

Hypertension was defined by two parameters: (1) two readings where systolic BP ≥140mm Hg and/or diastolic BP ≥90mm Hg [95], using the enrollment BP measurement along with a second BP reading from the clinical chart or (2) reported use of antihypertensive medications. Prediabetes was defined as a HbA1c between 5.7% and 6.4%. Diabetes was defined by three parameters: (1) a HbA1c ≥6.5% and random blood glucose ≥11.1 mmol/L or (2) a HbA1c between 5.7% and 6.4% and fasting blood glucose ≥7.0 mmol/L or (3) reported use of insulin or oral hypoglycemics.

Statistical Analysis

The sample size was based on an a priori estimated prevalence of diabetes among the PLHIV population of 16% to 25%[80,83,96]. Using a normal approximation to the binomial distribution, we needed a sample size of 588 to observe an estimate of 25% prevalence of T2D with a precision interval of +/- 3.5%.

Due to lower-than-expected numbers of diabetic participants in the sample, prediabetes and diabetes were combined to create a binary outcome for the regression analysis. Multivariable log-binomial regression was used to assess associations with prediabetes and diabetes. Covariates considered include age, sex, family history of T2D, time since HIV diagnosis, duration on ART, ART drugs, alcohol use, hypertension, body mass index (BMI) and waist circumference. Following bivariable analysis, covariates with a p-value of ≤0.05 were included in the multivariable model.

Among a sub-set of participants who had both FBG and HbA1c, covariates in the bivariable models in the primary analysis whose results were near-significant (p= ≤0.1) were fit using FBG as the outcome, to assess hyperglycemia as defined by HbA1c compared to FBG. A cut-off of 5.6mmol/L for FBG was used to create a binary outcome. Stata version 14 was used for all analyses (StataCorp, College Station, TX).

Results

Cohort demographics and prevalence of prediabetes and T2D

Of the 600 participants who completed study procedures, 217 (36.2%) were male, with a higher proportion of males observed in the peri-urban clinic compared to the rural clinic. [Table 2]. The median age was 46.8 years (interquartile range [IQR]: 41.6-53.1). One hundred and thirty-six (45.6%) participants from the rural clinic were hypertensive compared to 79 (26.2%) from the peri-urban clinic, and none of their medication history was recorded in the electronic medical system. Overall 145 (24.2%) reported being previously screened for diabetes, with a higher proportion 89 (29.9%) in the rural clinic compared to 56 (18.5%) in the peri-urban clinic. The median time since HIV diagnosis was 9.3 years (IQR: 7.6 -11.1), while the median duration on ART was 8.1 years (IQR: 6.5 -10.0). Majority (93%) were on a combination of two nucleoside reverse transcriptase inhibitors (NRTI); tenofovir [TDF] or zidovudine [AZT] and lamivudine [3TC]), and a non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz [EFV] or nevirapine. Only 7% were on a protease inhibitor.

Table 2: Demographics, anthropometric measurements, HIV disease and ART characteristics among PLHIV in Central Kenya

Covariate	All participants	Urban Clinic	Rural Clinic
	n=600	n=302	n=298
	Median (IQR) or n (%)	Median (IQR) or n (%)	Median (IQR) or n (%)
Age (years)	46.84 (41.55 to 53.12)	46.57 (41.17 to 53.04)	46.87 (42.03 to 53.36)
Sex (male)	217 (36.2%)	125 (41.4%)	92 (30.9%)
Education Level			
Primary	334 (55.7%)	155 (51.3%)	179 (60.1%)
Secondary	191 (31.8%)	107 (35.4%)	84 (28.2%)
Post-Secondary	49 (8.2%)	32 (10.6%)	17(5.7%)
College	7 (1.2%)	2 (0.7%)	4 (1.7%)
None	19 (3.2%)	6 (2.0%)	13 (4.4%)
Time since HIV diagnosis (years)	9.3 (7.6 to 11.1)	9.1 (7.7 to 11.02)	9.7 (7.6 to 11.4)
Time on ART	8.1 (6.5 to 10.0)	7.97(6.6 to 9.6)	8.3 (6.4 to 0.3)
Current ART Regimen			
NRTI+3TC+NNRTI	560 (93.3%)	284 (94.0%)	276 (92.6%)
NRTI+3TC+PI	39 (6.5%)	17 (5.6%)	22 (7.4%)
Other	1 (0.2%)	1 (0.4%)	0 (0.0%)
Previously diagnosed T2D	10 (1.7%)	3 (1.0%)	7 (2.3%)
Family history of T2D	125 (20.8%)	60 (19.9%)	65 (21.8%)
Smoking			
Never	431 (71.8%)	206 (68.2%)	225 (75.5%)
Previous	144 (24.0%)	82 (27.2%)	62 (20.8%)
Current	25 (4.2%)	14 (4.6%)	11 (3.7%)
Alcohol Use	63 (10.5%)	42 (13.9%)	21 (7.0%)
Hypertension	215 (35.8%)	79 (26.2%)	136 (45.6%)
BMI (kg/m^2)	24.14 (20.91 to 27.83)	24.75 (21.11 to 28.53)	23.81 (20.82 to 27.25)
Normal/Underweight	336 (56.0%)	156 (51.7%)	180 (60.4%)
Overweight	166 (27.7%)	85 (28.1%)	81 (27.2%)
Obese	98 (16.3%)	61 (20.2%)	37 (12.4%)
Waist-Hip Ratio (≥0.9 for males and ≥0.85 for females)	200 (33.3%)	158 (52.3%)	171 (57.4%)
Waist Circumference (>102 for males and >88 cm for females)	329 (54.83%)	102 (33.8%)	98 (32.9%)
Previous Blood Sugar Screening	145 (24.2%)	56 (18.5%)	89 (29.9%)
Random Blood Glucose	136 (93.8%)	54 (96%)	82 (92%)
Fasting Blood Glucose	8 (5.5%)	1 (2%)	7 (8%)
HbA1c	1 (0.7%)	1 (2%)	0 (0%)
Reasons for Blood Sugar Screening			
Free e.g. Medical camp	52 (35.9%)	19 (34%)	33 (37%)
Test annually by myself	41 (28.3%)	12 (21%)	29 (33%)
Test annually by physician	27 (18.6%)	13 (23%)	14 (16%)
Part of clinical work-up	122 (15.1%)	9 (16%)	13 (5%)
Due to familial history	1 (0.7%)	1 (2%)	0 (0%)
Others	2 (1.4%)	2 (4%)	0 (0%)

