

ASSESSING THE IMPACT OF TARGETED SCREENING AND TREATMENT OF DIABETES AND HYPERTENSION AMONG ADULTS LIVING WITH HIV IN NAIROBI, KENYA

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ABSTRACT

Individuals living with human immunodeficiency virus (HIV) today are living longer, thanks to expanded access to antiretroviral therapy (ART); however, this population is therefore increasingly at risk for many age-associated comorbidities. The future health of people living with HIV will therefore depend on the prevention and management of non-communicable diseases (NCDs), with consideration for integrated approaches to screening and treatment becoming increasingly important. This analysis applies a hybrid simulation of HIV and NCDs to examine the impact of providing screening and treatment for hypertension and diabetes at HIV facilities in Nairobi, Kenya. We combine a compartmental model of the HIV epidemic at a population level with a microsimulation of cardiovascular disease (CVD), and explore the impact of various strategies for targeting eligible individuals on ART, by age and gender, to receive NCD screening and treatment.

1 INTRODUCTION

The epidemic of human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) is one that has affected the lives of people from all across the world. The development of combination antiretroviral therapy (ART) in the mid-1990s changed the life expectancies of people living with HIV (PLHIV), therefore altering the corresponding population age structure. While the number of young people age 15-24 living with HIV saw a slight decline from 3.9 million in 2005 to 3.5 million in 2018, those who were older than 50 increased from 2.7 million to 7.5 million over the same time period (UNAIDS 2019).

As a result of this change in age structure, recent studies have found individuals living with HIV are increasingly at risk for many age-associated comorbidities, including cardiovascular, metabolic, pulmonary, and renal comorbidities; as well as non-AIDS-defining cancers (Schouten et al. 2014). The future of the HIV response is therefore linked to the future of the non-communicable disease (NCD) response. As people live longer with HIV and depend on ART for decades, the care of people living with HIV will increasingly focus on prevention and management of NCDs (Bekker et al. 2018). This study seeks to explore the potential impact of integrated approaches to HIV and NCD service delivery, using modeling methods and focusing specifically on the Kenyan context.

The HIV epidemic in Kenya is one of the largest globally, with an estimated 1.6 million individuals living with HIV in 2018 (resulting in a prevalence of 4.7% among adults age 15-49) (Avert 2019). At the same time, the burden of NCDs in Kenya is increasing—deaths due to NCDs increased from 35% of total deaths in 2003 to 45% in 2010 (Phillips-Howard et al. 2014). In 2015, Kenya published the STEPwise Survey for Non Communicable Diseases (STEPS), the first nationally representative survey to collect

comprehensive information on risk factors for NCDs among individuals ages 18 to 69 in Kenya (Kenya Ministry of Health 2015). The survey reported an age-standardized prevalence of hypertension at 24.5%, pre-diabetes at 3.1%, and diabetes mellitus at 2.4% (Wamai et al. 2018). Importantly, only 15.6% of those with hypertension were aware of their disease, and among those aware, only 26.9% were on treatment (Wamai et al. 2018). For those with pre-diabetes or diabetes mellitus, only 43.7% were aware of their condition (Wamai et al. 2018).

This study expands a prior study of the impact and cost-effectiveness of a community-wide integrated program for screening and treatment of HIV, hypertension, and diabetes in Kenya (Kasaie et al. 2020). Our former analysis suggested that while cost-effective, implementing such an intervention at a community-level may not be affordable. Here, we explore a more tailored approach for providing NCD screening and treatment at HIV facilities in Nairobi and examine the impact of various strategies for targeting eligible individuals according to age and gender to receive hypertension and diabetes testing and treatment.

2 METHODS

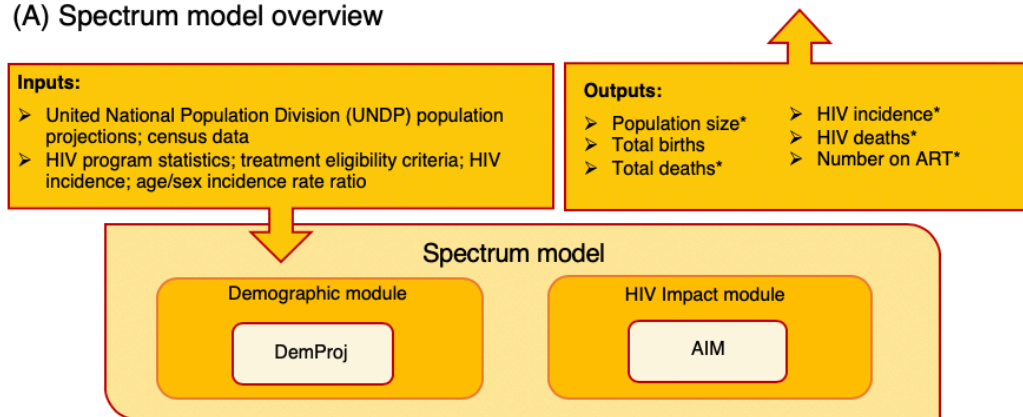
In this study, we apply a previously published hybrid simulation of HIV and NCDs in Kenya (Kasaie et al. 2020, Schnure 2020). Though we utilize the same model, this analysis builds on the prior study by evaluating the impact of a more targeted approach to screening and treatment for HIV and NCDs, as the results from the first paper suggested an infeasibly expensive strategy. Bridging a compartmental model of the HIV epidemic at a population-level with a microsimulation of cardiovascular disease (CVD), this hybrid model represents the co-epidemic of HIV, hypertension, and diabetes at an individual level (Figure 1). Each individual within the model is defined by their age, gender, HIV status, ART status, and CVD risk category. The simulation model is initialized in year 2019 and is followed to year 2030 under alternative scenarios.

We chose a hybrid approach due to the tradeoffs between both compartmental (population-based) modeling methods and microsimulation methods (Bobashev et al. 2007). While compartmental methods can be more manageable and allow for modeling HIV dynamics at a national scale, they are typically limited in their ability to represent the detailed population structure essential to modeling the natural history of CVD (Bobashev et al. 2007). On the other hand, though microsimulations are more representative, the burden of developing and calibrating such a model at a national scale to represent a coepidemic of HIV/NCDs can be quite significant. The use of a hybrid approach is not new to epidemiologic studies, and has further been used in healthcare settings or supply chain management—often combining discrete-event simulation, system dynamics, or agent-based methods (Bobashev et al. 2007, Brailsford 2015, Mielczarek et al. 2016, Brailsford et al. 2019).

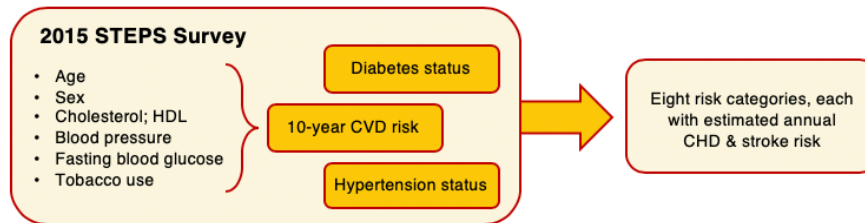
2.1 Population Structure and HIV Dynamics

The population structure and HIV dynamics are obtained from the latest regional Spectrum models in Kenya (Stover et al. 2014). Spectrum is a suite of easy to use policy models to support decision making for different diseases such as HIV, tuberculosis, malaria, etc. Spectrum includes, among others, the DemProj module for maintaining demographic projections (through modeling fertility, mortality, and migration), and the AIDS impact module (AIM) for projecting near-term HIV dynamics including the number of people living with HIV, new infections, and AIDS deaths by age and sex (Figure 1A). Country-specific Spectrum models are utilized by the Joint United Nations Programme on HIV/AIDS (UNAIDS) globally and are updated regularly by expert country teams.