ART, antiretroviral therapy; BMI body mass index; 3TC, lamivudine; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; T2D, type 2 diabetes

At enrollment, 10 (1.7%) of 600 participants were known to have diabetes. The prevalence of newly diagnosed T2D among those not known to be diabetic was 3.4% (20/590), with fourteen cases (2.4%) having diabetes as defined by HbA1c ≥6.5% and random blood glucose >11.1mmol/L and six cases having diabetes as defined by HbA1c 5.7% - 6.4% and fasting glucose ≥7.0mmol/L. The overall prevalence of diabetes was therefore 5% (30/600). The prevalence of prediabetes (HbA1c 5.7%-6.4%) was 15.3% (90/590) [Figure 10]. Nineteen (17%) of participants requested to return for fasting glucose failed to return.

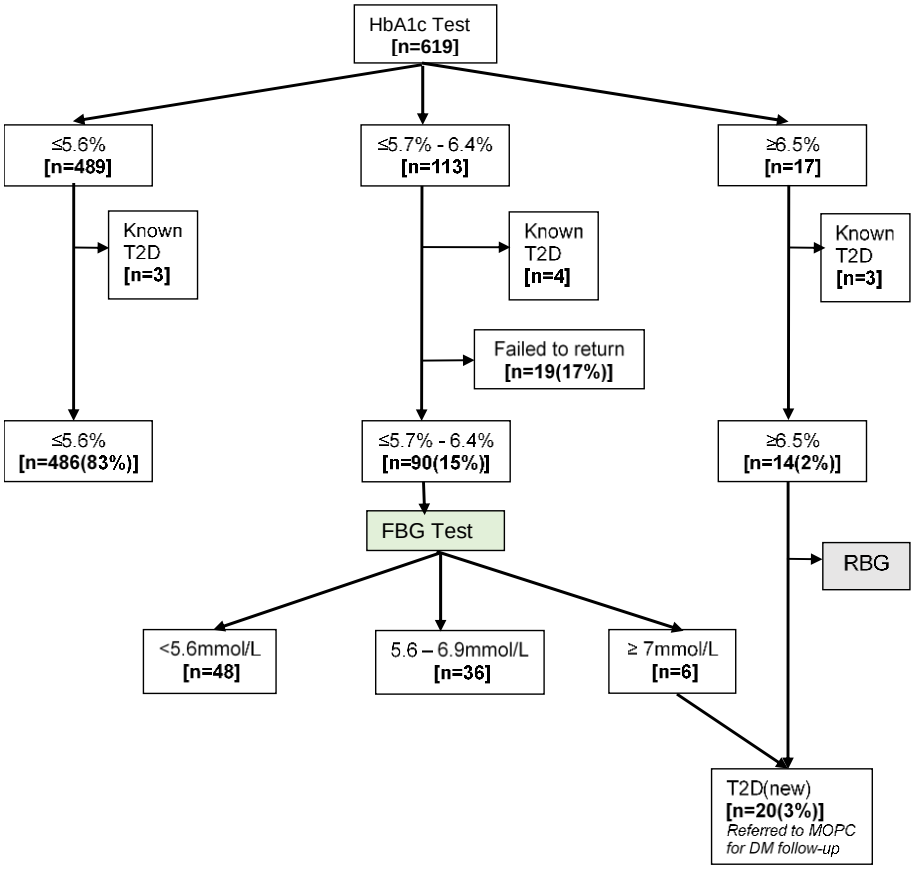


Figure 10: Prevalence of diabetes and prediabetes

Factors associated with prediabetes and diabetes

From the multivariable log-binomial regression, age was significantly associated with prediabetes and diabetes, with a 10% increase in the risk ratio for every 5-year increase in age. (Risk ratio [PR]: 1.10, CI: 1.02 to 1.18, p= 0.012). People with a family history of diabetes among their first-degree relatives were 1.43 times as likely to have prediabetes and diabetes (PR: 1.43, CI: 1.07 to 2.3, p= 0.015). Hypertensive patients were 1.57 times as likely to have prediabetes and diabetes compared to those without hypertension (PR: 1.57, CI: 1.17 to 2.10, p= 0.002) [Table 2]. Diabetic and pre-diabetic HbA1c values were more

than twice as likely among those who with central adiposity (waist circumference>102 cm for males and >88 cm for females) compared to those with normal waist circumference (PR: 2.11, CI: 1.57 to 2.84, p= <0.001). Bivariate analysis showed independent association at the p<0.10 level between elevated HbA1c and regimens with the NNRTI Efavirenz (PR: 1.81, CI: 1.28 to 2.56, p= 0.001) as well as regimens with TDF (PR: 1.53, CI: 0.97 to 2.41, p= 0.069). People on current or previous regimens containing EFV and TDF were twice as likely to have prediabetes and diabetes compared to those with neither drug in their regimen (PR: 2.04, CI: 1.26 to 3.30, p 0.004) [Table 3]. Time since HIV diagnosis, duration on ART, sex or being on a PI-containing regimen were not associated with prediabetes and diabetes in bivariable analyses and these factors were excluded from the multivariable model.

Table 3: Log-Binomial Regression for predictors of diabetes and prediabetes

Covariate	Unadjusted RR (95% CI)	p-value for unadjusted RR	Adjusted RR (95% CI)	p-value for adjusted RR
Age (5yrs)	1.17 (1.07 to 1.28)	0.001	1.10 (1.02 to 1.18)	0.012
Sex (male)	0.75 (0.52 to 1.08)	0.12		
Time since HIV diagnosis (years)	1.06 (0.99 to 1.15)	0.12		
Time on ART	1.06 (0.98 to 1.15)	0.17		
Family history of T2D	1.61 (1.13 to 2.3)	0.009	1.43 (1.07 to 1.90)	0.015
Alcohol Use	0.66 (0.34 to 1.29)	0.228		
Hypertension	1.7 (1.22 to 2.37)	0.002	1.57 (1.17 to 2.10)	0.002
Waist Circumference (>102 for males & >88 cm for females)	2.19 (1.57 to 3.05)	<0.001	2.11 (1.57 to 2.84)	<0.001
BMI				
Normal	REF			
Overweight	1.44 (0.96 to 2.15)	0.081		
Obese	2.15 (1.44 to 3.22)	<0.001		
ART (Having the drug as part of their combination)				
TDF (n=456)	1.53 (0.97 to 2.41)	0.069		
NVP (n=459)	1.06 (0.71 to 1.58)	0.789		
EFV (n=274)	1.81 (1.28 to 2.56)	0.001		
AZT (n=215)	0.82 (0.57 to 1.19)	0.299		
ABC (n=6)	0.9 (0.15 to 5.43)	0.909		
LPV/r (n=26)	0.61 (0.21 to 1.8)	0.374		
ATV/r (n=15)	0.72 (0.19 to 2.63)	0.614		
TDF#EFV	2.31 (1.30 to 4.12)	0.004	2.04 (1.26 to 3.30)	0.004

Among the sub-set of participants who had both FBG and HbA1c (n=172), the direction of association between the risk factors and elevated FBG remained the same, although statistical significance was lost due to the smaller sample size [Table 4].

Table 4:Sub-analysis using Fasting Blood Glucose as the outcome (n=172)

Covariate	Unadjusted RR (95% CI)	p-value for unadjusted RR	Adjusted RR (95% CI)	p-value for adjusted RR
Age (5yrs)	1.09 (1.00 to 1.19)	**0.053**	1.09 (1.00 to 1.19)	0.051
Hypertension	1.16 (0.84 to 1.60)	0.371		
Waist Circumference (>102 for males and >88 cm for females)	1.34 (0.97 to 1.86)	**0.077**	1.33 (0.96 to 1.83)	0.087

Discussion

The overall prevalence of newly-diagnosed diabetes using HbA1c was low (3.4%) in this virally- suppressed ART-mature cohort. Prevalence of prediabetes was high at 15.3%. Risk factors associated with prediabetes and diabetes included age, presence of hypertension, abnormal waist circumference and current or prior use of efavirenz and tenofovir. Hypertension was prevalent in over a quarter (36%) of the population, with higher proportions observed in the rural compared to the urban clinic. Participants from the rural clinic also had higher levels of awareness regarding diabetes and need for screening and had higher proportions of people previously screened for diabetes compared to the urban clinic. The higher prevalence of hypertension and awareness of diabetes screening in the rural clinic could be attributed to lower patient volume in the rural clinic compared to the urban clinic, allowing care providers to spend more time with the patient; hence increased opportunity for identification of hypertension and patient education.

Our findings are consistent with several recent studies which have reported modest prevalence of diabetes and its risk factors among individuals on ART in SSA: diabetes (0.5% to 8%),[97-101] pre-diabetes (12% to 21%)[80,82,83] and hypertension (12% to 39%).[76,102-104] Prevalence of diabetes in our study was similar to other recent studies in Kenya among HIV-positive individuals. [105,106] It was also consistent with the overall range of T2D prevalence estimates in Kenya at 3.5% to 5%. [107] The lower prevalence of T2D compared to other regions could be explained by the lower prevalence of other risk factors, like obesity and smoking, in our study population relative to PLHIV in other regions. These results support

previously published findings that except for ART use, PLHIV share similar risk factors for diabetes with the general population. Many studies have described an association between diabetes and age, hypertension, familial history and central adiposity; in both general populations and PLHIV sub-populations.[90,96,100,107-109]

The association of hyperglycemia with efavirenz is consistent with previously reported literature.[78,105,110-114] While TDF, an NRTI, has been shown to improve lipodystrophy and the lipid profile compared to other nucleoside reverse transcriptase inhibitors,[115,116] we observed an increased risk of prediabetes and diabetes among those on TDF, especially when combined with efavirenz. Previous descriptions of this have only been reported when TDF is combined with didanosine,[117] which was not the case in our study. This is particularly significant in Kenya, where a greater proportion of patients are on TDF and EFV as their first-line regimen, yet diabetes screening is emphasized only among the small proportion on PI-containing regimens. With the current national roll-out of integrase inhibitors as part of first-line therapy and whose effect on glycemia may not be well-established, a case can be made for diabetes and prediabetes screening to be offered to all PLHIV as part of comprehensive health services.

Despite a low prevalence of overt diabetes, the marked prevalence of prediabetes and other risk factors among a population who attend clinic regularly highlights an opportunity to screen for these modifiable risk factors. With up to 10% of people with prediabetes progressing to develop diabetes each year, identifying and addressing this through diet, lifestyle modification or metformin could reduce future risk of diseases such as stroke, myocardial infarction and peripheral arterial disease.