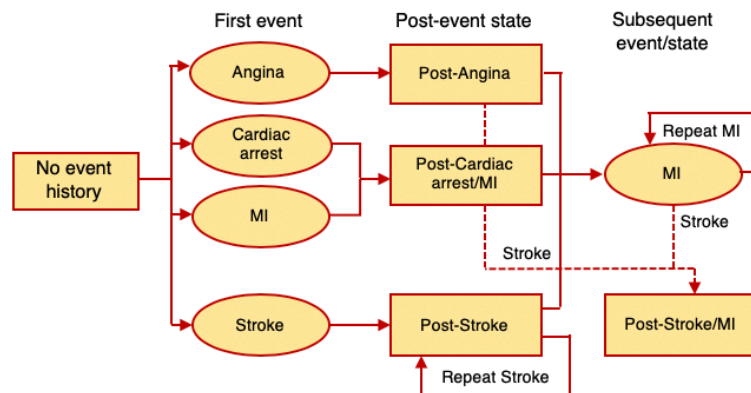
(A) Spectrum model overview



(B) CVD risk category creation



(C) CVD microsimulation overview



(D) Hybrid model approach

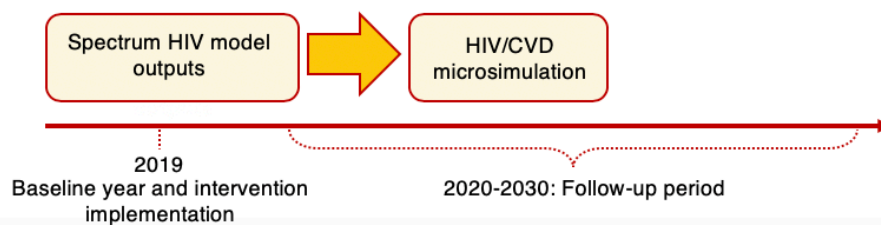


Figure 1: Microsimulation model overview. (A) Spectrum model overview, including main modules used and key inputs/outputs. (B) Process for deriving the underlying CVD risk profile. (C) CVD microsimulation overview and event natural history. (D) Hybrid model approach and simulation timeline.

The hybrid simulation is informed via aggregate data on population demographics and HIV epidemiology generated by the Spectrum model in each year. In this study, we applied the latest Spectrum model of regional HIV epidemic in Nairobi, Kenya, calibrated to the 2019 official estimates from UNAIDS. Specifically, the simulated population (by age and gender) and HIV epidemic (proportion of individuals infected with HIV and on ART) at baseline were calibrated to 2018's estimates from the Spectrum model. Annual population dynamics (such as population growth) and HIV dynamics (such as HIV incidence and mortality) were also updated based on projected outputs from the Spectrum model from year 2019 to 2030.

To estimate the morbidity and mortality associated with hypertension and diabetes, we focused on combined risk of future CVD events that could lead to disability or death (Subramanian et al. 2019). We first estimated the 10-year probability of CVD events for the population of Nairobi, and used these estimates to develop a population-level risk profile for future CVD events by gender and age. More information on the estimated CVD risk profile in Nairobi can be found in the prior publications (Kasaie et al. 2020).

2.1.1 Creating CVD Risk Profiles

To estimate the 10-year risk of CVDs, we applied the Framingham risk calculator model (D'Agostino et al. 2008) to individual-level data from the 2015 Kenya STEPS survey (Kenya Ministry of Health 2015), including total and high-density lipoprotein (HDL) cholesterol, blood pressure, fasting blood glucose, tobacco use, age, and gender (Figure 1B). Individuals were dichotomized as having high or low 10-year CVD risk based on a threshold of $\geq 10\%$. Hypertension and diabetes status were ascertained from the STEPS survey. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 and/or diastolic blood pressure (DBP) ≥ 90 , and diabetes was defined as fasting blood glucose ≥ 7.0 mmol/L (126 mg/dL) or being currently on medication for diabetes. Using this information, we categorized the STEPS population into eight CVD risk categories (Table 1) and estimated the population proportion falling in each category by age and gender. This risk profile was adjusted to match the reported prevalence of hypertension and diabetes among those age 15-70 years old in Nairobi.

Table 1: CVD risk categories.

CVD Risk Category	High 10-year CVD risk ($\geq 10\%$)	Hypertension	Diabetes
Category 1	No	No	No
Category 2	Yes	No	No
Category 3	No	Yes	No
Category 4	Yes	Yes	No
Category 5	No	No	Yes
Category 6	Yes	No	Yes
Category 7	No	Yes	Yes
Category 8	Yes	Yes	Yes

The CVD risk categories range from lowest (category 1) to highest (category 8) with regard to risk of future CVD events. The risk of first coronary heart disease (CHD) or stroke for individuals falling into each risk category was estimated using the corresponding Framingham calculators (D'Agostino et al. 1994, Expert Panel 2001). Once the event risks were estimated for all individuals, the median values were reported for each stratum of age/gender/CVD risk category.