This study is the first to our knowledge that reports on prevalence of diabetes using the standard ADA HbA1c definition in East Africa. Many previous studies have relied on a single test. Our strength was that we used a confirmatory test as per the ADA guidelines. (Fig 2) Nearly one in five of those asked to return the following day while fasting failed to come back, highlighting the difficulties posed by screening approaches that require multiple clinic visits. With similar prevalence findings to other studies using fasting glucose; our

findings add to the body of literature supporting use of point-of-care HbA1c screening, reducing the requirement for a return visit while fasting. [84,118]

Our study limitations include the failure to use 75g-OGTT test as the gold standard as part of our algorithm for T2D diagnosis. We did not assess the mean corpuscular volume (MCV) in this population, who are likely to have macrocytosis, a factor that could interfere with HbA1c values. We relied on the last hemoglobin (Hb) assessed in the preceding six months and did not assess a current Hb rule out anemia. Both macrocytosis and current low hemoglobin would likely be associated with falsely low HbA1c levels. Our findings may therefore underestimate the prevalence of elevated HbA1c in this population.

These findings are relevant as they reflect the growing population of PLHIV adults: older, with prolonged use of ART, virally-suppressed with immune reconstitution. Our findings of T2D among 5% and prediabetes among 15.3% of a mature ART cohort in Kenya supports universal HbA1c screening using POC screening methods as part of comprehensive HIV care services. With time and without intervention, it is expected that a proportion of those with prediabetes will develop overt diabetes. Longitudinal follow-up of these patients will be important in understanding the risk of progression and to better inform screening and intervention strategies for diabetes among the PLHIV in Sub-Saharan Africa.

Chapter 3: Cost and affordability of scaling-up point of care Hemoglobin A1c screening delivered through existing HIV treatment programs in Central Kenya

Abstract

Introduction

Screening for type 2 diabetes (T2D) using point-of-care glycated hemoglobin A1c (HbA1c) among PLHIV may be a viable option in sub-Saharan Africa in view of limited laboratory infrastructure. We estimated the cost and affordability of HbA1c screening delivered through existing HIV care and treatment services in Central Kenya.

Methods

A deterministic decision-tree model was constructed to simulate the budget impact of diabetes screening using HbA1c annually, over a 5-year time horizon for adults ≥35 years on ART, with a confirmatory random or fasting blood glucose for those with diabetes (HbA1c≥6.5%) and prediabetes (5.7% - 6.4%) respectively. Simulations were based on regional input estimates. Input costs were obtained from a prevalence study.Scenarios compared were universal screening vs risk-based screening, for those with hypertension and/or obesity. Sensitivity analyses for input parameters and costs were done.Costs are presented in 2018 US dollars ($).

Results

The cost of T2D screening using point of care HbA1c was, while that of a confirmatory blood glucose test on a different day was $6. The annual cost of identifying and confirming one person with T2D was $1,705 for the universal approach and $892 for the risk-based approach, contrasted to the annual average cost of dialysis due to diabetic nephropathy at $3,003 per patient. The cost categories with greatest impact on the budget were personnel and clinical supplies. High prevalence of T2D was associated with less impact of the unit test costs on total screening cost per person.

Conclusion

Screening for T2D using HbA1c is affordable. The main drivers of cost were staff and clinical supplies. Increase in prevalence of T2D was associated with robustness of total screening cost per person to unit test costs. Cost-efficiency can therefore be achieved through risk-based screening, where T2D prevalence is high, and reduction in unit test costs.

Introduction

Persons living with HIV (PLHIV) have a higher risk of developing type 2 diabetes (T2D) compared to those without HIV.[67,70] Chronic systemic inflammation associated with the virus and toxicity related to antiretroviral therapy (ART) have been linked to pancreatic insufficiency and peripheral insulin resistance.[71-73] Moreover, early initiation of ART with the test-and-treat approach has substantially improved life expectancy.[119,120] PLHIV are therefore experiencing age-associated metabolic conditions including T2D.[77,121]

If undetected and therefore left untreated, diabetes is associated with several complications, including nephropathy. Diabetic nephropathy occurs in 2-26% of diabetic patients globally.[122-124] Without any intervention, diabetic nephropathy occurs around 6.6 years (CI: 4.2-9.9 years) following diagnosis of T2D.[125] In Kenya, prevalence of chronic kidney disease is rising. Studies in SSA show prevalence of advanced nephropathy requiring dialysis ranges from 10.8% to 41% among people on ART.[103,126] The Kenya national health insurance program (NHIF) cites pay-outs for dialysis claims as the single largest cost incurred in 2017, with T2D and hypertension responsible for more than half of these cases. [127] Strict glycemic control may slow the rate of progressive renal injury even after overt dipstick-positive proteinuria has developed.[128,129] Screening for T2D and prediabetes, with early diagnosis and initiation of treatment is therefore beneficial in preventing the onset of long-term complications of diabetes.[130]

Although we did not assess cost-effectiveness in our study, literature shows that screening for T2D is cost-effective.[131,132] In Brazil, a national population-wide screening program showed significant reduction in the cumulative incidence of diabetic nephropathy and extended life expectancy following screening and initiation of T2D treatment. [133]

There is no clear consensus on the preferred screening test for T2D among PLHIV. While HbA1c at the designated cut points may have a lower sensitivity compared to the oral glucose tolerance test, [134] this may well be offset by its wider application due to convenience, increasing the number of diagnoses made. With advancement in technology, we now have validated point of care (POC) HbA1c testing devices and are a viable option to

consider in resource-constrained settings where poor laboratory infrastructure may limit access to lab-based HbA1c testing.[34,135,136]

With emphasis on integration of noncommunicable disease and HIV care, more implementation research is needed to figure out effective ways of achieving integration.[137-140] In Kenya, a lower-middle income country with HIV prevalence at 4.2% and per capita gross domestic product (GDP) of $2,010 in 2018; costs pertaining HIV testing, ART treatment, viral load and immune response monitoring are paid by the government. Other laboratory investigations or treatments, including those for T2D are paid out-of-pocket by the patient. Unlike developed nations, the cost of illness in T2D is largely direct costs.[141] Our objective was therefore to assess the cost and affordability of introducing POC HbA1c screening integrated within HIV care and treatment services in Central Kenya.

Methods

Study Design & setting

A budget impact analysis lens, performed using the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) framework was used.[142] Adopting a payer perspective, a deterministic cohort decision tree (Excel-based) was constructed, using a 5-year time horizon.

The study setting was in Central Kenya (Kirinyaga and Kiambu counties). We anticipated that diabetes screening using HbA1c would be offered to eligible adults in all health facilities offering HIV care and treatment services in these counties.

Epidemiological and clinical inputs

Eligible population

We identified the total population of adults in the region from the national census reports. We then applied the region-specific HIV prevalence rates on this population to obtain estimates of PLHIV. Estimates from the national program on the proportion of PLHIV aged ≥ 35 years were used.[106] Assuming they all were engaged in care, we estimated the total number of eligible patients using sub-national ART coverage estimates from multiple sources.[143,144] We also applied an annual marginal increase in total population[145] and an annual death rate among PLHIV, as reported in literature.[144] We assumed that ART coverage will increase over time, assuming a marginal rise in ART coverage annually to hit

90% by the end of the five years as per the UNAIDS 90:90:90 declaration. These model inputs are summarized in Table 5 below:

	Universal Screening	**Risk-Based Screening**	
Parameter	**Base Case**	**Base Case**	**Reference**
Eligible population			
Total population	1685770	-	[144]
PLHIV (HIV prevalence)	0.042	-	[143,144]
>35 years	0.48	-	[106]
Risk factors	-	0.445	Study, [146]
Decision Probabilities			
pDie	0.019	-	
pScreen1	0.9	-	
pD1	0.028	0.031	
pPreD1	0.15	0.21	
pD2	0.07	0.074	
pPreD2	0.4	0.426	
pScreen2	1	1	
pD3	0.07	0.074	
pBirths	0.02	-	[147]
pART Coverage	0.67 - 0.9	-	[143,144]

Table 5: Model Parameter Values

Scenarios

Current practice is opportunistic screening that is not paid for by the Ministry of Health (MoH). This was compared to two screening approaches: universal vs risk-based screening. In the universal approach, it was assumed that screening would be offered to everyone eligible, with a high uptake, informed by the great demand for screening observed during the study. In the risk-based approach, screening would be offered only to those with hypertension and/or are obese, key risk factors for T2D as observed in the study. Prevalence rates of these two risk factors, as well as T2D prevalence rates specific to these sub-groups as observed in the study were applied.

General model description

HbA1c was offered to the eligible population. If it was positive for T2D (HbA1c ≥6.5%), a confirmatory random blood glucose was done. If HbA1c was in the prediabetic range (5.7% - 6.4%), a fasting blood glucose (FBG) was done, where they could be classified as having no disease, remaining prediabetic (FBG 5.6 – 6.9 mmol/L) or being diabetic (FBG ≥7 mmol/L). Those who were prediabetic after these two tests would receive a repeat HbA1c after 6 months, as per ADA guidelines. This process would be repeated

annually. We applied the prevalence rates of diabetes and prediabetes observed in our screening prevalence study to the eligible population. These rates were comparable to other national surveys.[146] Our decision tree model is as shown in Figure 11 below:

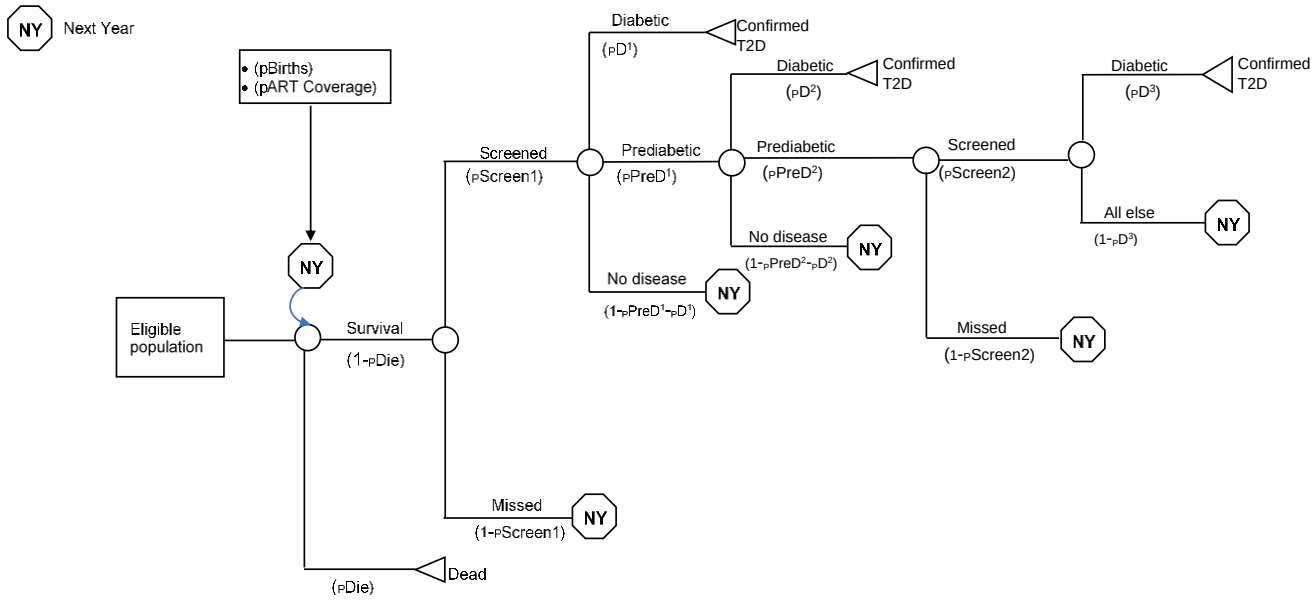


Figure 11:Decision tree model for the screening procedures

Cost inputs

To estimate the unit cost for screening, we utilized a bottom-up costing approach.[148] Cost data were obtained from study records and available market prices. These cost categories were divided into mutually exclusive inputs and activities, as per the WHO manual on cost data collection.[149] These were personnel, per diems, clinical supplies, clinical equipment, transport and maintenance, utilities, training, patient travel and data capture. Overheads were estimated as a proportion of the total costs.

Capital costs were annuitized over their useful lives. Costs of clinical supplies, transport and maintenance and other utilities were obtained from our screening study. Sample transport for quality validation costs were adjusted to reflect local transport and staff per diem rates, which were different from those used in the study. Data capture costs reflected the costs of setting up a tablet-based parallel electronic data collection system. The FTE distribution for the personnel costs was prorated to reflect the actual time spent on screening-specific duties. The annual average inflation rate as at Sep 2018 was applied.[150]

Cost of illness (diabetic nephropathy)

Annual treatment costs of microalbuminuria and macroalbuminuria, which would be incurred by all patients with diabetic nephropathy prior to and during dialysis, as well as costs of dialysis were obtained from a recent study done in Kenya. Prevalence of advanced nephropathy among PLHIV was estimated from local literature.[151,152] We assumed about half would need dialysis each year. These estimates are shown in the appendix.

Sensitivity Analyses

One and two way were conducted to take into account uncertainty in the input parameters and test the robustness of the results. We created probability distributions for cost parameters in the model with uncertainty, using a gamma distribution. For each cost parameter, we used the baseline value for the mean, estimating the standard error based on the approximation that the range used for the one-way sensitivity analysis represented a 95% confidence interval. This was used to determine the cost category with the largest impact on total cost. For T2D prevalence, deterministic two-way sensitivity analysis was done by varying the prevalence, based on standard error estimates derived from literature, and unit cost of a HbA1c test, based on ±50%.

Results

Base Case

The average unit costs for each POC HbA1c test was $42 and $6 for a confirmatory fasting or random blood glucose test on a different day, for 620 and 175 patients respectively. The cost categories and proportional distribution towards unit and total costs are shown in Table 6 below. The largest cost proportions were clinical supplies (45%) and personnel (41%). The data capture costs were comparable to costs of modifying existing electronic medical record systems in HIV clinics to include data fields that capture diabetes screening history and results.

Table 6: Cost categories for point of care HbA1c and blood glucose tests

Cost Category	Total program costs	POC-Specific Costs	Unit Cost (US$)	FBG/RBS-specific costs	Unit Cost (US$)
Salaries and Benefits*	9,900	9,900	16		
Per Diems	543	543	1		
Transport & Maintenance	1,449	1,449	2		
Office Supplies	16	16	0		
Clinical Supplies	11,688	11,594	19	94	0.54
Utilities	445	445	1		
Other Equipment	1,697	1,681	3	16	0.09
Training	60	60	0		
Patients - Travel	929	-	-	929	5.31
Data Capture	154	154	0		
Total Cost	**26,881**	**25,843**	**42**	**1,039**	**5.94**

*50% FTE for the nurse

These were associated with total costs of POC HbA1c screening ranging from $ 832,905 to US$ 1,078,150 over a 5 -year period for the universal screening strategy and US$ 411,810 to US$ 557,508 for the risk-based screening strategy with 90% screening uptake among the eligible population. To confirm T2D among those with a HbA1c ≥ 6.5% and those with prediabetes (HbA1c 5.7% -6.4%) using an additional blood glucose test(RBS/FBG), the costs ranged from $ 21,420 to $ 27,726 for the universal screening strategy and $ 14,160 to $ 19,170 for the risk-based screening strategy. For those who remained prediabetic and needed a follow-up HbA1c screening test after 6 months, the costs ranged from $ 50,807 to $ 65,767 for the universal screening strategy and $ 36,834 to $ 49,854 for the risk-based strategy. The incremental 5-year costs were therefore $ 5,184,934 for the universal strategy and $ 2,718,162 for the risk-based strategy, as shown in Table 7 below.

Table 7: Costs of screening over 5 years by screening strategy

			Universal Screening	*Risk-based Screening*
Year	**Screening Mix**	**Unit cost**	**Total cost**	**Total cost**
2018	PLHIV on ART	42	832,905	411,810
	Confirmatory FBG/RBS	6	21,420	14,160
	Repeat HbA1c at 6 months	42	50,807	36,834
	Total Screening Cost		**905,132**	**462,804**
2019	PLHIV on ART	42	892,131	446,796
	Confirmatory FBG/RBS	6	22,938	15,360
	Repeat HbA1c at 6 months	42	54,420	39,942
	Total Screening Cost		**969,489**	**502,098**
2020	PLHIV on ART	42	953,015	482,832
	Confirmatory FBG/RBS	6	24,504	16,602
	Repeat HbA1c at 6 months	42	58,134	43,176
	Total Screening Cost		**1,035,653**	**542,610**
2021	PLHIV on ART	42	1,015,002	519,750
	Confirmatory FBG/RBS	6	26,100	17,874
	Repeat HbA1c at 6 months	42	61,915	46,494
	Total Screening Cost		**1,103,017**	**584,118**
2022	PLHIV on ART	42	1,078,150	557,508
	Confirmatory FBG/RBS	6	27,726	19,170
	Repeat HbA1c at 6 months	42	65,767	49,854
	Total Screening Cost		**1,171,643**	**626,532**
Five-year Total			**5,184,934**	**2,718,162**

The number of people identified with T2D were 4,822 and 3,046 through the universal and risk-based screening strategies respectively (Table 8).