2.1.2 CVD Events and Outcomes

Within the microsimulation, individuals are assigned to a specified risk category upon entering the population and can only move to higher risk categories as they age over time. The risk of first CHD event or stroke is determined by individuals' age, sex and risk category as described above. The main CHD events include cardiac arrest, myocardial infarction (MI) and angina (Figure 1C). The risk of each CHD event is categorized based on event distribution percentages (Table 2). Following each CVD event, individuals experience a probability of acute mortality within the first year post-event; and if they survive, they experience an annual probability of post-event mortality for the remaining duration of their life. Following each event, individuals experience a risk of future MI or stroke. The parameters characterizing mortality and repeated event probabilities are described in Table 2.

Table 2: CVD progression and event probabilities.

Parameter	Value	Source
CHD event distribution (proportion of CHD events attributable to Cardiac arrest, MI, or Angina)		
Cardiac arrest	0.10	(Perman et al. 2011)
MI	0.35 (males); .20 (females)	(White et al. 1996)
Angina	0.55 (males); 0.70 (females)	Author calculation: 100% – [probability of cardiac arrest or MI]
Acute mortality (one-time probability of death following an event)		
Cardiac arrest	0.954	(Nichol et al. 2008)
MI	0.050	(Ogeng'o et al. 2010)
Angina	0.045	(Capewell et al. 2006)
Stroke	0.380	(Mudzi et al. 2012)
Annual mortality (annual probability of death following an event)		
Cardiac arrest	0.040/year	(Law et al. 2002)
MI	0.040/year	(Law et al. 2002)
Angina	0.030/year	(Law et al. 2002)
Stroke	0.050/year	(Law et al. 2002)
Repeat event annual risk (annual probability of new events following prior events)		
Repeat MI post-MI	0.064/year	(Jokhadar et al. 2004)
MI post-angina	0.035/year	(Hemingway et al. 2003)
Repeat stroke post-stroke	0.040/year	(Hardie et al. 2004)

2.2 NCD Treatment Status

The impact of treatment for either hypertension or diabetes is modeled as a reduction in the risk of future CHD and stroke events. The effect of hypertension treatment on the occurrence of CHD events was differential for those with and without diabetes. We estimated that a 10mm Hg reduction in SBP resulted in a relative risk of 0.88 for CHD events among those with diabetes and a relative risk of 0.77 among those without diabetes, using findings from a recent systematic review (Ettehad et al. 2016). The same reduction in SBP was also estimated to have a protective effect against stroke events, with a relative risk of 0.74, regardless of diabetic status (Ettehad et al. 2016). For diabetes treatment, we estimated that metformin (the recommended first-line drug for type 2 diabetes) would result in a 79% reduction in the incidence of CVD events and mortality based on another systematic review and meta-analysis (Lamanna et al. 2011).

2.3 Intervention Scenarios

We modeled a combination of baseline (status quo model) and intervention scenarios for NCD screening and treatment among people presenting to HIV facilities in the Nairobi Region. Given the minimal coverage of hypertension and diabetes treatment in Nairobi (as reported by the 2015 STEPS survey), we assumed no NCD treatment in the baseline scenario. The intervention scenarios were modeled by targeting HIV-infected individuals on ART in year 2020, who were screened and treated for hypertension and diabetes and were followed to year 2030. The targeted scenarios drew from the age-gender categories specified in Table 3, where 20+ indicates the population age 20 years and older.

Table 3: Modeled intervention scenarios and population sizes on antiretroviral therapy (ART) at baseline. Values represent the median and interquartile ranges (IQR) among 100 random simulations in year 2019.

Individuals drawn from:	Population size on ART at baseline		
	Median (IQR)		
	Total	Male	Female
20+ on ART	136,914 (136,754 - 137,138)	44,241 (44,125 - 44,384)	92,679 (92,473 - 92,845)
30+ on ART	116,760 (116,508 - 116,904)	39,341 (39,208 - 39,458)	77,404 (77,245 - 77,518)
40+ on ART	71,435 (71,270 - 71,629)	29,145 (29,029 - 29,263)	42,288 (42,179 - 42,398)
50+ on ART	25,166 (25,028 - 25,238)	12,429 (12,347 - 12,505)	12,716 (12,649 - 12,792)
60+ on ART	5,441 (5,395 - 5,479)	2,856 (2,813 - 2,886)	2,585 (2,561 - 2,620)