Table 8: Costs and yields per screening strategy

	Universal Screening	**Risk-based Screening**
5-year total cost	5,184,934	2,718,162
N$^{o/}$ screened	120,530	62,738
N$^{o/}$ identified with T2D	4,822	3,046
Unit cost of identifying and confirming T2D per person	1,705	892
N$^{o/}$ needed to screen (NNTS)	25	21

The cost of identifying and confirming one person with T2D was therefore 38% more cost efficient using the risk-based strategy compared to the universal strategy.

Our estimates show that over the 5-year period, the number of PLHIV with diabetic nephropathy would increase from 91 to 118, with half of them requiring dialysis.(Appendix) The costs of dialysis would increase by 29%, from $ 272,993 to $ 353,375. This would be associated with an average cost of $ 3,003 per patient on dialysis.

Affordability

According to the PEPFAR strategic direction summary, 2017 annual investments in HIV/AIDS amounted to US $ 726,103,003, 55% of which was earmarked for clinical care, treatment and support.[143]Assuming this amount remained the same over the 5-year period of analysis, overall budget impact of screening would be 0.63%-0.93% of the total budget and 1.15% to 1.7% of the care and treatment budget.

Sensitivity analyses

One-way sensitivity analyses showed that the incremental screening costs were most sensitive to personnel costs and costs of clinical supplies.(Figure 12).These were the costs of hiring a 50% FTE nurse and a program administrator at 20%FTE.

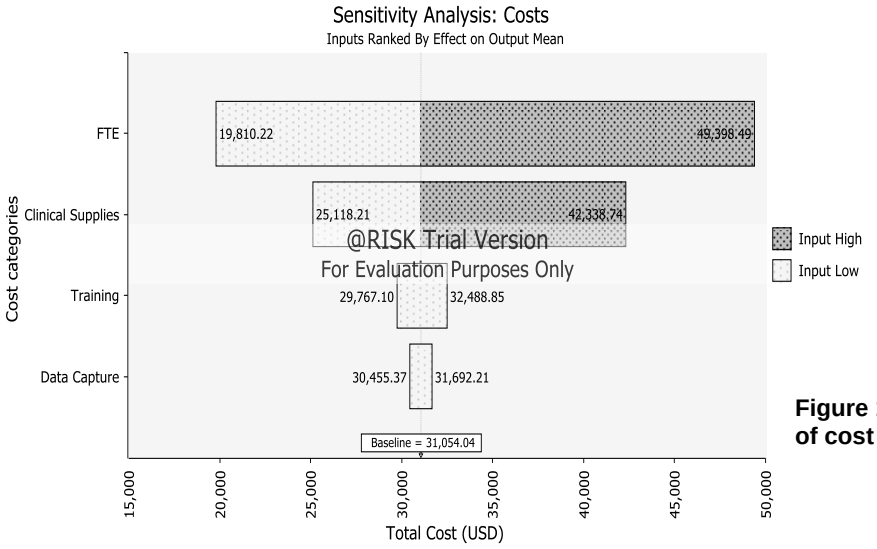


Figure 12: Sensitivity analysis of the effect of cost inputs on total screening costs

Two- way deterministic analysis of T2D prevalence and unit cost per HbA1c test showed that the higher the prevalence, the lower the impact of the unit of each test on the total screening cost per person, as shown in Figure 13 below.

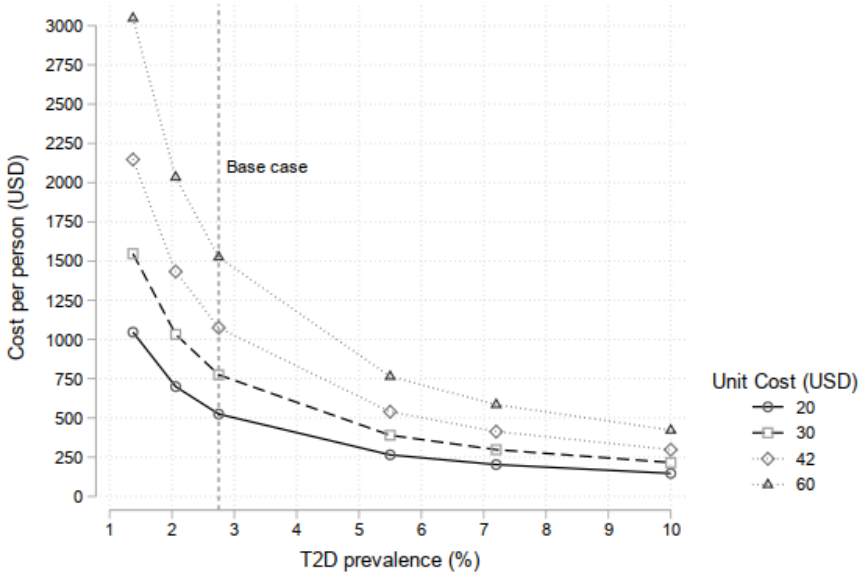


Figure 13: Sensitivity of total costs varying unit test costs and T2D prevalence

Discussion

At a unit cost of $ 42 for HbA1c and $ 6 for a confirmatory blood glucose test, it would cost the program $ 1,705 for universal screening and $ 892 for risk-based screening to identify one person with T2D annually, having needed to screen 25 people for the universal approach and 21 people for the risk-based screening approach. Assessing these as a proportion of the national HIV budget, these costs are affordable, as they are <1% of the total HIV budget. Comparing the costs to other interventions among HIV-infected people e.g. $ 1,455 for delivering integrated PrEP and ART to HIV sero-discordant couples, pap smear testing for cervical cancer screening every 3 years at $ 2,272 and $1,094 for partner notification services, our T2D screening costs of $ 892 - $ 1,705 are within range of other interventions among HIV-infected populations.[153-155]