To ensure fair comparison, intervention scenarios were compared at fixed coverage levels by screening a specific number of individuals in year 2019 across all scenarios and comparing the outcomes over the simulated period of 2020-2030. The decision to only screen individuals in 2019 does not reflect a public health reality, but rather a ‘proof of concept’ design. Practical implementation should consider screening policies scaled over multiple years. Screening coverage was defined in increments of 500 up to 5,000; followed by increments of 1,000 up to a maximum of 10,000 individuals. Here, the coverage level refers to the number screened for hypertension and diabetes, as opposed to those who are actually treated. Therefore, only a proportion of screened population who are diagnosed with the disease will receive treatment. To replicate realistic clinical practice, individuals initiated on diabetes treatment were regularly screened for hypertension and put on treatment immediately if needed (and vice versa).

2.4 Simulation Methods

We applied available computational services through the Maryland Advanced Research Computing Center (MARCC) to complete the simulation experiments. Each model was run on a single 2.5 GHz computational node with maximum memory of 117 GB. A total of 2,000 replications were run to complete the simulation experiments. Each simulation scenario generated outcomes including incident and cumulative CVD events and deaths, by gender and event type. To estimate improvements in each intervention scenario compared to baseline, a bootstrapping method was applied by randomly sampling one baseline and one intervention replication from the pool of available simulations, calculating the differences in main outcomes (e.g., CVD incidence and deaths), and repeating this process (sampling with replacement) until stable point estimates and variance were achieved. The bootstrap sample size was set to 1,500 random draws to overcome uncertainty fluctuations and allow for result convergence. The underlying simulation model is coded in C++, and post-simulation analyses are carried in R statistical package.

3 RESULTS

3.1 Population Summary

The simulated population size in 2020 (projected by the Spectrum model) was 5.4 million in 2020 and grew to 7.3 million by 2030, with a stable gender breakdown of 48% men and 52% women. Assuming no substantive changes in ART coverage levels (estimated at 68.6% in 2020), HIV prevalence declined from 4.03% in 2020 to 3.18% in 2030, with women having just under twice the HIV prevalence compared to men (5.04% among women and 2.96% among men in 2020 – Figure 2A). The baseline prevalence of hypertension and diabetes in the general population was estimated at 12.4% and 3.75%, respectively, in 2020. The age-specific prevalence of hypertension was higher among HIV-positive men than women (Figure 2B), but absolute numbers of individuals with hypertension were comparable because of the lower HIV prevalence among men. The age-specific prevalence of diabetes was higher for HIV-positive women (Figure 2C&D).

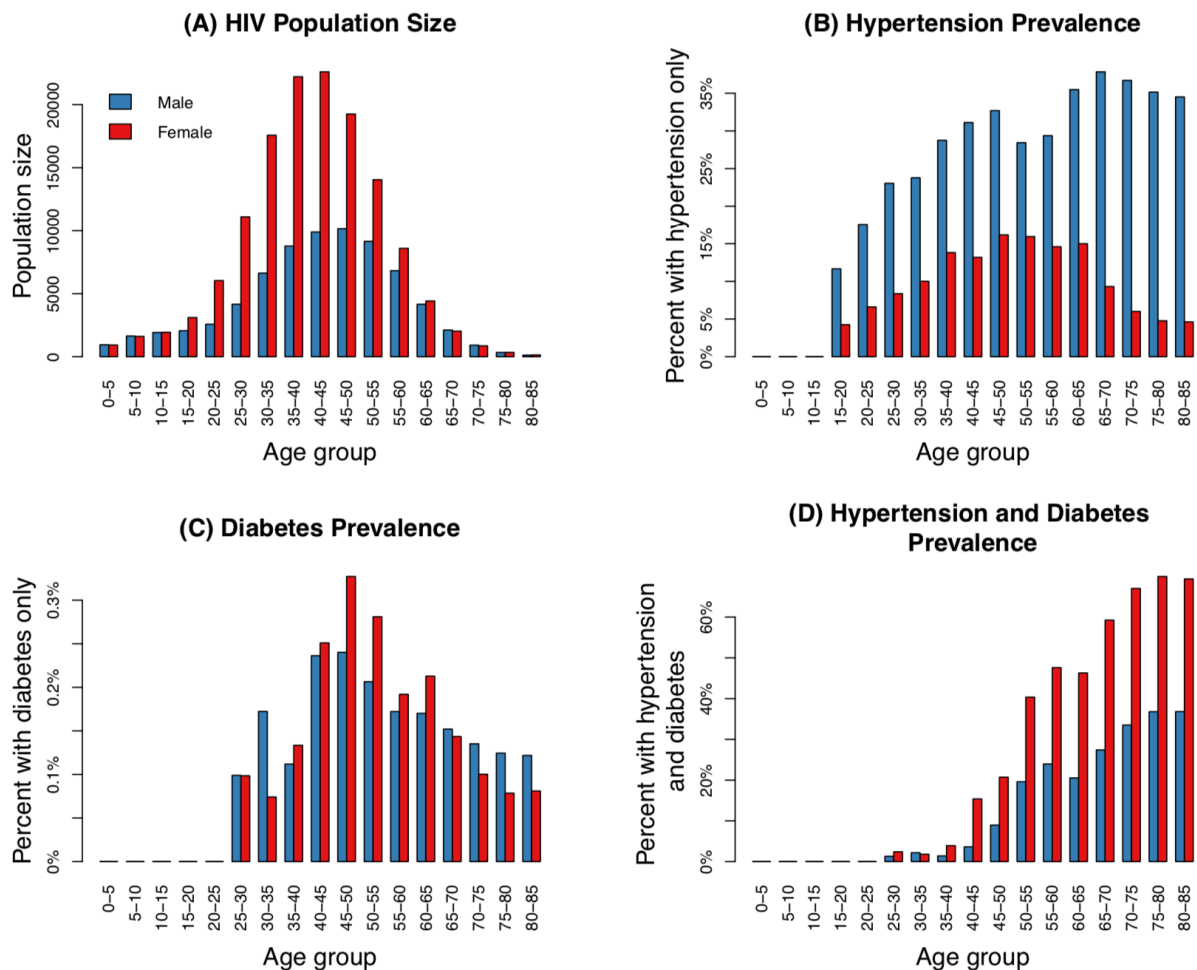


Figure 2: Age distribution and non-communicable disease prevalence among people living with HIV in Nairobi in 2020. Panel A presents the distribution of the HIV-positive population by age and gender; the

remaining panels present the prevalence among the HIV-positive population, according to age and gender, of hypertension only (panel B), diabetes only (panel C), and both hypertension and diabetes.

3.2 CVD Outcomes

Increase in coverage of hypertension and diabetes screening resulted in higher reductions in cumulative incidence of CVD events (Figure 3). When the number of individuals screened for hypertension and diabetes was kept constant, however, scenarios tailored to increasingly older age groups yielded greater reductions in CVD events as compared to the baseline. The efficiency of the 60+ scenario, for instance, is apparent in Figure 3: screening 5,000 individuals age 60 and over resulted in 147 total CVD events averted (or a 1.17% reduction in cumulative incidence from 2020 to 2030), compared to only 104 events averted (a 0.83% reduction in incidence) if the same number of individuals were screened from an eligible population age 50 and over instead.