Our assumptions and model inputs on diabetic nephropathy were fairly conservative and based on cross-sectional surveys, since no longitudinal studies have assessed its incidence and time-to-illness in SSA. At $ 3,002 per person treated for diabetic nephropathy, this is a fairly high cost, relative to Kenya's GDP of $ 2,010.

Our simulation showed that risk-based screening is cost efficient compared to universal screening. This is consistent with several cost-effectiveness studies in the general population.[132] With literature showing that HIV is associated with greater awareness and treatment of hypertension than T2D, including assessment of kidney function,[156-158] adding

risk-based screening of T2D among PLHIV with hypertension may be a feasible and cheaper strategy relative to universal screening.

The major drivers of unit costs were personnel and clinic supplies. For personnel, studies have shown that the time take to conduct diabetes screening reduces as staff get more familiar with the process.[159] Increase in experience allows people to know the process can therefore multitask e.g. do the blood draw and leave the test running while they continue with other counselling. Over time, this could lead to increased number of screenings by the same staff for the same time duration. Similarly, as patients get repeatedly exposed to this screening, the need for rigorous patient education would decrease; since repeat clients would need less counselling than new clients. This could also contribute to increased efficiency.

For the clinic supplies, the largest cost proportion for this category was test reagents. This highlights the importance of access to reasonably priced reagents. If diabetes screening were to be routinized as part of HIV care, this would be an assured demand for suppliers and the payer (in this case MoH) could benefit from lower reagent costs due to bulk pricing and would have bargaining power to negotiate for even lower prices. They could also negotiate for different partnership modalities that further reduce input costs e.g. equipment placement as opposed to leasing or upfront purchase.

From the sensitivity analysis, the total costs per person are sensitive to unit test costs when the prevalence of T2D is low and are more robust at higher T2D prevalence. This also supports the risk-based screening approach, which is associated with higher disease prevalence,[160] (EKRIPO) even as we seek to reduce the other input costs.

Our approach is appropriate and is consistent with the ISPOR guidelines which prefer static models for shorter time horizons. Other study strengths include sensitivity analysis accounting for parameter uncertainty and use of different screening scenarios, giving policy makers and other funders viable options as they estimate resources required to provide diabetes screening as an add-on service to PLHIV. Use of a validate POC device and a 2-step testing approach using standard definitions of diabetes and prediabetes allows for comparison of our findings with other studies. Our main limitation is that we were unable

to demonstrate cost-effectiveness of T2D screening, given the cross-sectional nature of our study. We are therefore unable to demonstrate the complete budget impact, as we do not have DALY's averted by screening.

Our results are likely generalizable to other settings in SSA. Specific to the risk-based approach, cost-efficiency is likely to remain fairly stable since those with risk factors are likely to have a higher prevalence of T2D, even if the general prevalence is low. Given that in many HIV programs screening for BMI and hypertension is already on-going, identifying these individuals at risk and screening them for T2D is an affordable strategy towards HIV-noncommunicable disease integrated care.

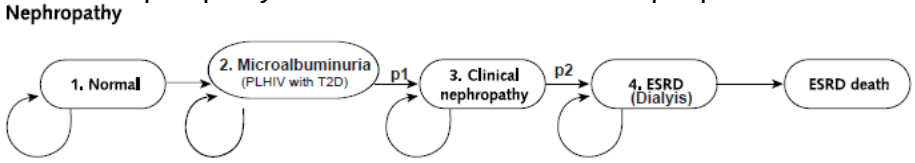
Conclusion and next steps

In conclusion, iris biometrics scanning is a feasible and highly acceptable among newly tested positive and PLHIV already engaged in care as a unique identifier. This can be integrated with existing EMR systems for program implementation and scale-up. Screening for diabetes and prediabetes using POC HbA1c showed a moderate prevalence of diabetes but a high prevalence of prediabetes, an important predictor of developing diabetes. Risk factors associated with this included age, family history of diabetes in first-degree relatives, hypertension, central adiposity and ever being on Tenofovir and Efavirenz. It is also affordable if it were to be integrated within the HIV care program in Central Kenya, with risk-based screening being more cost-efficient compared to universal screening.

Current science on HbA1c suggests that hemoglobin glycation rates may be genetically different based on race, and so caution when interpreting HbA1c cut-offs that are validated in primarily Caucasian populations.[161] Future directions for this work include validating HbA1c cut-off points among HIV-infected populations in SSA, by comparing HbA1c performance in this population to the gold standard glucose tolerance test and even continuous glucose monitoring.

Appendices

Diabetic Nephropathy: Markov model and model input parameters



The model is used to follow the disease progression of all members of the cohort. At the end of each 1-year period, portions of the cohort can move from one disease state to another or stay in the same disease state. ESRD (end-stage renal disease).

Input Parameter	Base case	Reference
p1	0.11	[152]
p2	0.5	[151]
Annual clinical Rx cost (US$)	303	[162]
Annual dialysis cost (US$)	5,400	[162]

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