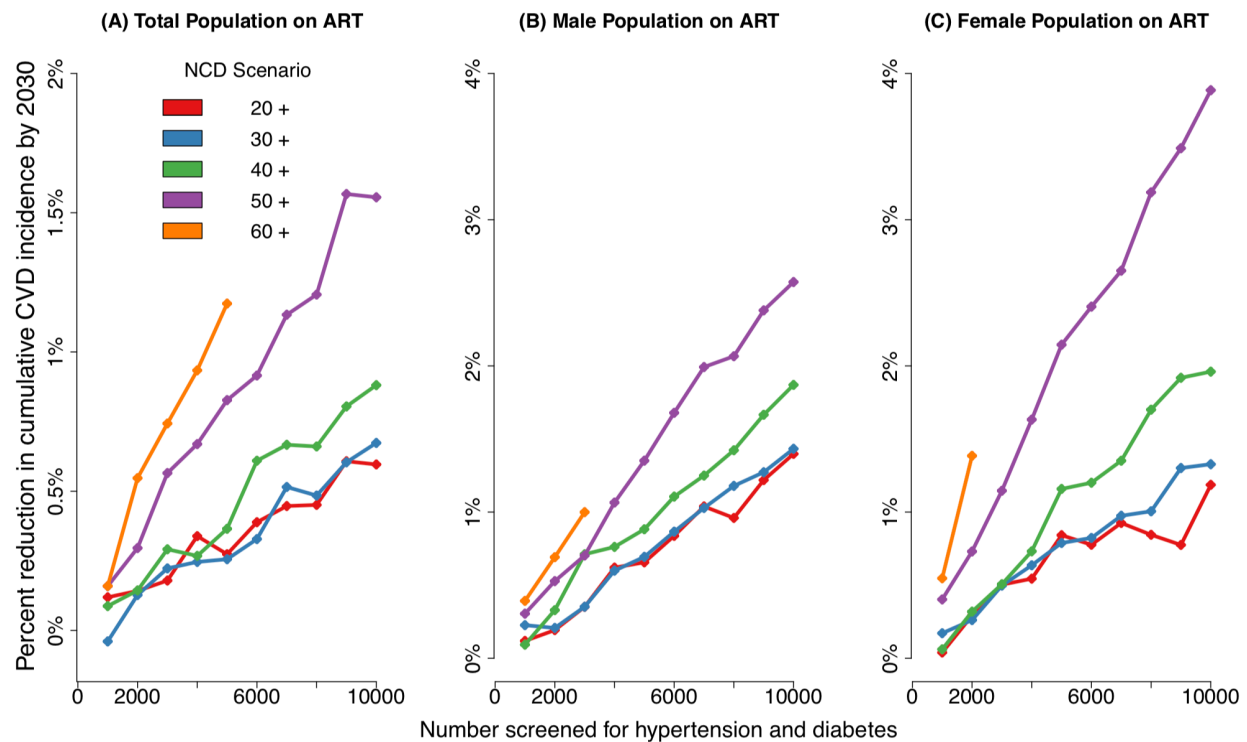


Figure 3: Percent reduction in total cardiovascular disease (CVD) event incidence by age-targeting scenario and gender. This figure presents the percent of total baseline CVD events projected to be averted under each of the combined male/female age-targeting scenarios. Each line represents a different NCD scenario in which individuals are screened from a target population of the given age (e.g., 20+ indicates that individuals are screened from the total adult population age 20 years and over).

Further comparisons by gender suggested similar improvements in outcomes at higher levels of screening coverage and when targeting interventions at older age groups (Figure 3B&C). However, the benefit of age-targeting was more pronounced among women than men. For instance, at a screening coverage of 10,000 among men, targeting men age 40 and over resulted in a 1.87% reduction in cumulative CVD incidence, compared to a 2.57% reduction in CVD incidence if the intervention was targeted to men age 50 and over. For women, on the other hand, screening 10,000 women of age 40 and over resulted in a 1.96% reduction in CVD incidence, compared to 3.89% if those age 50 and over were targeted instead.

Thus, the absolute additional gain (in terms of reduction in CVD incidence) from narrowing the target age from 40 or over to 50 or over was estimated at 1.93% among women compared to 0.70% among men.

When comparing in terms of the absolute impact (number of CVD events averted), the impact was often greater among men compared to women, particularly at younger ages. For example, even though screening 10,000 individuals age 20 and over resulted in a similar percent reduction in CVD incidence for both men and women (1.40% and 1.19%, respectively), the absolute impact of intervention was greater among men (108 CVD events averted) than women (56 events averted – Figure 4). These results were more pronounced among younger age groups and did not hold among older age groups: the absolute impact of targeting 10,000 individuals age 50 and over was similar for both men and women (192 events and 197 events, respectively).

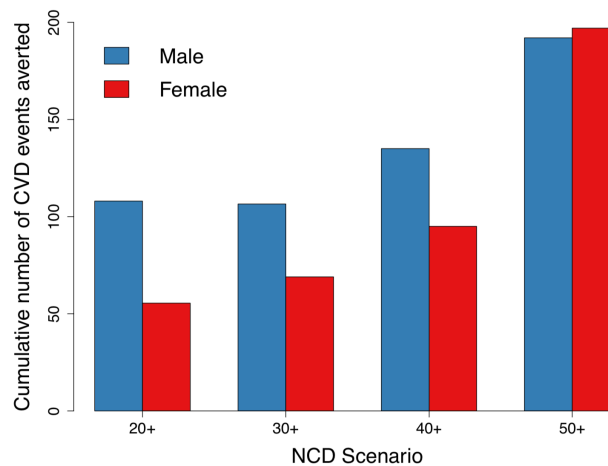


Figure 4: Cumulative CVD events averted by different targeting scenarios. Each grouping represents a different NCD scenario in which individuals are screened from a target population of the given age (e.g., 20+ indicates that individuals are screened from the male or female adult population age 20 years and over). The results are presented only for one coverage level in which 10,000 individuals were screened in each NCD scenario.

4 DISCUSSION AND CONCLUSIONS

This study explored the potential impact of an integrated approach to HIV and NCD service delivery, modeling the outcomes of various scenarios in which individuals with HIV presenting to HIV care facilities in Nairobi, Kenya are screened and treated for hypertension and diabetes. At similar level of screening for hypertension and diabetes, scenarios tailored to increasingly older age groups yielded greater reductions in CVD events. By gender, the relative benefit of age-targeting was more pronounced among women than men. i.e., scenarios focusing on more narrow, older age groups resulted in higher percent reduction in CVD events among women compared to men. However, the absolute impact (i.e., number of CVD events averted) was higher among scenarios targeting men (compared to those targeting women), suggesting that strategies targeting men could still have substantial impact.

These findings are especially important in resource limited settings with limited capacity for NCD screening and treatment among high-risk subpopulations. Such settings might consider, for instance, first strengthening efforts for NCD screening and treatment among individuals over the age of 60 who are experiencing the highest risk of CVD events. With greater resources, such programs can be expanded to younger age groups such as those age 50- or 40-and-above. Further expansions could then seek to screen younger men, given our findings that programs screening even relatively younger men could avert CVD events within 10 years of implementation. Importantly, however, policymakers should weigh these

recommendations against ethical consideration that screening and treatment guidelines should not exclude individuals seeking care. As such, the interpretation of our findings is not to withhold treatment from younger men or women, but rather to augment efforts among the highest risk subpopulations.

Our findings are limited by simplifying assumptions employed in the HIV Spectrum model and the microsimulation of CVDs. This includes, among others, the assumptions of homogeneity with each risk-groups and random mixing among subpopulations in the Spectrum model that can affect the future projections of HIV incidence. Though the CVD microsimulation allows for more flexibility as far as individual-level heterogeneities, we had to adopt a simplifying assumption for categorizing population into eight CVD risk categories and assuming a fixed likelihood of CVD events within each category. Furthermore, the modeling approach did not allow for dynamic changes in CVD risk over time within each stratum of age and gender, while in reality variation in smoking habits and diet could affect individual-level CVD risks over time. The interpretation of these results is also limited by the lack of data on the epidemiology of NCDs among African populations. Even when data were available from Kenya specifically (such as the 2015 STEPS survey), small sample sizes limit the degree of certainty that can be drawn from results. Future research on the NCD burden and treatment coverage in both the general African population and the population living with HIV must be conducted if we are to properly understand and combat the growing dual epidemic in these settings. Furthermore, our current analysis did not evaluate the cost effectiveness implications of increasingly tailored screening programs. This serves as an important area of research for future studies.

Given resource constraints, our results indicate that tailored NCD screening programs for individuals living with HIV in Nairobi might consider first focusing on those age 60 and over and then expanding into younger age groups (particularly among men). While these insights should not be taken as a strong policy recommendation, they serve as a starting point to encourage future research efforts into integrated HIV and NCD care. Importantly, more information is needed on the burden of NCDs and risk for CVD events among people living with HIV. Our analysis uses data and methods collected from general populations (e.g., the STEPS survey, the Framingham Heart Study) as a proxy where data on HIV populations is lacking. In order to make true clinical recommendations for management of NCDs among people living with HIV, future research must investigate issues such as the differences in NCD burden or mortality among HIV-positive individuals compared to the general population; potential clinical interactions between HIV and NCDs; and the effect of ART duration on NCD outcomes.

Integration of HIV and NCD care presents an opportunity to more efficiently reach a growing population in need. Countries in sub-Saharan Africa with the highest burdens of HIV must face the reality of an aging HIV population that is increasingly at risk for many age-associated comorbidities. This analysis examined the impact of screening and treating this population for such comorbidities in an effort to improve future cardiovascular outcomes and the general health and well-being of the HIV community.

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